

# Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis

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#### ABSTRACT

**Objectives:** Despite sleep disturbances being a central complaint in patients with chronic fatigue syndrome (CFS), evidence of objective sleep abnormalities from over 30 studies is inconsistent. The present study aimed to identify whether sleep-specific phenotypes exist in CFS and explore objective characteristics that could differentiate phenotypes, while also being relevant to routine clinical practice.

**Design:** A cross-sectional, single-site study.

**Setting:** A fatigue clinic in the Netherlands.

**Participants:** A consecutive series of 343 patients meeting the criteria for CFS, according to the Fukuda definition.

**Measures:** Patients underwent a single night of polysomnography (all-night recording of EEG, electromyography, electrooculography, ECG and respiration) that was hand-scored by a researcher blind to diagnosis and patient history.

**Results:** Of the 343 patients, 104 (30.3%) were identified with a Primary Sleep Disorder explaining their diagnosis. A hierarchical cluster analysis on the remaining 239 patients resulted in four sleep phenotypes being identified at saturation. Of the 239 patients, 89.1% met quantitative criteria for at least one objective sleep problem. A one-way analysis of variance confirmed distinct sleep profiles for each sleep phenotype. Relatively longer sleep onset latencies, longer Rapid Eye Movement (REM) latencies and smaller percentages of both stage 2 and REM characterised the first phenotype. The second phenotype was characterised by more frequent arousals per hour. The third phenotype was characterised by a longer Total Sleep Time, shorter REM Latencies, and a higher percentage of REM and lower percentage of wake time. The final phenotype had the shortest Total Sleep Time and the highest percentage of wake time and wake after sleep onset.

**Conclusions:** The results highlight the need to routinely screen for Primary Sleep Disorders in clinical practice and tailor sleep interventions, based on phenotype, to patients presenting with CFS. The results are discussed in terms of matching patients' self-reported sleep to these phenotypes in clinical practice.

#### ARTICLE SUMMARY

##### Article focus

- Despite 85–90% of patients with chronic fatigue syndrome (CFS) reporting unrefreshing sleep, previous research has been unable to reliably identify specific irregularities in objective sleep.
- To explore the possibility that sleep problems in this population are not homogeneous and that several sleep-specific phenotypes exist in this population which are amenable to different treatment approaches.

##### Key messages

- Over 30% of individuals with CFS met the diagnostic criteria for Sleep Apnoea or Periodic Limb Movement (PLM) Disorder that could explain their current diagnosis.
- The sleep in those with CFS, without Sleep Apnoea or PLM Disorder, centred around four specific sleep-disturbed phenotypes, with 89.1% demonstrating quantitative criteria for insomnia or hypersomnolence.
- Each sleep-phenotype in CFS comprised objective characteristics that could be assessed and differentiated using patient's self-reports in primary care.

##### Strengths and limitations of this study

- This is the first study to suggest, and identify, specific sleep-phenotypes in a large sample of patients with CFS.
- The objective findings can be easily translated and applied in routine primary care.
- A limitation is the use of a single-night of polysomnography.

#### INTRODUCTION

Chronic fatigue syndrome (CFS), as defined by the international consensus definition,<sup>1</sup> is a condition characterised by profound fatigue, of definite onset, which has persisted for at least 6 months, and causes substantial disruption to the individual's

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daily functioning. In addition to fatigue, at least four other key symptoms are required to fulfil diagnostic criteria, including muscle and joint pain, headache, cognitive dysfunction and unrefreshing sleep. Thus defined, CFS affects between 0.23% and 2.6% of the adult population.<sup>2-4</sup> There are several theories as to the pathogenesis of CFS. However, it is most likely that the development and maintenance of CFS are multifactorial. Predisposing factors include a general propensity to both emotional and physical distress, a history of abuse, being more than usually physically active and being perfectionist.<sup>5-8</sup> Precipitating events include viruses such as glandular fever and major life events.<sup>9 10</sup> Several factors appear to be involved in the maintenance of symptoms. Physiologically, evidence suggests dysregulation of the hypothalamic pituitary adrenal (HPA) axis, increased cytokine production and HPA responsiveness to cytokines,<sup>11 12</sup> hypersensitivity in the central nervous system (ie, central sensitisation)<sup>13 14</sup> and autonomic dysfunction.<sup>15 16</sup> Two studies also highlight the importance of illness beliefs and behaviours.<sup>17 18</sup> Individuals who adopt all or nothing coping styles in response to symptoms (ie, push on through until they crash out) and attribute broad ranges of everyday symptoms to their illness are more likely to develop CFS postvirally. In sum, research suggests that in CFS multiple processes in distinct domains, such as physiology, illness beliefs, inconsistent activity, sleep disturbance, medical uncertainty and lack of guidance, can interact to maintain or exacerbate symptoms.<sup>19</sup>

