

Sleep Abnormalities in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Review

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a chronic, disabling illness that affects approximately 0.2% of the population. Non-restorative sleep despite sufficient or extended total sleep time is one of the major clinical diagnostic criteria; however, the underlying cause of this symptom is unknown. This review aims to provide a comprehensive overview of the literature examining sleep in CFS/ME and the issues surrounding the current research findings. Polysomnographic and other objective measures of sleep have observed few differences in sleep parameters between CFS/ME patients and healthy controls, although some discrepancies do exist. This lack of significant objective differences contrasts with the common subjective complaints of disturbed and unrefreshed sleep by CFS/ME patients. The emergence of new, more sensitive techniques that examine

the microstructure of sleep are showing promise for detecting differences in sleep between patients and healthy individuals. There is preliminary evidence that alterations in sleep stage transitions and sleep instability, and other physiological mechanisms, such as heart rate variability and altered cortisol profiles, may be evident.

Future research investigating the etiology of non-restorative sleep in CFS/ME may also help us to uncover the causes of non-restorative sleep and fatigue in other medical conditions.

Keywords: Chronic fatigue syndrome, myalgic encephalomyelitis, sleep, non-restorative sleep, sleep disorders, fatigue, sleepiness

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1.0 INTRODUCTION

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a medically unexplained disabling illness, with prevalence estimates of between 0.007% and 2.8% of the general adult population.¹⁻³ It is primarily characterized by persistent relapsing fatigue of at least 6 months in duration that reduces activity levels. Other key features of the disorder include post-exertion malaise of either physical or mental exertion, memory and concentration difficulties, muscle pain, headaches, tender lymph nodes, sore throat, and non-restorative sleep. Of direct relevance to the current review, patients often report daytime sleepiness, feeling unrefreshed upon waking despite sufficient or extended total sleep time, extended sleep including daytime napping, and other sleep-related symptoms, such as difficulty falling asleep and disturbed sleep.^{2,4,5} Since the late 1980s, research in the area of CFS/ME has begun to focus on examining and determining the cause of non-restorative sleep and sleep disturbance in CFS/ME, and how these symptoms may relate or contribute to patients' daytime fatigue. The current review aims to provide a comprehensive overview of these studies, describe where the field currently stands on this issue, and outline potential directions for future research.

2.0 HISTORICAL OVERVIEW OF DIAGNOSTIC CRITERIA

Clusters of symptoms including chronic fatigue, cognitive and mood impairments, sleep difficulties and pain have

been observed in clinical practice for centuries. A collection of symptoms similar to that of CFS/ME, including fatigue, depression, headache, impotence and neuralgia, were first reported in the 19th century.⁶ The diagnosis "neurasthenia" was popularized by American neurologist George Beard to describe this collection of symptoms.⁷ With increasing sophistication of psychiatric diagnoses over time, diagnosis of neurasthenia has declined, however, the symptoms described in these early patients closely match those we now recognize in CFS/ME today.

The name "chronic fatigue syndrome" was first suggested in 1988, and most commonly used by the medical and scientific community to describe the illness. However, the name CFS has been rejected by many patients, patient advocacy groups and some doctors as it undermines and trivializes the illness. Since 1969, myalgic encephalomyelitis (ME) has been included in the World Health Organization's International Classification of Diseases (ICD-10), and although is clinically distinct from CFS, the two terms are used interchangeably. Due to the stigma of the name "chronic fatigue syndrome," the illness is often referred to as CFS/ME.

It is important to make a distinction between CFS/ME and fibromyalgia (FM). FM is a chronic medical disorder characterized by widespread pain, a heightened pain response, and sleep disturbance,⁸ and is commonly comorbid with CFS/ME.⁹ Given the overlapping symptoms and lack of a diagnostic test, it is important for research studies to have clear criteria for distinguishing these two conditions. This review will focus on research that has specifically examined sleep in CFS/ME.

2.1 Research Definition

The first working case definition of chronic fatigue syndrome was introduced in 1988 by the United States Centers for Disease Control and Prevention (CDC).¹⁰ The development of a case definition allowed for a systematic and comprehensive approach to defining the etiology and pathophysiology of CFS/ME. These definitions, along with the 1988¹¹ and 1990¹² Australian definitions, and the 1991 Oxford, UK definition,¹³ have played an essential role in orienting clinical research, and facilitating consistency and homogeneity of samples across research studies. Although these initial criteria were considered quite restrictive, the diagnostic criteria did not specifically exclude a sleep disorder. As a result, early studies that examined the association between sleep complaints and functional disability in CFS/ME suggested that a primary sleep disorder may be the cause of unrefreshed sleep in some patients.

In 1994, a revision to the case definition and a set of research guidelines for use in studies of CFS patients was proposed by the Centers for Disease Control and Prevention.¹⁴ These guidelines (known as the Fukuda criteria) used more relaxed definitions than the 1988 criteria, requiring only four criteria beyond fatigue for diagnosis, and not excluding non-psychotic psychiatric disorders. Given that there is no laboratory test for diagnosing CFS/ME, and the etiology is typically unknown, CFS/ME was seen as a diagnosis of exclusion. This was reflected in the new criteria by specifically excluding comorbid conditions such as a treatable sleep disorder (e.g., obstructive sleep apnea [OSA] and narcolepsy) and other potential causes of fatigue (e.g., substance abuse, psychiatric disorder). Unrefreshing sleep was the only criteria relating to sleep, with other sleep disturbances not a criterion. Although alternative definitions have been proposed,¹⁵ the 1994 Fukuda criteria are considered the international accepted research definition. However, it was recognized that the Fukuda criteria and other broadly inclusive criteria¹⁵ do not adequately discriminate CFS/ME patients from those with other conditions such as major depressive disorder. Additionally, since the Fukuda criteria were primarily developed to inform clinical research excluding comorbid conditions, such as treatable sleep disorders, they may not be appropriate to use exclusively for clinical diagnoses, which are often more broadly defining.

