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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, whilst 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 'otherwise healthy' patients meeting criteria for CFS, according to the Fukuda definition.

Measures: Patients underwent a single night of polysomnography (all-night recording of Electroencephalography, Electromyography, Electrooculography, Electrocardiogram and Respiration) that were 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 identified at saturation. Of the 239 patients, 89.1% met quantitative criteria for at least one objective sleep problem. A one-way ANOVA confirmed distinct sleep profiles for each sleep phenotype. Relatively longer sleep onset latencies, longer REM latencies, and smaller percentages of both Stage 2 and REM characterized 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 low 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.

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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.

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Article Focus

- Despite 85-90% of patients with 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 diagnostic criteria for Sleep Apnoea or Periodic Limb Movement Disorder that could explain their current diagnosis.
- The sleep in those with CFS, without Sleep Apnoea or Periodic Limb Movement 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:

- 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.

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INTRODUCTION

Chronic Fatigue Syndrome (CFS), as defined by the international consensus definition[1] 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 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 0.23-2.6% of the adult population[2-4]. There are several theories as to the pathogenesis of CFS. However it is likely the development and maintenance of CFS is multifactorial. Predisposing factors include a general propensity to both emotional and physical distress, history of abuse, being more than usually physically active, and being perfectionist[5-8]. Precipitating events include viruses such as glandular fever and major life events[9-10]. 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[11-12], and autonomic dysfunction[13-14]. Two studies also highlight the importance of illness beliefs and behaviours[15-16]. Individuals who adopt all or nothing coping styles in response to symptoms (i.e. push on through until they crash out) and attribute broad ranges of everyday symptoms to their illness are more likely to develop CFS post-virally. In sum, research suggests 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[17].

As mentioned above, unrefreshing sleep is one key diagnostic characteristic of CFS[1]. It is also one of the most common symptom complaints[18-19] with 87-95% of patients reporting sleep difficulties[20] that do not improve over the course of the illness[21]. Where the purpose of sleep is subject to intense debate, its importance to human health and well-being is undeniable. Examinations of individuals deprived or restricted of sleep consistently demonstrate deteriorations in mood, cognition, and

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performance[22]. 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 (e.g. the secretion of growth hormone, consolidation of memory) [23-24]. 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 but 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[25]. This suggests 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 sleep disorders (notably obstructive sleep apnoea) are occasionally identified during PSG assessments with CFS patient cohorts[26-29].

Although over 30 Polysomnographic (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[26, 30-34]. Moreover, reporting practices differ widely making interpretation and comparisons difficult (e.g. studies report the percentage of each sleep and wake stage as an index of Sleep Period Time, Total Sleep Time or even Time in Bed[28-

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[29; 35-42] whilst others report minutes of each stage[43-47]. What can be concluded from previous PSG studies is in each study deviations from 'normal sleep' exist but there is no consistent pattern. For example, where two studies[43-44] report poor sleep efficiencies and 'normal range' REM latencies, others[35-36,44] found 'normal range' sleep efficiencies and short REM latencies and others still report a normal sleep efficiency and a long REM latency[40] or poor sleep efficiency and long REM latencies[47]. Moreover, the picture remains unclear after controlling for the severity of patients' self-reported sleep complaints[48-49]. Although differences in protocol, definitional criteria, and reporting criteria may, to some extent, explain these differences, an alternative explanation is sleep difficulties in individuals with CFS are not homogenous and various sleep phenotypes exist in this population.

To clarify the specific characterisation of sleep in CFS, the current study examined polysomnographic 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, are these 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 males 271 females) referred for a single-night polysomnographic (PSG) study at a fatigue clinic in the Netherlands. The referral criteria for PSG investigation were that the patient, a) met diagnostic criteria for CFS according the Fukuda definition (1), b) they were drug-free for at least two-weeks prior to the overnight study, and c) their symptoms could not be explained by a physical or psychological illness (e.g. anxiety or depression). Patients gave informed consent to take part in the study and then were interviewed and medically screened for the referral criteria by a registered physician and a registered psychiatrist.

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Patients arrived at the clinic two hours before normal bedtime for electrode placement and bio-calibration. The PSG montage comprised a standard 10/20 (i.e. F_4-M_1, C_4-M_1, O_2-M_1 and C_z with backups at F_3-M_2, C_3-M_2, O_1-M_2 and F_{pz}). Additional channels were used for EOG (E_1 and E_2 referenced to M_2), EMG (chin and anterior tibialis placements), ECG, and airflow, effort, body position, and oximetry (via pulse oximeter). Filter settings were set to American Academy of Sleep Medicine[50] guidelines (e.g. low 0.3Hz / high 35Hz for EEG and EOG) with a sampling rate of 500Hz. Impedances were maintained below 5KΩ. Participants 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-second epochs, according to AASM guidelines. The scorer was blind to the aims of the study. The mean recording period was just over 8 hours (508.5 $\pm$ 63.11 minutes). Descriptions of all sleep variables are detailed in Table 1.