As aforementioned, unrefreshing sleep is one key diagnostic characteristic of CFS.<sup>1</sup> It is also one of the most common symptom complaints,<sup>20 21</sup> with 87-95% of patients reporting sleep difficulties (Gotts ZM, unpublished PhD thesis) that do not improve over the course of the illness.<sup>22</sup> Where the purpose of sleep is the subject of intense debate, its importance to human health and well-being is undeniable. Examinations of individuals deprived of or restricted from sleep consistently demonstrate deteriorations in mood, cognition and performance.<sup>23</sup> The purpose of each different sleep stage is also unclear, although it is generally agreed that the lighter stages of sleep (stage 1 sleep and stage 2 sleep) afford transitions between wakefulness and sleep and then between slow wave sleep (SWS) and Rapid Eye Movement sleep (REM). SWS and REM are believed to confer recuperative, restorative and learning properties for the individual (eg, the secretion of growth hormone, consolidation of memory).<sup>24 25</sup> Therefore, the proportion of each sleep stage and timing of entry into each sleep stage, SWS and REM in particular, are important for the long-term maintenance of human physical and mental health.

Symptoms such as unrefreshing sleep may not only be markers of CFS; they may also serve to maintain it. For instance, there may be reciprocal links between sleep quality, sleep-wake regulation and fatigue. There is evidence of this. For instance, studies have shown that adopting activity and sleep management strategies

improves HPA axis functioning as measured by cortisol levels.<sup>26</sup> This suggests that further investigation of sleep disturbance of CFS is of more than academic importance but may highlight new avenues for intervention. From a clinical perspective, it is also important to study sleep more thoroughly in CFS as it may highlight some areas of diagnostic ambiguity. For instance, previous studies have shown that sleep disorders (notably obstructive-sleep apnoea) are occasionally identified during polysomnographic (PSG) assessments with CFS patient cohorts.<sup>27-30</sup>

Although over 30 PSG studies on individuals with CFS exist, conclusive statements about the type of sleep abnormalities in this population are difficult. Few studies report a full characterisation of both sleep continuity (the timing, efficiency and amount of sleep obtained) and sleep architecture (amount of each sleep or wake stage and the timing of transitions to each sleep stage), with some studies providing no PSG data at all.<sup>27 31-35</sup> Moreover, reporting practices differ widely, making interpretation and comparisons difficult (eg, studies report the percentage of each sleep and wake stage as an index of Sleep Period Time, Total Sleep Time (TST) or even Time in Bed),<sup>29 30 36-43</sup> while others report the number of minutes spent in each stage.<sup>44-48</sup> What can be concluded from previous PSG studies is that, in each study, deviations from 'normal sleep' exist, but there is no consistent pattern. For example, where two studies<sup>44 45</sup> report poor sleep efficiencies and 'normal range' REM latencies, others<sup>36 37 45</sup> found 'normal range' sleep efficiencies and short REM latencies and yet others still report a normal sleep efficiency and a long-REM latency (REML)<sup>41</sup> or poor sleep efficiency and long-REM latencies.<sup>48</sup> Moreover, the picture remains unclear after controlling for the severity of patients' self-reported sleep complaints.<sup>49 50</sup> Although differences in protocol, definitional criteria and reporting criteria may, to some extent, explain these differences, an alternative explanation is that sleep difficulties in individuals with CFS are not homogeneous and various sleep phenotypes exist in this population.

To clarify the specific characterisation of sleep in CFS, the current study examined PSG data for a single night of sleep in a large group of CFS patients, to determine whether specific sleep disturbances exist in this group, and if so, whether they are consistent across all patients.