2.2 Clinical Guidelines

In 2003, an Expert Medical Consensus Panel with extensive experience in the research and clinical management of CFS/ME developed the Canadian Clinical Case Definition.¹⁶ This document was created specifically to inform healthcare professionals. The Canadian Criteria has incorporated a larger spectrum of potential symptoms, aimed to assist recognition of the “interrelationships of each patient’s symptoms and their coherence into a syndrome of related symptoms.”¹⁶ This updated clinical definition captured, in addition to chronic fatigue, the issue of post-exertion malaise. These criteria also highlight mental fatigue (loss of cognitive function and alertness) as well as physical fatigue (lack of energy and strength). Sleep disturbance is recognized as a major feature of CFS/ME in the Canadian Criteria. Specifically, sleep and circadian rhythms disturbances are listed, including early, middle, and late insomnia, and reversed or abnormal diurnal and sleep rhythms. Further, periodic limb and

restless legs syndrome are reported to accompany these other changes in sleep in many cases. These criteria also recognize the importance of ruling out a treatable sleep disorder, such as upper airway resistance syndrome and OSA.

Most recently, International Consensus Criteria (ICC) have been developed.¹⁷ The ICC build from the Canadian Criteria to identify the distinct characteristic patterns of symptom clusters of CFS/ME. These new definitions relaxed the requirement for symptoms to have persisted for at least 6 months, giving the physician more temporal control of when the diagnosis of CFS/ME can be made. Sleep disturbances were divided into two categories: disturbed sleep patterns, including insomnia, prolonged sleep including naps, frequent awakenings, and vivid dreams/nightmares; and unrefreshed sleep, including excessive daytime sleepiness.¹⁷ Importantly, these updated criteria serve to not only diagnose patients in the clinical setting, but to also assist in identifying patients for research studies.

3.0 DIFFERENTIAL DIAGNOSES

The diagnostic overlap between CFS/ME and primary sleep disorders has been documented in a number of studies. Prior to the revision of the diagnostic criteria for CFS/ME in 1994, two studies reported that over half of their CFS/ME patients had a sleep disorder as assessed by overnight polysomnography (PSG).^{5,18} These sleep disorders include hypersomnia, sleep maintenance and sleep initiation insomnia, OSA, narcolepsy, and periodic limb movement disorder, as well as inadequate sleep hygiene. CFS/ME patients were found to have higher levels of fatigue and sleep disturbance than patients with multiple sclerosis⁵; those with a comorbid sleep disorder reported greater functional impairment.¹⁸ Since these studies included CFS/ME patients with a suspected sleep disorder who were attending the sleep clinic, rather than randomly selected or consecutive patients, these figures are mostly likely inflated.

Subsequent to the 1994 guideline revisions, Fossey et al. (2004) observed prevalence rates > 50% of ICSD-classified primary sleep disorders (OSA and movement disorders) in CFS/ME patients.¹⁹ Similarly, Le Bon and colleagues examined the prevalence of primary sleep disorders and objective sleepiness in CFS/ME and found that 46% of the 46 unselected patients who met Fukuda criteria for CFS/ME also presented with OSA (using a criterion of AHI > 5), and a further 5% presented with periodic limb movement disorder.²⁰ On multiple sleep latency testing (MSLT), an objective measure of sleep propensity, 30% of the patients were classified as clinically sleepy. Objective (MSLT) and subjective (Stanford Sleepiness Scale) measures of sleepiness, however, were not associated with a subjective fatigue measure, suggesting that the fatigue experienced by CFS/ME patients is separate from the expression of sleepiness. Importantly, this study compared CFS/ME patients with and without a primary sleep disorder and found that they could not be separated on clinical presentation. The authors concluded that the symptoms of CFS/ME are clearly distinct from those of primary sleep disorders, and the illness is more than simply a somatic expression of an underlying sleep disorder or sleepiness.²⁰

Larger population-based studies of CFS/ME patients have also provided some insight into the rates of sleep disorders in CFS/ME patients over time.^{15,21} Approximately 20% of CFS/

ME patients in these studies were found to have either OSA or narcolepsy, with one study reporting that 20% of patients were given an alternative diagnosis of sleep disorder at 3-year follow-up.²¹ Subclinical levels of sleep disordered breathing have also been reported in some studies.^{15,22}

From a clinical standpoint, early studies that examined prevalence of comorbid sleep disorders provide new insights into the syndrome and potential differential diagnoses and highlight the importance of considering a potential sleep disorder as a cause of unexplained fatigue.²³ While there is overwhelming evidence of the distinction between CFS/ME and sleep disorders,²⁴ some researchers argue that a diagnosis of OSA should *not* be an exclusion criterion for CFS/ME. It is argued that primary sleep disorders do not influence the core symptoms of CFS/ME and therefore should be considered a comorbid condition.²⁵ Indeed, in clinical practice many physicians treat primary sleep disorders concurrently with CFS/ME rather than exclude these patients. CPAP therapy in CFS/ME patients with comorbid OSA has been found to improve some daytime features, such as cognitive and daytime sleepiness; however, the underlying fatigue state remains.²⁵ The magnitude of OSA in CFS/ME also depends on what diagnostic threshold is used for OSA. Le Bon and colleagues acknowledge that if an AHI cutoff of 20/h was used in their study (rather than AHI < 5), OSA would only be prevalent in 11% of their CFS/ME sample (as opposed to nearly 50%).²⁰ These figures are comparable to the prevalence of sleep disordered breathing in the general population.²⁶ Thus it could be argued that primary sleep disorders are a comorbid condition that occur at a similar frequency in CFS/ME to the general population and are therefore not reflective of the disorder itself.