Table 1: Description of sleep variables

Total Sleep Time (minutes)	Amount of time asleep
Sleep Onset Latency (minutes)	Length of time from lights out to first episode of stage 2 sleep
Wake After Sleep Onset (minutes)	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
Sleep Efficiency	Percentage of overall time spent in bed asleep
REM Latency	Length of time to first REM stage
AHI Index	Number of apnoea or hypopnia events per hour of sleep
% N1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
% N2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
% N3 (of TST)	Percentage of recorded slow wave sleep over the total time asleep
% REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
% WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

RESULTS

An initial examination of the Apnoea Hypopnoea Index (AHI) and Periodic Limb Movements (PLM's) indices indicated that 104 (43 males and 61 females) of the original 343 referrals (30.3%) met AASM

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criteria for either sleep apnoea (AHI ≥ 15; n = 101) or a periodic limb movement disorder (PLMs ≥ 5; n =17) (14 participants met criteria for both disorders). The overall sleep profile of the remaining 239 patients (Mean Age 34.4±11.84; 210 females and 29 males) was highly variable indicating the presence of phenotypes (Figure 1).

Insert Figure 1 Here

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 =.8. The final grouping variables included in the cluster analysis were; age, sex, BMI, AHI's, PLM index, Number of Awakenings, Number of Arousals per hour, Total Sleep Time (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 REM Latency (REML). The Euclidean squared distance measure of similarity was used to group patients according to the included variables.

There were 6 clustering iterations overall (going from 8 clusters to 2). The fourth iteration was chosen as saturation point as it was where the agglomeration schedule and dedrogram had the highest reduction in the number of groupings (from six groups to four groups = reduction of 33%) whilst retaining at least 5% of the total sample size in each group (i.e. n ≥ 11). This latter rule was chosen to afford sufficient power for inferential data analysis to occur.

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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 ($F(3,235)=1.95, p=.12$) or BMI ($F(3,235)=.82, p=.48$) but a significant sex difference was observed ($X^2(3)=10.54, p<.02$). On inspection of the sex frequencies in each group, there was a significantly higher ratio of males to females (35.71% male) in the first group compared to the other three groups (17.65%, 9.59%, and 4.17% male respectively) although due to the number of males in the overall sample (12.13%) this is likely to be artefact. 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).

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
Demographics						
Age	35.79 (12.39)	37.29 (12.72)	32.99 (10.82)	35.54 (14.49)	1.95	n.s.
BMI	24.86 (5.68)	23.85 (4.63)	23.41 (4.03)	22.81 (3.86)	0.82	n.s.
Sleep Variables						
Total Sleep Time (minutes)	270.95 (41.85)ab	387.03 (46.1)acd	473.21 (45.82)bce	264.15 (74.43)de	188.1	p<.001
Sleep Onset Latency (minutes)	107.79 (42.09)abc	30.97 (29.13)ad	19.17 (14.71)bd	28.94 (27.54)c	67.26	p<.001
Wake After Sleep Onset (minutes)	75.79 (39.35)ab	82.12 (45.25)cd	35.45 (25.39)ace	180.2 (58.48)bde	119.7	p<.001
Number of Awakenings (over TSP)	15.21 (8.06)	14.75 (11.62)ab	9.54 (5.85)a	16.96 (9.26)b	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	n.s.
REM Latency	173.22 (55.03)abc	57.71 (34.31)ad	47.01 (28.22)be	84.46 (48.21)cde	63	p<.001
AHI Index	3.43 (3.46)	4.58 (4.39)	4.73 (4.04)	3.54 (4.19	0.92	n.s.
% N1 (of TST)	21.84 (13.36)a	14.35 (9.14)b	12.55 (7.37)ac	24.22 (14.82)bc	14.15	p<.001
% N2 (of TST)	27.57 (13.15)ab	38.82 (12.36)a	38.44 (12.14)b	36.95 (13.66)	3.46	p<.02
% N3 (of TST)	44.46 (20.45)abc	31.07 (11.05)a	31.78 (12.41)b	29.28 (16.42)c	4.64	p<.004
% REM (of TST)	6.11 (4.58)abc	15.16 (5.47)ad	17.19 (5.57)be	9.65 (6.35)cde	26.46	p<.001
% WAKE (of TSP)	60.32 (21.09)abc	25.75 (11.61)ade	11.03 (6.16)bdf	75.26 (22.92)cef	271.6	p<.001

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First Phenotype

The first phenotype comprised 14 patients with the longest Sleep Onset and REM Latencies 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 REM latencies, 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 all three other phenotypes.

Third Phenotype

The third phenotype comprised 146 patients with the highest Total Sleep Time and percentage of REM. Additionally, this group demonstrated the shortest Sleep Onset and REM Latencies, lowest wake after sleep onset and percentages of wake time and Stage 1 sleep, and the lowest number of awakenings. Statistically, Total Sleep Time, percentage wake, and wake after sleep onset differentiated this phenotype from each of the others.

Fourth Phenotype

The fourth phenotype comprised 24 patients who demonstrated the highest wake after sleep onset, percentages of wake and Stage 1 sleep, and the highest number of awakenings. This group were also the lowest in terms of Total Sleep Time, number of arousals per hour, and percentage of SWS. Statistically, only wake after sleep onset and percentage of wake differentiated this group from each of the others.