## METHOD

A cross-sectional, single-site observational study was undertaken on a consecutive series of 343 patients (mean age 37.21±12.42 years; 72 men and 271 women) referred for a single-night PSG study at a fatigue clinic in the Netherlands. The referral criteria for PSG investigation were that the patient (1) met diagnostic criteria for CFS according to the Fukuda definition, (2) they were drug-free for at least 2 weeks prior to the overnight study and (3) their symptoms could not be explained by a physical or psychological illness (eg, anxiety or

depression). Patients gave informed consent to take part in the study and were then interviewed and medically screened for the referral criteria by a registered physician and a registered psychiatrist. The Ethics Committee for the School of Life Sciences at Northumbria University had approved the study.

Patients arrived at the clinic 2 h before normal bedtime for electrode placement and biocalibration. The PSG montage comprised a standard 10/20 (ie, F<sub>4</sub>-M<sub>1</sub>, C<sub>4</sub>-M<sub>1</sub>, O<sub>2</sub>-M<sub>1</sub> and C<sub>z</sub> with backups at F<sub>3</sub>-M<sub>2</sub>, C<sub>3</sub>-M<sub>2</sub>, O<sub>1</sub>-M<sub>2</sub> and F<sub>pz</sub>). Additional channels were used for electro-oculography (EOG; E<sub>1</sub> and E<sub>2</sub> referenced to M<sub>2</sub>), electromyography (chin and anterior tibialis placements), ECG, and airflow, effort, body position and oximetry (via a pulse oximeter). Filter settings were set to the American Academy of Sleep Medicine<sup>51</sup> guidelines (eg, low 0.3 Hz/high 35 Hz for EEG and EOG) with a sampling rate of 500 Hz. Impedances were maintained below 5 k $\Omega$ . Participants slept in the laboratory overnight and were allowed to retire to bed when they wished and left to naturally wake in the morning. Scoring was conducted manually by a registered BRPT-certified technician at 30 s epochs, according to the AASM guidelines. The scorer was blind to the aims of the study. The mean recording period was just over 8 h (508.5 $\pm$ 63.11 min). Descriptions of all sleep variables are detailed in [table 1](#).

### Analytic strategy

A hierarchical cluster analysis was used to determine the number of phenotypes within the present sample after excluding those with Sleep Apnoea or Periodic Limb Movement (PLM) Disorder. Cluster analysis is a data-reduction technique that examines patterns among a set of variables to form homogeneous groups. The Euclidean squared distance measure of similarity method was chosen for the cluster analysis as it uses the progressive distance between variables to form the groups and does not rely upon standardised data. As cluster analysis can be affected by multicollinearity, a

correlation matrix was used to exclude variables that were highly correlated with one another. A one-way analysis of variance (ANOVA) was used to examine which of the sleep variables differentiated the phenotypes.

### RESULTS

An initial examination of the Apnoea Hypopnoea Index (AHI) and PLM indices indicated that 104 (43 men and 61 women) of the original 343 referrals (30.3%) met the AASM criteria for either sleep apnoea (AHI $\geq$ 15; n=101) or a PLM disorder (PLMs $\geq$ 5; n=17) (14 participants met the criteria for both disorders). The overall sleep profile of the remaining 239 patients (mean age 34.4 $\pm$ 11.84; 210 women and 29 men) was highly variable, indicating the presence of phenotypes ([figure 1](#)).

A hierarchical cluster analysis, using Ward's method, was undertaken to determine the number of groups (clusters) within the remaining 239 patients. Prior to the cluster analysis, a correlation matrix was examined to avoid multicollinearity influencing the cluster model. On this basis, four variables were excluded (height, weight, sleep efficiency and number of spontaneous arousals per hour) for having correlation coefficients with one or more variables above r=0.8. The final grouping variables included in the cluster analysis were: age, sex, body mass index (BMI), AHI's, PLM index, Number of Awakenings, Number of Arousals per hour, TST, Sleep Latency (SL), Wake After Sleep Onset (WASO), percentage of %N1 (stage 1 sleep) of TST, %N2 (stage 2 sleep) of TST, %N3 (SWS) of TST, %WAKE of TST, %REM of TST and REML. The Euclidean squared distance measure of similarity was used to group patients according to the included variables.