In addition to generalized joint and muscle myalgia, which are integral features of the diagnostic criteria, CFS/ME is also associated with comorbid pain conditions including irritable bowel syndrome and migraine headaches. Pain experienced by CFS/ME patients may also play a critical role in sleep disturbance. Studies of FM have found that both subjective sleep quality measures and phasic alpha sleep are associated with pain sensitivity.²⁷ There is a potential bidirectional relationship between sleep and pain—pain disrupts sleep, and sleep disruption enhances pain. Firstly, pain causes disruption to sleeping pattern and increases sleep onset latency. Experimental manipulations of pain stimuli to the muscles during sleep have revealed decreased delta and increased alpha activity of the sleep EEG, and impaired sleep quality.^{28,29} CFS/ME patients are found to have more self-reported awakenings during sleep due to pain compared to depressed patients and healthy controls.³² On the other hand, sleep disturbance also leads to reduced pain thresholds during waking.³⁰ Pain and fatigue symptoms, similar to those reported in CFS/ME and FM, have been induced in healthy individuals by disrupting SWS.³⁰ Thus, it has been posited that the physiological arousals that are observed during sleep reflect a vigilant nocturnal state that contributes to daytime fatigue, pain, and hypersensitivity, and subjective feelings of non-restorative sleep. The influence of myalgic symptoms on sleep disturbance in CFS/ME has received little research attention to date.

Some patients with CFS/ME have comorbid psychiatric or somatoform illness, such as depressive disorder or fibromyalgia, which do not rule out a diagnosis of CFS/ME. Given that

sleep disturbance is a common symptom of psychiatric conditions,³¹ it could be argued that sleep disturbance in CFS/ME is a secondary consequence of comorbid depression. Studies that have explored this potential link by comparing sleep study results of CFS/ME patients with and without a psychiatric comorbidity suggest that sleep disturbances are common in both subtypes, and therefore do not appear to be solely the result of underlying depression.^{4,32} All of these studies mentioned above have been critical for highlighting CFS/ME as an autonomous syndrome.

4.0 MACROSTRUCTURE MEASURES OF SLEEP IN CFS/ME

Table 1 presents studies that have compared sleep parameters of CFS/ME patients to healthy controls using polysomnography. Of 24 papers reviewed, only 15 used recognized diagnostic criteria for patient recruitment, and only these 15 are included in **Table 1**. Of these 15, only 10 reported that they excluded patients who were on medication or asked patients to withdraw from their medication for 2 weeks prior to the study.

Studies examining traditional sleep parameters as measured by PSG have reported variable and nonspecific differences in sleep parameters between CFS/ME patients and controls. The reason for the discrepancy may be due in part to differences in selection criteria (e.g., medication status), the type of control group used, or characteristics of the recorded night (e.g., first night of recording only, home recordings), which also make comparisons between studies difficult. First night effects are apparent in CFS/ME patients who do not have a primary sleep disorder,³³ and therefore studies that have only used one night of recording may not provide an accurate picture of the patient's typical sleep.

Reflecting the disturbed sleep reported by many CFS/ME patients, an increased number^{18,34,35} and duration^{18,34,36} of intermittent awakenings have been reported. However, using an adaptation night prior to the main sleep recording night, Reeves et al. found no difference in sleep efficiency between CFS/ME patients and controls.¹⁵ This study, however, enforced bed and wake times for both groups, and as such may not have captured true sleep efficiencies that the participants would typically experience. When patients and controls have been allowed to go to bed at their usual bed time, reduced total sleep time (TST) and sleep efficiency are observed in the CFS/ME group, both in single-night PSG recording in the laboratory,^{22,37,38} and in some,^{18,35} but not all³⁶ at-home studies. Togo et al. (2008) examined this observation further by stratifying their patients into those who reported sleepiness upon waking, and those who reported more sleepiness in the evening. Using this distinction, they found that those who reported morning sleepiness had lower sleep efficiencies and more periods of interrupted sleep.³⁸

Sleep onset latencies are often longer in CFS/ME patients compared to healthy control subjects, suggesting that some patients may have difficulties initiating sleep.^{4,37} It has been reported that CFS/ME patients may have differential parasympathetic activity at sleep onset, which may contribute to delayed sleep latency.³⁹ This finding could also reflect poor sleep hygiene or extended sleep periods and napping, which may reduce sleep drive at night.