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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 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 a Primary Sleep Disorder (sleep apnoea or PLMD) is important and underscores the need to assess for Primary Sleep Disorders (PSDs) in CFS populations. As recommended treatment strategies for some PSDs differ considerably from those for CFS (e.g. 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 (i.e. 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 comparing percentages of each sleep stage in 'normal' adult sleepers (i.e. $\leq$5% wake, between 2-5% stage 1, between 45-55% stage 2, between 13-23% SWS, and between 20-25% REM[51]) to the present sample this group fall outside the range on all these variables. The present sample are spending more time awake and in the lighter stages of sleep (stage 1 and 2 sleep), and less time in deeper sleep stages of sleep (i.e. stage 2 sleep and SWS) and in REM. Further, using the quantitative benchmarks of sleep disturbance outlined by Edinger[52] it can be seen that where sleep efficiency and sleep latencies appear to be on the cusp of 'normal' sleep in the present sample (85% sleep efficiency is considered normal and a sleep latency of $\geq$30 denotes a sleep problem), wake after sleep onset appears to be almost twice as long as is considered problematic

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(≥30 minutes 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 dendogram identified two groups partially related (i.e. groups one and four) and two that were largely independent (i.e. groups two and three). This configuration was confirmed by the ANOVA showing statistically significant differences in sleep continuity and architecture variables between the groups. That said, where statistical significance and relative characterisation (e.g. 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 (i.e. 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 to nitrazepam, and lormetazapam appears better in reducing sleep latencies than zoplicone[53]. As such tailoring treatment options to the presenting sleep problems in this population is likely to be more effective (Table 3).

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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 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 High amounts of Stage 2 Sleep	No difficulties in getting off to sleep and few awakenings but feelings or evidence of a 'restless' nights sleep
3	High Total Sleep Time Low amounts of time awake during the night Low number of wake periods during the night	High amounts of REM Sleep Short Sleep Onset Latency Low number of Awakenings Short REM Latencies 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 Highest amounts of time awake during the night	Low Total Sleep Time Low number of arousals per hour during the night 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.

Another, albeit related, consideration is the presence within the final sample of PSDs for which PSG is either not routinely recommended or where stand-alone it is insufficient for a definitive diagnosis[50]. Most relevant to the present sample are insomnia disorder and hypersomnolence disorders. Interestingly, groups one and four appear to be characterised by insomnia-like symptoms (i.e. difficulties initiating sleep or maintaining sleep) whereas groups two and three appear to share overlapping characteristics with disorders characterised by poor sleep quality (Table 2). In relation to group three there is some overlap with hypersomnolence disorders (the term hypersomnolence will replace hypersomnia under the DSM-5) as 14 patients (9.59%) slept for nine hours or longer and eight patients (5.48%) demonstrated the main polysomnographically defined symptom of narcolepsy (i.e. a REM Latency of less than 15 minutes). For group two 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[54] increased amounts are likely to relate to both higher levels of autonomic

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and cortical arousal inhibiting deep sleep. As such, a PSG study with adjunct sleep history interviews, sleep diaries, actigraphy, and/or 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 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 approximately 6% of the population meeting diagnostic criteria for insomnia[55] and 5% meeting diagnostic criteria for hypersomnia[56] the present data do not reflect this with 213 of the 239 (89.1%) participants, without apnoea or PLMS, meeting at least one quantitative criteria 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[43]. That said, where Le Bon and colleagues demonstrated significant differences between nights one and two 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[43] sample also demonstrated an 'inverse first-night-effect' whereby they slept better on the first night compared to the second. This issue of the first-night-effect in CFS is further complicated by other studies which have shown no such effect in this population[29]. It is likely that inconsistencies in the first-night-effect reflect typical night-to-night variability[57-59] in addition to situation-specific factors relating to the PSG on the first and second nights. What would be ideal, albeit expensive, is a PSG study over several nights (e.g. at least fourteen continuous nights are suggested for insomnia[60]) to ensure 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, ideally after ruling out PSDs, individuals should be interviewed about their sleep (usually over the last

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month) and provide 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 periodic limb movement 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.

Contributions – All authors (JGE, ZMG, VD, JLN, PdR, DD) were involved in the design of the study. PdR and DD conducted the study and JGE and ZMG analysed the data. The first draft was written by JGE, JLN, VD and ZMG and was edited by all authors. All authors approved the final version of the manuscript.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
X Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
X Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
X Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
X Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