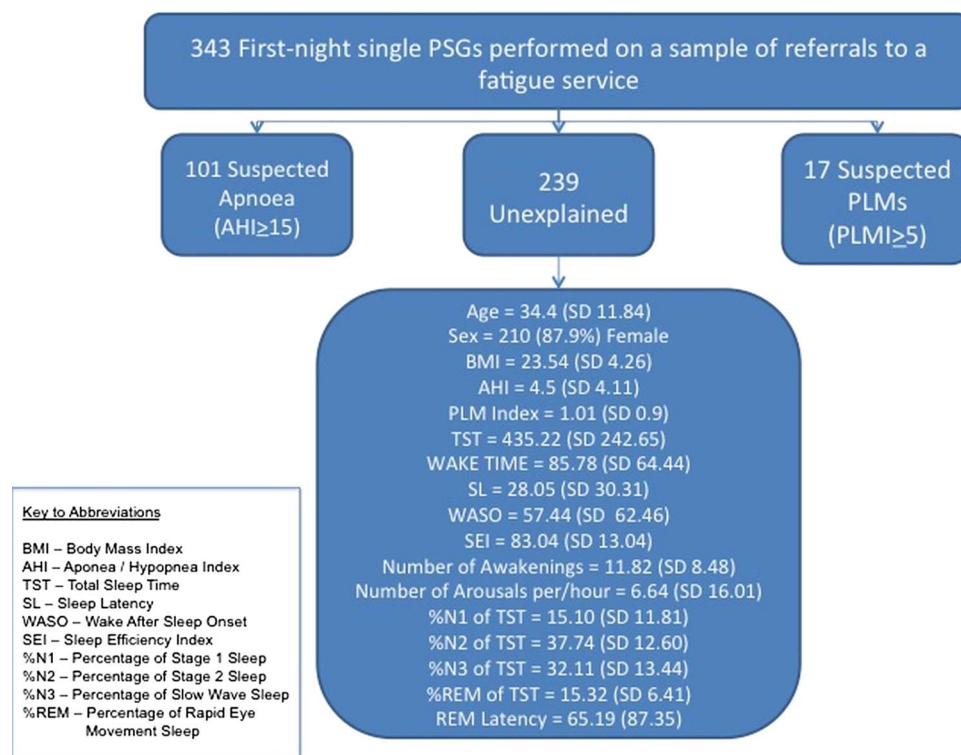
There were six clustering iterations overall (going from 8 to 2 clusters). The fourth iteration was chosen as the saturation point as it was the point where the agglomeration schedule and dendrogram had the highest reduction in the number of groupings (from six groups to four groups=reduction of 33%) while retaining at least 5% of the total sample size in each group

**Table 1** Description of sleep variables

Total sleep time (min)	Amount of time asleep
Sleep Onset Latency (min)	Length of time from lights out to first episode of stage 2 sleep
Wake After Sleep Onset (min)	Number of minutes of recorded wake following first episode of stage 2 sleep
Number of awakenings (over TSP)	Number of wake bouts following first episode of stage 2 sleep
Number of arousals	Number of arousals over the entire sleep period
REM Latency	Length of time to first REM stage
AHI Index	Number of apnoea or hypopnea events per hour of sleep
Percentage of N1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
Percentage of N2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
Percentage of N3 (of TST)	Percentage of recorded slow wave sleep over the total time asleep
Percentage of REM (of TST)	Percentage of recorded REM sleep over the total time asleep
Percentage of WAKE (of TSP)	Percentage of recorded wake over the total sleep period (ie, how long they were awake following first episode of stage 2 sleep)

REM, rapid eye movement; TSP, total sleep period; TST, total sleep time.

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**Figure 1** Study overview.

(ie,  $n \geq 11$ ). This latter rule was chosen to afford sufficient power for inferential data analysis to occur.

A one-way ANOVA was undertaken on the four groups to determine which sleep variables significantly differentiated the groups. There were no overall differences between the groups on age ( $p=0.12$ ) or BMI ( $p=0.48$ ). On inspection of the sex frequencies in each group, there was a higher ratio of men to women in the first group compared with the other three groups. However, as two groups contained less than five men, this could not be tested statistically. In relation to the polysomnography variables, there were no group differences in the number of arousals per hour or AHI index scores (PLMs were not included as less than 10% of the total sample had a PLM index), but significant differences were observed on all the other sleep variables (table 2).

### First phenotype

The first phenotype comprised 14 patients with the longest Sleep Onset and REMLs and the highest percentage of SWS. Moreover, this group had the lowest percentages of both stage 2 sleep and REM sleep. Statistically; this phenotype differed from the other three groups in terms of longer Sleep Onset and REMLs and a lower percentage of REM.