Table 1—Summary of literature investigating sleep, measured polysomnographically, in CFS/ME patients compared to healthy controls, using standard diagnostic criteria

Author, year	Criteria Used	Subjects	Medication Status	Outcome Measures	Findings
Sharpley 1997 ³⁶	Fukuda	20 CFS/ME (psychiatric illness excluded), 20 controls	Psychotropic medication users excluded.	Subjective reports, sleep diary, 1 night home-based PSG	CFS/ME reported poor quality, unrefreshing sleep, and daytime napping. CFS/ME had ↑ TIB and time awake after sleep onset, and ↓ SE. No difference between CFS/ME and controls on PSG-measured TST. N = 7 CFS/ME patients had abnormal PSG (5 with sleep initiation and maintenance problems, 1 with early awakening).
Watson 2003 ^{44,†}	Fukuda	22 twin pairs discordant for CFS/ME	No medication for > 2 weeks	2 nights of PSG, SDQ (insomnia symptoms)	CFS/ME twin reported ↑ insomnia symptoms and poor sleep ratings. No difference in PSG measures of insomnia. ↑ % REM in CFS/ME twin. Suggests sleep state misperception
Ball 2004 ^{45,†}	Fukuda	22 twin pairs discordant for CFS/ME	No medication for > 2 weeks	2 nights of PSG	CFS/ME twin displayed ↑ %SWS and REM sleep. No other objective differences in sleep architecture in CFS/ME twin compared to healthy twin.
Reeves 2006 ^{15,^}	Fukuda	43 CFS, 43 controls	Medication continued*	2 nights PSG, MSLT	No difference in PSG sleep architecture or MSLT
Majer 2007 ^{46,^}	Fukuda	35 CFS, 40 controls	Medication continued*	2 nights PSG, MSLT, subjective sleep quality	CFS/ME report poorer sleep quality, no difference on MSLT or PSG. CFS/ME patients perceive poor sleep in the absence of objective sleep problems.
Neu 2007 ^{47,#}	Fukuda	28 "pure" CFS, age and gender match controls	No medication for > 2 weeks	PSQI, fatigue severity scale, PSG	CFS/ME reported poorer sleep on PSQI. No difference in PSG sleep parameters (e.g., SWS). Sleep quality misperception may exist in CFS/ME
LeBon 2007 ^{48,#}	Fukuda	28 "pure" CFS, 27 OSA, 27 healthy controls	No medication for > 2 weeks	2 nights PSG, distribution of NREM sleep	CFS/ME display ↑ NREM sleep, and ↑ ratios of SWS-to-light sleep than controls and OSA patients
Armitage 2007 ^{49,†}	Fukuda	13 twin pairs discordant for CFS/ME	No medication for > 2 weeks	3 nights in lab: adaptation, baseline, sleep delay. Power spectral analysis	CFS/ME exhibited ↓ SWA power in first NREM period after delayed sleep; baseline SWA similar between CFS/ME and controls. CFS/ME blunted SWA response to sleep challenge
Kishi 2008 ⁵⁰	Fukuda	22 CFS, 22 control all female, no MDD same menstrual phase	Not reported	Overnight PSG, duration and transition statistics	↓ relative frequency of REM to NREM transition in CFS/ME, causing significantly ↑ transitions from REM and S1 to awake. Normal continuation of sleep in S1 and REM is disrupted in CFS/ME
Togo 2008 ³⁸	Fukuda	12 CFS/ME+ FM, 14 CFS, 26 controls. No MDD	Medication use excluded	Overnight PSG	↑SWS in CFS/ME who reported feeling less sleepy upon waking. CFS/ME display ↓ sleep efficiency, TST, REM. Stratified group based on sleepiness (AM vs PM). AM sleepy group had more periods of interrupted sleep during night.
Armitage 2009 ^{51,†}	Fukuda	14 twin pairs discordant for CFS/ME	No medication for > 2 weeks	2 nights PSG, power spectral analysis	CFS/ME display no sleep micro or macro architectural changes, thus sleep measures cannot explain the fatigue.
Decker 2009 ⁵²	Fukuda	35 CFS, 40 controls	Medication continued*	2 nights PSG, FFT, power spectral analysis	CFS/ME displayed ↓ delta power during SWS, but ↑ in S1 and REM compared to controls. Alpha, theta, sigma, beta ↓ during SWS, REM, S2
Neu 2009 ²⁴ (replication of Le Bon 2007)	Fukuda	32 CFS/ME, 30 OSA, 14 controls	No medication for > 2 weeks	2 nights PSG: NREM proportions and ratios	CFS/ME displayed ↑ NREM sleep, and ↑ ratios of SWS-to-light sleep compared to controls and OSA patients
Creti 2010 ⁵³	Reeves, 2005	47 CFS/ME	Medication use NOT excluded	Overnight PSG, actigraphy, self-report	Sleep diary most related to PSG and actigraphy. TST and SE differentiated insomnia symptoms. EDS, fatigue, unrefreshed sleep not related to qualitative or quantitative methods
Kishi 2011 ⁵⁴	Fukuda	14 CFS/ME without FM, 12 CFS/ME with FM, 26 controls, all female	Medication use excluded	Overnight PSG, transition probabilities and rates between sleep stages, and duration in each stage	Probability of transitions from REM to waking significantly higher in CFS/ME than controls. Differences in transition probabilities between CFS/ME + FM and CFS/ME alone, suggesting that they are separate illnesses with distinct problems of sleep regulation.

#Same subjects. †Same subjects. ^Same subjects. *Sleep-affecting medications statistically controlled for in sleep analysis. EDS, excessive daytime sleepiness; FFT, fast Fourier transform; FM, fibromyalgia; MDD, Major Depressive Disorder; MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement sleep; S1, stage 1 sleep; S2, stage 2 sleep; SDQ, sleep disorders questionnaire; SE, sleep efficiency; SL, sleep latency; SSS, Stanford Sleepiness Scale; SWA, slow wave activity; SWS, slow wave sleep; TIB, time in bed; TST, total sleep time.