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X Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
X Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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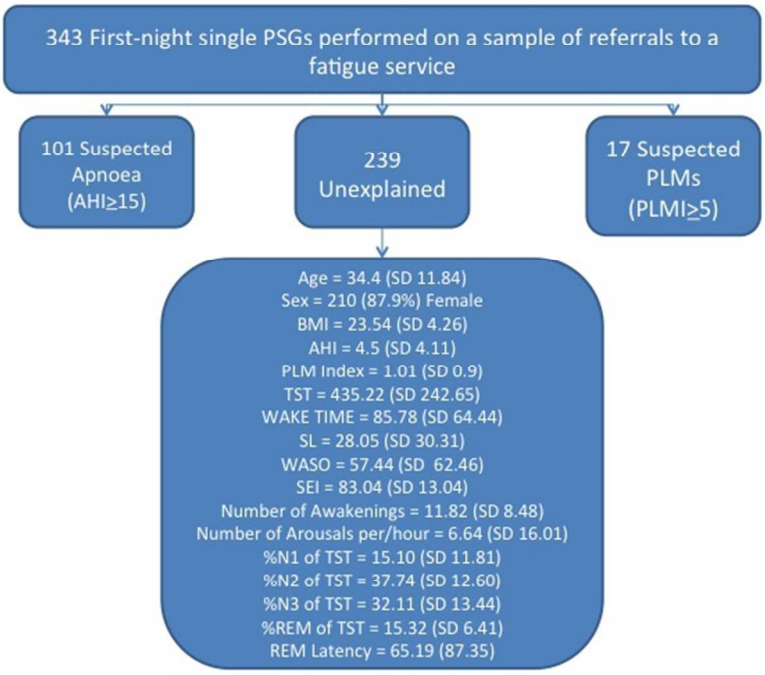
Figure 1: Study Overview



Study Overview
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Are there sleep-specific phenotypes in patients with Chronic Fatigue Syndrome? A cross-sectional polysomnography analysis

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Secondary Subject Heading:	Patient-centred medicine, General practice / Family practice, Evidence based practice
Keywords:	INTERNAL MEDICINE, SLEEP MEDICINE, STATISTICS & RESEARCH METHODS, MENTAL HEALTH

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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, whilst 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 criteria for CFS, according to the Fukuda definition.

Measures: Patients underwent a single night of polysomnography (all-night recording of Electroencephalography, Electromyography, Electrooculography, Electrocardiogram and Respiration) that were 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 identified at saturation. Of the 239 patients, 89.1% met quantitative criteria for at least one objective sleep problem. A one-way ANOVA 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 characterized 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 low 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.

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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.

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Article Focus

- Despite 85-90% of patients with 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 diagnostic criteria for Sleep Apnoea or Periodic Limb Movement Disorder that could explain their current diagnosis.
- The sleep in those with CFS, without Sleep Apnoea or Periodic Limb Movement 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:

- 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.

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INTRODUCTION

Chronic Fatigue Syndrome (CFS), as defined by the international consensus definition[1] 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 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 0.23-2.6% of the adult population[2-4]. There are several theories as to the pathogenesis of CFS. However it is likely the development and maintenance of CFS is multifactorial. Predisposing factors include a general propensity to both emotional and physical distress, history of abuse, being more than usually physically active, and being perfectionist[5-8]. Precipitating events include viruses such as glandular fever and major life events[9-10]. 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[11-12], hypersensitivity in the Central Nervous System (i.e. central sensitisation)[13-14], and autonomic dysfunction[15-16]. Two studies also highlight the importance of illness beliefs and behaviours[17-18]. Individuals who adopt all or nothing coping styles in response to symptoms (i.e. push on through until they crash out) and attribute broad ranges of everyday symptoms to their illness are more likely to develop CFS post-virally. In sum, research suggests 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[19].

As mentioned above, unrefreshing sleep is one key diagnostic characteristic of CFS[1]. It is also one of the most common symptom complaints[20-21] with 87-95% of patients reporting sleep difficulties[22] that do not improve over the course of the illness[23]. Where the purpose of sleep is subject to intense debate, its importance to human health and well-being is undeniable. Examinations of individuals

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deprived or restricted of sleep consistently demonstrate deteriorations in mood, cognition, and performance[24]. 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 (e.g. the secretion of growth hormone, consolidation of memory) [25-26]. 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 but 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[27]. This suggests 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 sleep disorders (notably obstructive sleep apnoea) are occasionally identified during PSG assessments with CFS patient cohorts[28-31].

Although over 30 Polysomnographic (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[28, 32-36]. Moreover, reporting practices differ widely making interpretation and comparisons difficult (e.g. studies report the percentage of

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each sleep and wake stage as an index of Sleep Period Time, Total Sleep Time or even Time in Bed[30-31; 37-44] whilst others report minutes of each stage[45-49]. What can be concluded from previous PSG studies is in each study deviations from 'normal sleep' exist but there is no consistent pattern. For example, where two studies[45-46] report poor sleep efficiencies and 'normal range' REM latencies, others[37-38,46] found 'normal range' sleep efficiencies and short REM latencies and others still report a normal sleep efficiency and a long REM latency[42] or poor sleep efficiency and long REM latencies[49]. Moreover, the picture remains unclear after controlling for the severity of patients' self-reported sleep complaints[50-51]. Although differences in protocol, definitional criteria, and reporting criteria may, to some extent, explain these differences, an alternative explanation is sleep difficulties in individuals with CFS are not homogenous and various sleep phenotypes exist in this population.