### Second phenotype

The second phenotype comprised 55 patients with the highest percentage of stage 2 sleep and the highest number of arousals per hour, although neither of these

variables statistically separated them from the other three phenotypes.

### Third phenotype

The third phenotype comprised 146 patients with the highest TST and percentage of REM. Additionally, this group demonstrated the shortest Sleep Onset and REMLs, lowest WASO and percentages of wake time and stage 1 sleep, and the lowest number of awakenings. Statistically, TST, percentage wake and WASO differentiated this phenotype from each of the others.

### Fourth phenotype

The fourth phenotype comprised 24 patients who demonstrated the highest WASO, percentages of wake and stage 1 sleep, and the highest number of awakenings. This group was also the lowest in terms of TST, number of arousals per hour and percentage of SWS. Statistically, only WASO and percentage of wake differentiated this group from each of the other groups.

## DISCUSSION

The aim of the study was to determine whether specific sleep phenotypes existed in patients with CFS. A large consecutive series of patients, meeting the criteria for CFS, underwent a single night of polysomnography to determine the presence or absence of distinct sleep phenotypes. The first finding, over 30% of individuals meeting diagnostic criteria for CFS, also demonstrated that a Primary Sleep Disorder (PSD; sleep apnoea or

**Table 2** Characteristics of sample of individuals with CFS

Grouped variable clusters	Group 1 (N=14)	Group 2 (N=55)	Group 3 (N=146)	Group 4 (N=24)	F	p Value
<b>Demographics</b>						
Age	35.79 (12.39)	37.29 (12.72)	32.99 (10.82)	35.54 (14.49)	1.95	ns
Sex	5 Males (35.71%)	10 Males (17.65%)	14 Males (9.59%)	1 Male (4.17%)	*	*
BMI	24.86 (5.68)	23.85 (4.63)	23.41 (4.03)	22.81 (3.86)	0.82	ns
<b>Sleep Variables</b>						
Total Sleep Time (min)	270.95 (41.85) <sub>ab</sub>	387.03 (46.1) <sub>acd</sub>	473.21 (45.82) <sub>bce</sub>	264.15 (74.43) <sub>de</sub>	188.07	p< .001
Sleep Onset Latency (min)	107.79 (42.09) <sub>abc</sub>	30.97 (29.13) <sub>ad</sub>	19.17 (14.71) <sub>bd</sub>	28.94 (27.54) <sub>c</sub>	67.26	p< .001
Wake After Sleep Onset (min)	75.79 (39.35) <sub>ab</sub>	82.12 (45.25) <sub>cd</sub>	35.45 (25.39) <sub>ace</sub>	180.2 (58.48) <sub>bde</sub>	119.74	p< .001
Number of Awakenings (over TSP)	15.21 (8.06)	14.75 (11.62) <sub>ab</sub>	9.54 (5.85) <sub>a</sub>	16.96 (9.26) <sub>b</sub>	10.52	p< .001
Number of Arousals	3.57 (9.21)	10.91 (23.01)	6.2 (15.26)	1.38 (4.13)	2.24	ns
REM latency	173.22 (55.03) <sub>abc</sub>	57.71 (34.31) <sub>ad</sub>	47.01 (28.22) <sub>be</sub>	84.46 (48.21) <sub>cde</sub>	63	p< .001
AHI index	3.43 (3.46)	4.58 (4.39)	4.73 (4.04)	3.54 (4.19)	0.92	ns
Percentage of N1 (of TST)	21.84 (13.36) <sub>a</sub>	14.35 (9.14) <sub>b</sub>	12.55 (7.37) <sub>ac</sub>	24.22 (14.82) <sub>bc</sub>	14.15	p< .001
Percentage of N2 (of TST)	27.57 (13.15) <sub>ab</sub>	38.82 (12.36) <sub>a</sub>	38.44 (12.14) <sub>b</sub>	36.95 (13.66)	3.46	p< .02
Percentage of N3 (of TST)	44.46 (20.45) <sub>abc</sub>	31.07 (11.05) <sub>a</sub>	31.78 (12.41) <sub>b</sub>	29.28 (16.42) <sub>c</sub>	4.64	p< .004
Percentage of REM (of TST)	6.11 (4.58) <sub>abc</sub>	15.16 (5.47) <sub>ad</sub>	17.19 (5.57) <sub>be</sub>	9.65 (6.35) <sub>cde</sub>	26.46	p< .001
Percentage of WAKE (of TSP)	60.32 (21.09) <sub>abc</sub>	25.75 (11.61) <sub>ade</sub>	11.03 (6.16) <sub>bd</sub>	75.26 (22.92) <sub>cef</sub>	271.62	p< .001

Note: Letters sharing the same subscript are significantly different.