Actigraphy studies potentially provide a more ecologically valid assessment of TST, sleep efficiency, and sleep onset latency parameters, as measurements are made in a naturalistic setting where patients can follow their usual sleep routines. A study in children with CFS/ME reported that continuous sleep of > 10 h, measured with actigraphy, was not uncommon.⁴⁰ Impaired daily sleep/wake rhythms and disturbed sleep were observed in those children who displayed an irregular sleep type. These studies can also examine whether changes in the circadian timing of sleep are evident, such as a delayed sleep phase. Most actigraphy studies to date have examined diurnal activity patterns in CFS/ME patients,⁴¹ and there are currently mixed findings relating to circadian rhythm disturbances.^{42,43}

The sleep architecture of CFS/ME patients may differ from that of healthy individuals. Stage 3 sleep or slow wave sleep (SWS) is typically observed for approximately a fifth of the sleep period in young healthy individuals.⁵⁵ A number of studies have reported reduced time in SWS in CFS/ME patients relative to controls^{4,38} and between monozygotic twins discordant for CFS/ME.⁴¹ These effects are independent of depression and FM.^{4,24}

Alpha-delta sleep is an atypical electroencephalographic (EEG) pattern recorded during NREM sleep. In normal sleep, alpha activity is characteristic of drowsy wakefulness, and delta activity indicates restorative NREM sleep. Alpha-delta sleep was first observed during studies of sleep EEG of patients with psychiatric illness who presented with fatigue. The appearance of alpha-delta sleep, or alpha intrusions, during SWS has been reported in some early studies of CFS/ME patients.^{37,56} The appearance of alpha-delta sleep in these patients was initially thought to be the cause of non-restorative sleep. However, whether the patients in these studies had a “pure” diagnosis of CFS/ME or potentially some feature of FM is unclear. Later studies failed to find this phenomenon,^{51,57} and the role of alpha-delta sleep in the pathophysiology of CFS/ME has since been questioned.

The amount of SWS and slow wave activity (SWA; power density in the delta frequency) are determined by prior wakefulness. For example, SWS and SWA are found to increase following periods of sleep deprivation or restriction, when there is a build-up of homeostatic sleep pressure.⁵⁸ As such, SWA during NREM sleep is often used as a marker of sleep homeostasis. A study by Armitage and colleagues exploited this phenomenon by exposing 13 monozygotic twins discordant for CFS/ME to a sleep delay schedule.⁴⁹ After 2 baseline nights in the laboratory, a mild sleep challenge was imposed, involving a sleep delay of 4 hours, followed by a regular sleep length “recovery” period. Although no differences in SWA during baseline sleep were found, the CFS/ME twin expressed significantly less SWA in the first NREM period after the sleep delay. Additionally, the time course of dissipation of SWA across the night was altered in the CFS/ME twin. The authors concluded that CFS/ME is associated with impaired sleep homeostasis and basic sleep drive. Interestingly, the cytokine systems are intimately involved with sleep regulation; increased SWA also occurs in response to acute infection, with proinflammatory cytokines increasing SWS.⁵⁹ Alteration in SWA may therefore be associated with the systemic inflammation found in CFS/ME.⁶⁰ Further research examining SWA and immune dysfunction in CFS/ME would be valuable for understanding this potential link.

The distribution and amount of REM sleep in CFS/ME is not as clearly defined as that of SWS. Reduced REM sleep in CFS/ME patients is reported in some studies,^{35,38} whereas others have observed a higher percentage of REM sleep in CFS/ME relative to controls.^{37,45,61} When statistically controlling for medication use, no difference in REM sleep latency was observed between controls and CFS/ME patients,¹⁵ suggesting that medications used by these patients may play a role in some sleep architecture differences previously reported. Perhaps the clearest findings have been derived from twin studies, as described earlier. In these studies, no differences in REM sleep are observed between the CFS/ME twin and the healthy twin.⁵¹

To date, approximately 273 clinically diagnosed CFS/ME patients have been assessed using PSG, with less than half of these patients studied not using medication. Based on these limited data, there appear to be very few differences in sleep architecture or TST between CFS/ME patients and healthy individuals, with mixed findings for SWA and SWS. The distribution of SWS and the frequency of sleep stage transitions appear to differ between CFS/ME patients, healthy controls, and other sleep disorders. Of the 4 twin studies published, increased SWS and REM sleep are typically reported in the CFS twin, with evidence for an impaired sleep homeostatic response, but no differences on power spectral analysis were observed. Studies that have had utilized co-twin control methodology have the added benefit of controlling for many genetic and environmental factors that are typically not accounted for in either CFS/ME or sleep research, making for a more powerful and robust design.⁴⁴

Based on these data, it appears that CFS/ME does not have a characteristic objective sleep disturbance found across all patients. As a result, some researchers have concluded that CFS/ME patients do not have abnormal sleep, and objective sleep measures do not account for subjective reports of non-restorative sleep. Studies using traditional PSG measures have been unable to shed light on a cause for the experience of non-restorative sleep.

5.0 DISCREPANCY BETWEEN OBJECTIVE AND SUBJECTIVE REPORTS OF SLEEPINESS

While CFS/ME patients present with fatigue as their primary symptom, whether they also experience excessive daytime sleepiness is less clear cut. The consensus from a number of studies is that pathological sleepiness objectively measured using multiple sleep latency tests (MSLT) is not observed in CFS/ME patients.^{15,46,62} This is despite CFS/ME patients reporting higher levels of subjective sleepiness and poorer sleep quality than healthy controls.^{24,53,61}

There are a few possible explanations for this discrepancy between objective and subjective sleepiness measures. Firstly, it has been suggested by some authors that CFS/ME patients have sleep quality misperception.^{15,61} Interestingly, poor self-rated health and depressive symptoms have been found to be associated with over reporting of sleep difficulties and underestimation of sleep efficiency.⁶³ However, it is unlikely that this discord is truly a global phenomenon across all CFS/ME patients, and perhaps reflects more of a generalized issue among all patients experiencing sleep disturbance, such as insomnia.⁶⁴ It may be that sleep disturbed individuals more closely monitor

their sleep habits and patterns and are more in tune to changes in their sleep.