To clarify the specific characterisation of sleep in CFS, the current study examined polysomnographic 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, are these 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 males 271 females) referred for a single-night polysomnographic (PSG) study at a fatigue clinic in the Netherlands. The referral criteria for PSG investigation were that the patient, a) met diagnostic criteria for CFS according the Fukuda definition (1), b) they were drug-free for at least two-weeks prior to the overnight study, and c) their symptoms could not be explained by a physical or psychological illness (e.g. anxiety or depression). Patients gave informed consent to take part in the study and then were interviewed and medically

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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 two hours before normal bedtime for electrode placement and bio-calibration. The PSG montage comprised a standard 10/20 (i.e. F_4-M_1, C_4-M_1, O_2-M_1 and C_z with backups at F_3-M_2, C_3-M_2, O_1-M_2 and F_{pz}). Additional channels were used for EOG (E_1 and E_2 referenced to M_2), EMG (chin and anterior tibialis placements), ECG, and airflow, effort, body position, and oximetry (via pulse oximeter). Filter settings were set to American Academy of Sleep Medicine[52] guidelines (e.g. low 0.3Hz / high 35Hz for EEG and EOG) with a sampling rate of 500Hz. Impedances were maintained below 5KΩ. 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-second epochs, according to AASM guidelines. The scorer was blind to the aims of the study. The mean recording period was just over 8 hours (508.5 $\pm$ 63.11 minutes). Descriptions of all sleep variables are detailed in Table 1.

Table 1: Description of sleep variables

Total Sleep Time (minutes)	Amount of time asleep
Sleep Onset Latency (minutes)	Length of time from lights out to first episode of stage 2 sleep
Wake After Sleep Onset (minutes)	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
Sleep Efficiency	Percentage of overall time spent in bed asleep
REM Latency	Length of time to first REM stage
AHI Index	Number of apnoea or hypopnia events per hour of sleep
% N1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
% N2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
% N3 (of TST)	Percentage of recorded slow wave sleep over the total time asleep
% REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
% WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

Analytic Strategy

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A hierarchical Cluster Analysis was used to determine the number of phenotypes within the present sample after excluding those with Sleep Aponea or Periodic Limb Movement Disorder. Cluster analysis is a data reduction technique that examines patterns amongst a set of variables to form homogenous 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 Periodic Limb Movements (PLM's) indices indicated that 104 (43 males and 61 females) of the original 343 referrals (30.3%) met AASM criteria for either sleep apnoea (AHI $\geq$ 15; n = 101) or a periodic limb movement disorder (PLMs $\geq$ 5; n =17) (14 participants met criteria for both disorders). The overall sleep profile of the remaining 239 patients (Mean Age 34.4$\pm$11.84; 210 females and 29 males) was highly variable indicating the presence of phenotypes (Figure 1).

Insert Figure 1 Here

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

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were excluded (Height, Weight, Sleep Efficiency, and number of Spontaneous Arousals per hour) for having correlation coefficients with one or more variables above r =.8. The final grouping variables included in the cluster analysis were; age, sex, BMI, AHI's, PLM index, Number of Awakenings, Number of Arousals per hour, Total Sleep Time (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 REM Latency (REML). The Euclidean squared distance measure of similarity was used to group patients according to the included variables.

There were 6 clustering iterations overall (going from 8 clusters to 2). The fourth iteration was chosen as saturation point as it was where the agglomeration schedule and dedrogram had the highest reduction in the number of groupings (from six groups to four groups = reduction of 33%) whilst retaining at least 5% of the total sample size in each group (i.e. $n \geq 11$). 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=.12) or BMI (p=.48). On inspection of the sex frequencies in each group, there was a higher ratio of males to females in the first group compared to the other three groups. However, as two groups contained less than 5 males 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).

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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
Demographics						
Age	35.79 (12.39)	37.29 (12.72)	32.99 (10.82)	35.54 (14.49)	1.95	n.s.
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	n.s.
Sleep Variables						
Total Sleep Time (minutes)	270.95 (41.85)ab	387.03 (46.1)acd	473.21 (45.82)bce	264.15 (74.43)de	188.07	p<.001
Sleep Onset Latency (minutes)	107.79 (42.09)abc	30.97 (29.13)ad	19.17 (14.71)bd	28.94 (27.54)c	67.26	p<.001
Wake After Sleep Onset (minutes)	75.79 (39.35)ab	82.12 (45.25)cd	35.45 (25.39)ace	180.2 (58.48)bde	119.74	p<.001
Number of Awakenings (over TSP)	15.21 (8.06)	14.75 (11.62)ab	9.54 (5.85)a	16.96 (9.26)b	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	n.s.
REM Latency	173.22 (55.03)abc	57.71 (34.31)ad	47.01 (28.22)be	84.46 (48.21)cde	63	p<.001
AHI Index	3.43 (3.46)	4.58 (4.39)	4.73 (4.04)	3.54 (4.19	0.92	n.s.
% N1 (of TST)	21.84 (13.36)a	14.35 (9.14)b	12.55 (7.37)ac	24.22 (14.82)bc	14.15	p<.001
% N2 (of TST)	27.57 (13.15)ab	38.82 (12.36)a	38.44 (12.14)b	36.95 (13.66)	3.46	p<.02
% N3 (of TST)	44.46 (20.45)abc	31.07 (11.05)a	31.78 (12.41)b	29.28 (16.42)c	4.64	p<.004
% REM (of TST)	6.11 (4.58)abc	15.16 (5.47)ad	17.19 (5.57)be	9.65 (6.35)cde	26.46	p<.001
% WAKE (of TSP)	60.32 (21.09)abc	25.75 (11.61)ade	11.03 (6.16)bdf	75.26 (22.92)cef	271.62	p<.001