\*Statistical tests of between-group sex differences could not be performed due to the small number of men in each group.

AHI, Apnoea Hypopnoea Index; BMI, body mass index; CFS, chronic fatigue syndrome; TSP, total sleep period; TST, total sleep time; REM, rapid eye movement.

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PLMD) is important and underscores the need to assess for PSDs in CFS populations. As the recommended treatment strategies for some PSDs differ considerably from those for CFS (eg, Continuous Positive Airway Pressure for apnoea vs sleep management strategies in CFS), it is important to direct the individual to, or adjunct, appropriate care pathways as soon as possible. This finding also questions the ability to differentiate fatigue associated with sleep apnoea or PLMD from that associated with CFS. Here, family members and/or carers may be helpful for diagnosis sensitivity as they are likely to be aware of nocturnal breathing disturbances (ie, heavy snoring, gasping or pauses in breathing).

The overall PSG results (after excluding sleep apnoea and PLMD) confirm objective sleep difficulties in patients with CFS. When the percentages of each sleep stage in 'normal' adult sleepers (ie,  $\leq 5\%$  wake, between 2% and 5% stage 1, between 45% and 55% stage 2, between 13% and 23% SWS and between 20% and 25% REM<sup>52</sup>) are compared with those in the present sample, it is seen that this group falls outside the range for all these variables. The present sample is spending more time awake and in the lighter stages of sleep (stages 1 and 2 sleep), and less time in the deeper sleep stages of sleep (ie, stage 2 sleep and SWS) and in REM. Further, using the quantitative benchmarks of sleep disturbance outlined by Edinger *et al*,<sup>53</sup> it can be seen that where sleep efficiency and SLs appear to be on the cusp of 'normal' sleep in the present sample (85% sleep efficiency is considered normal and SL of  $\geq 30$  denotes a sleep problem), WASO appears to be almost twice as long as is considered problematic ( $\geq 30$  min tends to denote a sleep problem). Together, these findings indicate that sleep is an objectively verifiable problem for patients with CFS that should be addressed clinically.

The cluster analysis identified, at saturation, four sleep phenotypes. The dendrogram identified two groups partially related (ie, groups 1 and 4) and two that were largely independent (ie, groups 2 and 3). This configuration was confirmed by ANOVA showing statistically significant differences in sleep continuity and architecture variables between the groups. That said, where statistical significance and relative characterisation (eg, highest in variable WX and Y and lowest in variable Z) are important in understanding between-group differences, the more salient question is whether these four groups are clinically relevant in terms of specific sleep treatments in patients with CFS. The use of different pharmacological agents (benzodiazepines, z-hypnotics or stimulants) or therapeutic interventions (ie, Cognitive Behavioural Therapy for Insomnia or behavioural modification strategies) has been shown to have differential effects on specific aspects of sleep continuity and architecture. For example, zolpidem appears to have a better impact on the number of awakenings and perceived quality of sleep compared with nitrazepam, and lormetazepam appears to be better in reducing SLs than zopiclone.<sup>54</sup> As such, tailoring treatment options to the sleep problems presenting in this population is likely to be more effective (table 3).

Another consideration, albeit related, is the presence within the final sample of PSDs for which PSG is either not routinely recommended or where, as stand-alone, it is insufficient for a definitive diagnosis.<sup>51</sup> Most relevant to the present sample are insomnia disorder and hypersomnolence disorders. Interestingly, groups 1 and 4 appear to be characterised by insomnia-like symptoms (ie, difficulties initiating sleep or maintaining sleep), whereas groups 2 and 3 appear to share overlapping characteristics with disorders characterised by poor sleep