A second possibility is that the discrepancy reflects issues with definitions and measurement tools used to determine fatigue and sleepiness. Outside of the sleep arena, fatigue and sleepiness are ill-defined concepts with overlap in their definitions and are often used interchangeably. This can make it difficult for both patients and clinicians to correctly distinguish between the two states.⁶⁵ Further, currently there is a lack of a clear and reliable subjective measure that differentiates the two states. One study examined whether current measures correctly distinguish between sleepiness and fatigue, by comparing CFS/ME and OSA patients whose primary symptom is daytime sleepiness.⁶⁶ In this study, a clear distinction between subjective measures between the 2 patient groups was observed, with CFS/ME reporting the most fatigue and OSA patients reporting higher levels of sleepiness. However, there was some overlap in the levels of subjective sleepiness between the 2 groups, combined with the well-recognized discordance between objective and subjective sleepiness in the CFS/ME group. This study highlights the need for more precise tools and analyses for distinguishing these 2 states.

Another explanation for differences in objective and subjective measures of sleep in CFS/ME is that potential nocturnal neurophysiological disturbances that result in the non-restorative sensation following sleep in CFS/ME patients are not detected by traditional sleep variables or sleep stage distributions measures. More sensitive micro-analyses of the sleep EEG and other nocturnal parameters are currently being explored in this population.

6.0 MICROSTRUCTURE MEASURES OF SLEEP IN CFS/ME

While objective sleep parameters do not clearly predict subjective reports of sleep disturbance, other physiological measures may have more promise for detection of alterations in CFS/ME patients' sleep. Stage shifts^{4,34} and dynamic stage transitions⁵⁰ have been shown to discriminate CFS/ME patients and healthy controls. The relative frequency of REM to NREM transition is lower in CFS/ME, while there are significantly more transitions from REM and stage 1 sleep to wakefulness.⁵⁰ Normal continuation of sleep in stage 1 and REM is disrupted in CFS/ME, which may contribute to feelings of non-restorative sleep upon waking.

More recently, studies have utilized alternative methods for quantifying EEG in CFS/ME patients, which provide a more sensitive method for evaluation of sleep abnormalities. Power spectral analysis using fast Fourier transform (FFT) has been used in a few recent studies,^{51,52} with conflicting results. Decker reported differences in delta power, with reduced delta power observed in SWS and increased delta power during stage 1 and REM sleep in 35 CFS/ME patients relative to 40 healthy controls.⁵² Reductions in alpha power were observed most strongly during REM but were also seen in SWS and stage 2 in the CFS/ME subjects. The finding of attenuated delta power complements the reduced SWA reported previously following sleep delay,⁴⁹ providing further evidence of an altered sleep homeostat in CFS/ME. In contrast, Armitage found no difference in

any frequency band between twins discordant for CFS/ME.⁵¹ There is a clear need for future research utilizing this method of sleep EEG analysis to clarify these findings.

It is also plausible that CFS/ME patients may experience arousals during sleep that are not detected using traditional scoring methods.⁶⁷ Supporting this idea, more microarousals have been observed in the sleep of CFS/ME patients than healthy control subjects.^{24,66} Recently, other methods of arousability or sleep instability have been developed and used in this population. Cyclic alternating pattern (CAP) is an EEG-derived measure of sleep instability, which is reflected as periodic EEG activity during NREM sleep.^{68,69} In contrast, periods of Non-CAP are indicative of consolidated sleep. CAP is somewhat distinct from typically measured arousals from sleep, both as a phenomenon and in terms of how they are scored.⁶⁹ Clinical studies of insomniacs have found strong correlations between CAP rate (ratio of total CAP time to total NREM sleep time) and subjective reports of sleep quality.⁷⁰ This measure may therefore provide a more specific marker of sleep quality than the arousal index derived from PSG. Only one study to date has examined CAP rate in CFS/ME patients.²² Despite having similar NREM sleep times, CFS/ME patients had higher CAP rates than matched controls, indicating higher NREM sleep instability in their CFS/ME patients. Abnormal CAP rate was also accompanied by an increase in slow wave delta power. Interestingly, there was no difference in arousal indices between the patient and control groups. A number of CFS/ME patients in this study, however, were found to have nasal cannula flow limitation, indicative of upper airway resistance syndrome (UARS), which may have influenced the findings. CAP has also been associated with UARS and other sleep related breathing disorders previously.⁷¹ Whether the higher CAP rate observed in CFS/ME patients was solely a result of UARS is unclear. Importantly, CAP was associated with both subjective fatigue and sleepiness ratings, as has been found previously in other sleep disordered populations.⁷⁰

Taken together, these studies indicate that conventional sleep stage scoring methods use may not be sensitive enough to detect microstructural changes in CFS/ME patients. Consideration of these microstructure methods for analyzing the sleep EEG may provide a fruitful alternative for uncovering subtle differences during sleep in individuals reporting non-restorative sleep and daytime fatigue.