Notes

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

First Phenotype

The first phenotype comprised 14 patients with the longest Sleep Onset and REM Latencies 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 REM latencies, 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 all three other phenotypes.

Third Phenotype

The third phenotype comprised 146 patients with the highest Total Sleep Time and percentage of REM. Additionally, this group demonstrated the shortest Sleep Onset and REM Latencies, lowest wake after sleep onset and percentages of wake time and Stage 1 sleep, and the lowest number of

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awakenings. Statistically, Total Sleep Time, percentage wake, and wake after sleep onset differentiated this phenotype from each of the others.

Fourth Phenotype

The fourth phenotype comprised 24 patients who demonstrated the highest wake after sleep onset, percentages of wake and Stage 1 sleep, and the highest number of awakenings. This group were also the lowest in terms of Total Sleep Time, number of arousals per hour, and percentage of SWS. Statistically, only wake after sleep onset and percentage of wake differentiated this group from each of the others.

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 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 a Primary Sleep Disorder (sleep apnoea or PLMD) is important and underscores the need to assess for Primary Sleep Disorders (PSDs) in CFS populations. As recommended treatment strategies for some PSDs differ considerably from those for CFS (e.g. 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 (i.e. heavy snoring, gasping or pauses in breathing).

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The overall PSG results (after excluding sleep apnoea and PLMD) confirm objective sleep difficulties in patients with CFS. When comparing percentages of each sleep stage in 'normal' adult sleepers (i.e. ≤5% wake, between 2-5% stage 1, between 45-55% stage 2, between 13-23% SWS, and between 20-25% REM[53]) to the present sample this group fall outside the range on all these variables. The present sample are spending more time awake and in the lighter stages of sleep (stage 1 and 2 sleep), and less time in deeper sleep stages of sleep (i.e. stage 2 sleep and SWS) and in REM. Further, using the quantitative benchmarks of sleep disturbance outlined by Edinger[54] it can be seen that where sleep efficiency and sleep latencies appear to be on the cusp of 'normal' sleep in the present sample (85% sleep efficiency is considered normal and a sleep latency of ≥30 denotes a sleep problem), wake after sleep onset appears to be almost twice as long as is considered problematic (≥30 minutes 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 dendogram identified two groups partially related (i.e. groups one and four) and two that were largely independent (i.e. groups two and three). This configuration was confirmed by the ANOVA showing statistically significant differences in sleep continuity and architecture variables between the groups. That said, where statistical significance and relative characterisation (e.g. 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 (i.e. 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 to nitrazepam, and lormetazapam appears

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better in reducing sleep latencies than zoplicone[55]. As such tailoring treatment options to the presenting sleep problems in this population is likely to be more effective (Table 3).

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 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 High amounts of Stage 2 Sleep	No difficulties in getting off to sleep and few awakenings but feelings or evidence of a 'restless' nights sleep
3	High Total Sleep Time Low amounts of time awake during the night Low number of wake periods during the night	High amounts of REM Sleep Short Sleep Onset Latency Low number of Awakenings Short REM Latencies 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 Highest amounts of time awake during the night	Low Total Sleep Time Low number of arousals per hour during the night 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.

Another, albeit related, consideration is the presence within the final sample of PSDs for which PSG is either not routinely recommended or where stand-alone it is insufficient for a definitive diagnosis[52]. Most relevant to the present sample are insomnia disorder and hypersomnolence disorders. Interestingly, groups one and four appear to be characterised by insomnia-like symptoms (i.e. difficulties initiating sleep or maintaining sleep) whereas groups two and three appear to share overlapping characteristics with disorders characterised by poor sleep quality (Table 2). In relation to group three there is some overlap with hypersomnolence disorders (the term hypersomnolence will replace hypersomnia under the DSM-5) as 14 patients (9.59%) slept for nine hours or longer and eight patients (5.48%) demonstrated the main polysomnographically defined symptom of narcolepsy (i.e. a REM Latency of less than 15 minutes). For group two there is no obvious overlap with a

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specific DSM-5-defined sleep disorder although as Stage 2 sleep has been associated with hormonal and autonomic regulation[56] 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 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 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 diagnostic criteria for insomnia[57] and 5% meeting diagnostic criteria for hypersomnia[58] the present data do not reflect this with 213 of the 239 (89.1%) participants, without apnoea or PLMS, meeting at least one quantitative criteria 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[45]. 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 one and two 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[45] sample also demonstrated an 'inverse first-night-effect' whereby they slept better on the first night compared to the second. This issue of the first-night-effect in CFS is further complicated by other studies which have shown no such effect in this population[31]. It is likely that inconsistencies in the first-night-effect reflect typical night-to-night variability[59-61] in addition to situation-specific factors, such as acclimating to a new environment, relating to the PSG on the first and second nights. What would be ideal, albeit expensive, is a PSG

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study over several nights (e.g. at least fourteen continuous nights are suggested for insomnia[62]) to ensure 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, ideally after ruling out PSDs, individuals should be interviewed about their sleep (usually over the last month) and provide 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 periodic limb movement 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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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, whilst 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 ~~'otherwise healthy'~~ patients meeting criteria for CFS, according to the Fukuda definition.