**Table 3** Characteristics (statistical and phenomenological) of patients with CFS

Sleep phenotype	Central differential features	Associated diagnostic features	How this may present subjectively
1	Long Sleep Onset Latency, Long REM Latency, High amounts of Slow Wave Sleep and low amounts of REM	Low amounts of stage 2 sleep	Problems in getting off to sleep but when asleep few awakenings. The sleep that is obtained is of normal quality
2		High number of arousals per hour and high amounts of stage 2 sleep	No difficulties in getting off to sleep and few awakenings but feelings or evidence of a 'restless' night sleep
3	High Total Sleep Time, low amounts of time awake during the night and low number of wake periods during the night	High amounts of REM Sleep, Short Sleep Onset Latency, Low number of Awakenings, Short REM Latencies and low amounts of stage 1 sleep	No difficulties in getting off to sleep and few awakenings but feelings of being unrefreshed on waking despite a significant amount of time in bed asleep
4	Highest number of wake periods during the night and highest amounts of time awake during the night	Low Total Sleep Time, Low number of arousals per hour during the night and Low amounts of Slow Wave Sleep	Short sleep duration and although no difficulties getting off to sleep lots of awakenings for significant periods of time. Also increased feelings of daytime sleepiness

CFS, chronic fatigue syndrome; REM, Rapid Eye Movement.

quality (table 2). In relation to group 3, there is some overlap with hypersomnolence disorders (the term hypersomnolence will replace hypersomnia under the DSM-5) as 14 patients (9.59%) slept for 9 h or longer and eight patients (5.48%) demonstrated the main polysomnographically defined symptom of narcolepsy (ie, an REML of less than 15 min). For group 2, there is no obvious overlap with a specific DSM-5-defined sleep disorder, although as stage 2 sleep has been associated with hormonal and autonomic regulation,<sup>55</sup> increased amounts are likely to relate to both higher levels of autonomic and cortical arousal inhibiting deep sleep. As such, a PSG study with adjunct sleep history interviews, sleep diaries, actigraphy and/or a Multiple Sleep Latency Test or Maintenance of Wakefulness test would be valuable tools in determining whether these groups share all the diagnostic features of each PSD.

The findings from the present study should be viewed with the limitations in mind. There was no control group to determine the extent to which the four phenotypes exist in the general population. That said, with 6–10% of the population meeting the diagnostic criteria for insomnia<sup>56</sup> and 5% meeting the diagnostic criteria for hypersomnia,<sup>57</sup> the present data do not reflect this with 213 of the 239 (89.1%) participants, without apnoea or PLMS, meeting at least one quantitative criterion for insomnia or hypersomnia. It could also be argued that a single night of polysomnography may not be enough to capture the sleep of patients with CFS due to the first-night-effect.<sup>44</sup> The first-night-effect is a commonly observed response to the first night of sleeping in an unusual environment, such as a sleep laboratory, whereby aspects of sleep can be affected. That said, where Le Bon and colleagues demonstrated significant differences between nights 1 and 2 in a cohort of individuals with CFS, these differences were not largely evident in the sleep architecture and many differences in the sleep continuity variables disappeared after those with psychiatric illnesses were excluded from the analysis. Interestingly, over 25% of Le Bon *et al's*<sup>44</sup> sample also demonstrated an 'inverse first-night-effect' whereby they slept better on the first night compared with the second night. This issue of the first-night-effect in CFS is further complicated by other studies which have shown no such effect in this population.<sup>30</sup> It is very likely that inconsistencies in the first-night-effect reflect typical night-to-night variability<sup>58–60</sup> in addition to situation-specific factors, such as acclimating to a new environment, relating to PSG on the first and second nights. What would be ideal, albeit expensive, is a PSG study over several nights (eg, at least 14 continuous nights are suggested for insomnia<sup>61</sup>) to ensure that these issues are accounted for. That said, what may be more practical is to determine how information from the present study can inform, in conjunction with other assessments, actual clinical practice. One suggestion is that, ideally after ruling out PSDs, individuals should be interviewed about their sleep (usually over the last month) and

provided a sleep diary. This information would provide a subjective account that could be matched to the four phenotypes (as in table 3) to inform treatment.

Overall, the results suggest a significant overlap between CFS and a variety of symptoms of sleep disturbance. One night of PSG is sufficient to tease apart, and exclude, those with apnoea and PLM disorders from four other distinct sleep phenotypes in patients with CFS. Interestingly, these four phenotypes tend to mirror symptoms related to sleep quality and quantity that are amenable to different treatment strategies. As such, clinicians tailoring sleep-based interventions for patients with CFS should be mindful of these phenotypes.

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