7.0 OTHER MEASURES OF SLEEP DISTURBANCE

7.1 Autonomic Activity Measures in CFS/ME

Autonomic activity alterations, such as hypotension and reduced heart rate variability (HRV), are a common feature of CFS/ME,⁷² and are a feature of the diagnostic criteria. In healthy individuals, autonomic nervous system dynamics also have characteristic profiles during sleep onset,⁷³ and different sleep stages and depths of sleep.⁷⁴ In some CFS/ME patients, the autonomic dysfunction observed during waking also transfers into sleep.⁷⁵ HRV during sleep is consistently found to be significantly lower in CFS/ME patients compared to well-matched controls, reflecting a reduction in nocturnal parasympathetic activity.^{39,43,75,76} Decreased HRV is thought to reflect a

persistent state of autonomic hypervigilance. The influence of daytime physical activity, however, should not be dismissed as a potential confounder. Regression analyses have also demonstrated that HRV is the best predictor of subjective sleep quality in CFS/ME patients in one study.³⁹

Cardiopulmonary coupling (CPC) is another emerging technique, used as a measure of sleep quality and stability based solely on the electrocardiogram (ECG) signal.⁷⁷ This technique records both heart rate (R-R interval) and respiration dynamics to generate a spectrogram of cardiopulmonary coupling. Based on this output, one can determine periods of high-frequency and low-frequency coupling, indicative of high and low sleep stability. CPC has been used to demonstrate sleep instability in sleep disordered populations,⁷⁷ major depressive disorder,⁷⁸ and fibromyalgia.⁷⁹ There is preliminary evidence that sleep quality and stability measured by CPC is poor in CFS/ME patients, with reduced high-frequency coupling and increased low-frequency coupling.⁸⁰ Studies utilizing such autonomic activity techniques indicate that autonomic measures during sleep may be a promising mechanism associated with non-restorative sleep in CFS/ME.⁴³

7.2 Hormone Profiles

Substantial research examining the pathophysiology of CFS/ME indicates that the hypothalamic-pituitary axis (HPA) may be implicated in this disorder.^{81,82} The HPA also plays an important role in sleep regulation.⁸³ Dysregulation of the HPA has been examined using salivary cortisol profiling in a few studies.⁸⁴⁻⁸⁶ Morning cortisol levels upon awakening, recognized as an indicator of the HPA response to stress, were attenuated in CFS/ME patients compared to healthy controls,⁸⁵ with this difference most evident in females with CFS/ME.⁸⁴ Given that CFS/ME is 2 to 3 times more prevalent in women, it has been proposed that sex differences in hypocortisolism may explain the increased risk of CFS in women.⁸⁴

Heightened IL-6 plasma levels have also been reported in CFS/ME patients,⁸⁷ possibly reflecting the low levels of systemic inflammation associated with CFS/ME. However, whether increased levels of IL-6 in this study were directly related to CFS/ME or other confounders such as BMI and underlying sleep disorders is unclear. IL-6 has been implicated in the pathogenesis of psychological and physiological fatigue in healthy individuals,⁸⁸ and has been reported in other patient groups that suffer debilitating fatigue, such as cancer patients.⁸⁹ Of direct relevance to this review, altered levels of IL-6 are also associated with somnolence and chronic sleep restriction.⁵⁹ It is plausible that a link between IL-6 or other inflammatory markers and sleep disturbance in CFS/ME exists; this remains an interesting hypothesis that warrants further investigation.

7.3 Neuroimaging

Neuroimaging studies have allowed researchers to examine the sleeping brain in healthy subjects. These techniques have also applied to clinical populations, including primary insomnia,⁹⁰ OSA,^{91,92} and depression.⁹³ Particularly in primary insomnia, functional neuroimaging studies during sleep have helped understand the neurophysiological underpinnings of sleep dysregulation in these patients. In line with the hyperarousal theory of primary insomnia, patients were found to have abnormally

high regional brain activity during sleep compared to controls subjects.⁹⁴ This is proposed as one of the mechanisms contributing to sleep state misperception and sleep disturbance found in such patients. A growing number of studies are using functional neuroimaging to examine CFS/ME patients during wake (see Lange⁹⁵ for a review). These studies have typically observed altered neural activity during performance of a fatiguing cognitive task in CFS/ME patients relative to controls, in the absence of performance impairment, potentially reflecting greater perceived cognitive effort.^{96,97} Future studies may also benefit from examining neural function and cerebral blood flow in CFS/ME patients during sleep.

8.0 DIRECTIONS FOR FUTURE RESEARCH

There are still many unanswered questions regarding the pathogenesis and nature of sleep disturbance and unrefreshed sleep in CFS/ME. Sleep disturbance may precipitate CFS/ME, may alter or complicate its course by worsening fatigue, pain, or mood, or may represent an independent factor unrelated to fatigue itself. With the development of new standardized criteria for diagnosing CFS/ME, more homogenous patient samples and comparability across studies will be afforded for future research. Standardized research designs with less rigid imposition of sleep-wake times, and control over medication use and symptoms and comorbid conditions (such as pain and depression) will assist in understanding the state of sleep in CFS/ME.