Measures: Patients underwent a single night of polysomnography (all-night recording of Electroencephalography, Electromyography, Electrooculography, Electrocardiogram and Respiration) that were 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 identified at saturation. Of the 239 patients, 89.1% met quantitative criteria for at least one objective sleep problem. A one-way ANOVA 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 characterized 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 low 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.

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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.

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Article Focus

- Despite 85-90% of patients with 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 diagnostic criteria for Sleep Apnoea or Periodic Limb Movement Disorder that could explain their current diagnosis.
- The sleep in those with CFS, without Sleep Apnoea or Periodic Limb Movement 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:

- 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.

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INTRODUCTION

Chronic Fatigue Syndrome (CFS), as defined by the international consensus definition[1] 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 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 0.23-2.6% of the adult population[2-4]. There are several theories as to the pathogenesis of CFS. However it is likely the development and maintenance of CFS is multifactorial. Predisposing factors include a general propensity to both emotional and physical distress, history of abuse, being more than usually physically active, and being perfectionist[5-8]. Precipitating events include viruses such as glandular fever and major life events[9-10]. 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[11-12], hypersensitivity in the Central Nervous System (i.e. central sensitisation)[13-14], and autonomic dysfunction[15-16]. Two studies also highlight the importance of illness beliefs and behaviours[17-18]. Individuals who adopt all or nothing coping styles in response to symptoms (i.e. push on through until they crash out) and attribute broad ranges of everyday symptoms to their illness are more likely to develop CFS post-virally. In sum, research suggests 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[19].

As mentioned above, unrefreshing sleep is one key diagnostic characteristic of CFS[1]. It is also one of the most common symptom complaints[20-21] with 87-95% of patients reporting sleep difficulties[22] that do not improve over the course of the illness[23]. Where the purpose of sleep is subject to intense debate, its importance to human health and well-being is undeniable. Examinations of individuals

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deprived or restricted of sleep consistently demonstrate deteriorations in mood, cognition, and performance[24]. 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 (e.g. the secretion of growth hormone, consolidation of memory) [25-26]. 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 but 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[27]. This suggests 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 sleep disorders (notably obstructive sleep apnoea) are occasionally identified during PSG assessments with CFS patient cohorts[28-31].

Although over 30 Polysomnographic (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[28, 32-36]. Moreover, reporting practices differ widely making interpretation and comparisons difficult (e.g. studies report the percentage of

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each sleep and wake stage as an index of Sleep Period Time, Total Sleep Time or even Time in Bed[30-31; 37-44] whilst others report minutes of each stage[45-49]. What can be concluded from previous PSG studies is in each study deviations from 'normal sleep' exist but there is no consistent pattern. For example, where two studies[45-46] report poor sleep efficiencies and 'normal range' REM latencies, others[37-38,46] found 'normal range' sleep efficiencies and short REM latencies and others still report a normal sleep efficiency and a long REM latency[42] or poor sleep efficiency and long REM latencies[49]. Moreover, the picture remains unclear after controlling for the severity of patients' self-reported sleep complaints[50-51]. Although differences in protocol, definitional criteria, and reporting criteria may, to some extent, explain these differences, an alternative explanation is sleep difficulties in individuals with CFS are not homogenous and various sleep phenotypes exist in this population.

To clarify the specific characterisation of sleep in CFS, the current study examined polysomnographic 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, are these 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 males 271 females) referred for a single-night polysomnographic (PSG) study at a fatigue clinic in the Netherlands. The referral criteria for PSG investigation were that the patient, a) met diagnostic criteria for CFS according the Fukuda definition (1), b) they were drug-free for at least two-weeks prior to the overnight study, and c) their symptoms could not be explained by a physical or psychological illness (e.g. anxiety or depression). Patients gave informed consent to take part in the study and then were interviewed and medically

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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 two hours before normal bedtime for electrode placement and bio-calibration. The PSG montage comprised a standard 10/20 (i.e. F_4-M_1, C_4-M_1, O_2-M_1 and C_z with backups at F_3-M_2, C_3-M_2, O_1-M_2 and F_{pz}). Additional channels were used for EOG (E_1 and E_2 referenced to M_2), EMG (chin and anterior tibialis placements), ECG, and airflow, effort, body position, and oximetry (via pulse oximeter). Filter settings were set to American Academy of Sleep Medicine[52] guidelines (e.g. low 0.3Hz / high 35Hz for EEG and EOG) with a sampling rate of 500Hz. Impedances were maintained below 5KΩ. 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-second epochs, according to AASM guidelines. The scorer was blind to the aims of the study. The mean recording period was just over 8 hours (508.5 ± 63.11 minutes). Descriptions of all sleep variables are detailed in Table 1.