Non-restorative sleep has a fairly distinct subjective definition; however, the physiological markers that underlie this experience and the extent to which alterations in sleep relate to the experience of non-restorative sleep in these patients are relatively unknown. Does non-restorative sleep stem from hyperarousability, sleep hygiene, or circadian rhythm disturbance, or is it biologically driven in some other way? Is the nature of non-restorative sleep in CFS/ME similar to that experienced in other clinical conditions and by healthy individuals on occasion, or is it a heterogeneous phenomenon? There may also be other symptoms that CFS/ME patients experience that could cause non-restorative sleep, such as upper airway resistance syndrome, food intolerance, or immunological and metabolic changes. Emergence of new methods for analyzing the microstructure of sleep have allowed researchers to detect more subtle EEG changes in CFS/ME patients during sleep. Given that very little is known about the nature and cause of non-restorative sleep, these studies have opened up new avenues for investigating sleep disturbance and non-restorative sleep, not only in CFS/ME but other clinical conditions such as insomnia.

Having a clearer understanding about the pathophysiology of non-restorative sleep in CFS/ME may lead to better treatment options for patients. For example, one theory for the non-restorative sleep experienced in insomnia suggests that negative cognitions trigger autonomic arousal during wakefulness that transfers into sleep.⁹⁸ Nocturnal arousal is often treated by reducing hyperarousability and cognitions during the day, using cognitive behavioral therapy⁹⁹ or mindfulness based techniques,¹⁰⁰ with the aim of reducing arousal at night. If a similar arousal phenomenon is found during sleep in CFS/ME, then insomnia-based treatments have the potential to be utilized in CFS/ME patients.

More precise tools and analyses for differentiating fatigue and sleepiness are needed. Distinguishing these two states remains a diagnostic challenge for clinicians. While there are validated objective and subjective measures of sleepiness, only subjective measures currently exist for assessing fatigue. Development of an objective measure of fatigue and a questionnaire that assesses both fatigue and sleepiness would be useful not only in the context of CFS/ME, but for assessing other disorders in which both sleepiness and fatigue are a feature. In addition, further research into the relationship between sleep and fatigue is greatly needed.

Patients commonly report improved sleep following some treatment regimes, such as graded exercise therapy and antibiotic treatment for imbalances in gut microbial flora. There are avenues for research into objective assessments of sleep before and after treatment, and to follow the time course of changes in sleep as patients' symptoms improve. Future studies are needed to explore the interaction of sleep homeostasis, SWA, and immune system activation in CFS/ME, given the changes in immune function that are observed in these patients.⁶

The issue surrounding possible sleep state misperception in CFS/ME raises the question of whether abnormalities in sleep associated with CFS/ME are similar to those found in other populations that experience sleep misperception, such as insomnia, or whether they are specific to CFS/ME. This also raises the question of whether CFS/ME patients report a bigger discrepancy between objective and subjective measures of sleep compared to other medical conditions, and is this relative to the experience of non-restorative sleep? Understanding the association between these two conditions may provide insight into the mechanisms of sleep misperception. Future studies will benefit by incorporating subjective, physiological and behavioral measures of sleep to gain a broader insight into the nature of sleep disturbance of CFS/ME.

Finally, CFS/ME may provide a unique insight into the link between non-restorative sleep and fatigue. Other clinical conditions also experience non-restorative sleep and fatigue, such as FM, narcolepsy, and coronary heart disease,^{101,102} as well as a high number of otherwise healthy individuals.¹⁰³ It is plausible that there may be subgroups of such people with fatigue and non-restorative sleep with similar underlying symptoms and etiologies, or, alternatively, there may be a continuum of such symptoms with CFS/ME being at the upper end of the spectrum. Given the constellation of physiological and psychological symptoms characterizing CFS/ME, examining sleep and fatigue in CFS/ME patients may allow us to better understand the neurobiology and etiology of fatigue in other patient populations.

SUMMARY AND CONCLUSIONS

CFS/ME is a complex and severely debilitating condition. Non-restorative sleep, reduced sleep quality, and extended periods of sleep are commonly reported, however the basis of these symptoms are unclear. The heterogeneities associated with this disorder make it challenging for researchers to study and make cross-study comparisons difficult. While there is little evidence of sleep architecture differences between CFS/ME and healthy individuals, many patients subjectively report sleep disturbance and unrefreshed sleep, highlighting a potential disconnect be-

tween objective and subjective measures of sleep. There is preliminary evidence that alteration in sleep stage transitions and sleep instability, and other physiological mechanisms such as heart rate variability and altered cortisol profiles, may be implicated in the sleep difficulties of this population. Further research is required to investigate the cause of non-restorative sleep and fatigue in CFS/ME, which may aid understanding of this symptom in other medical conditions.

ABBREVIATIONS

CAP, cyclical alternating pattern
 CDC, United States Centers for Disease Control and Prevention
 CFS, chronic fatigue syndrome
 CPAP, continuous positive airway pressure
 CPC, cardiopulmonary coupling
 ECG, electrocardiogram
 EDS, excessive daytime sleepiness
 EEG, electroencephalogram
 FFT, fast Fourier transform
 FM, fibromyalgia
 HPA, hypothalamic-pituitary axis
 HRV, heart rate variability
 ICC, International Consensus Criteria
 ICD-10 International Classification of Diseases
 ICSD, International Classification of Sleep Disorders
 IL-6, interleukin 6
 MDD, Major Depressive Disorder
 ME, myalgic encephalomyelitis
 MSLT, multiple sleep latency test
 OSA, obstructive sleep apnea
 PI, Primary Insomnia
 PSG, polysomnography
 PSQI, Pittsburgh Sleep Quality Index
 S1, stage 1 sleep
 S2, stage 2 sleep
 SDQ, Sleep Disorder Questionnaire
 SE, sleep efficiency
 SL, sleep latency
 SSS, Stanford Sleepiness Scale
 SWA, slow wave activity
 SWS, slow wave sleep
 TIB, time in bed
 TST, total sleep time

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