Table 1: Description of sleep variables

Total Sleep Time (minutes)	Amount of time asleep
Sleep Onset Latency (minutes)	Length of time from lights out to first episode of stage 2 sleep
Wake After Sleep Onset (minutes)	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
Sleep Efficiency	Percentage of overall time spent in bed asleep
REM Latency	Length of time to first REM stage
AHI Index	Number of apnoea or hypopnia events per hour of sleep
% N1 (of TST)	Percentage of recorded stage 1 sleep over the total time asleep
% N2 (of TST)	Percentage of recorded stage 2 sleep over the total time asleep
% N3 (of TST)	Percentage of recorded slow wave sleep over the total time asleep
% REM (of TST)	Percentage of recorded Rapid Eye Movement sleep over the total time asleep
% WAKE (of TSP)	Percentage of recorded wake over the whole sleep period (from lights out to lights on)

Analytic Strategy

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A hierarchical Cluster Analysis was used to determine the number of phenotypes within the present sample after excluding those with Sleep Aponea or Periodic Limb Movement Disorder. Cluster analysis is a data reduction technique that examines patterns amongst a set of variables to form homogenous 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 Periodic Limb Movements (PLM's) indices indicated that 104 (43 males and 61 females) of the original 343 referrals (30.3%) met AASM criteria for either sleep apnoea (AHI $\geq$ 15; n = 101) or a periodic limb movement disorder (PLMs $\geq$ 5; n =17) (14 participants met criteria for both disorders). The overall sleep profile of the remaining 239 patients (Mean Age 34.4$\pm$11.84; 210 females and 29 males) was highly variable indicating the presence of phenotypes (Figure 1).

Insert Figure 1 Here

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

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were excluded (Height, Weight, Sleep Efficiency, and number of Spontaneous Arousals per hour) for having correlation coefficients with one or more variables above r =.8. The final grouping variables included in the cluster analysis were; age, sex, BMI, AHI's, PLM index, Number of Awakenings, Number of Arousals per hour, Total Sleep Time (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 REM Latency (REML). The Euclidean squared distance measure of similarity was used to group patients according to the included variables.

There were 6 clustering iterations overall (going from 8 clusters to 2). The fourth iteration was chosen as saturation point as it was where the agglomeration schedule and dedrogram had the highest reduction in the number of groupings (from six groups to four groups = reduction of 33%) whilst retaining at least 5% of the total sample size in each group (i.e. n ≥ 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 (~~F(3,235)=1.95,~~p=.12) or BMI (~~F(3,235)=.82,~~p=.48). ~~but a significant sex difference was observed ($X^2(3)=10.54,p<.02$).~~ On inspection of the sex frequencies in each group, there was a ~~significantly~~ higher ratio of males to females ~~(35.71% male)~~ in the first group compared to the other three groups ~~(17.65%, 9.59%, and 4.17% male respectively)~~. However, as two groups contained less than 5 males this could not be tested statistically. ~~although due to the number of males in the overall sample (12.13%) this is likely to be artefact.~~ 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

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less than 10% of the total sample had a PLM index), but significant differences were observed on all the other sleep variables (Table 2).

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
Demographics						
Age	35.79 (12.39)	37.29 (12.72)	32.99 (10.82)	35.54 (14.49)	1.95	n.s.
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	n.s.
Sleep Variables						
Total Sleep Time (minutes)	270.95 (41.85)ab	387.03 (46.1)acd	473.21 (45.82)bce	264.15 (74.43)de	188.07	p<.001
Sleep Onset Latency (minutes)	107.79 (42.09)abc	30.97 (29.13)ad	19.17 (14.71)bd	28.94 (27.54)c	67.26	p<.001
Wake After Sleep Onset (minutes)	75.79 (39.35)ab	82.12 (45.25)cd	35.45 (25.39)ace	180.2 (58.48)bde	119.74	p<.001
Number of Awakenings (over TSP)	15.21 (8.06)	14.75 (11.62)ab	9.54 (5.85)a	16.96 (9.26)b	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	n.s.
REM Latency	173.22 (55.03)abc	57.71 (34.31)ad	47.01 (28.22)be	84.46 (48.21)cde	63	p<.001
AHI Index	3.43 (3.46)	4.58 (4.39)	4.73 (4.04)	3.54 (4.19	0.92	n.s.
% N1 (of TST)	21.84 (13.36)a	14.35 (9.14)b	12.55 (7.37)ac	24.22 (14.82)bc	14.15	p<.001
% N2 (of TST)	27.57 (13.15)ab	38.82 (12.36)a	38.44 (12.14)b	36.95 (13.66)	3.46	p<.02
% N3 (of TST)	44.46 (20.45)abc	31.07 (11.05)a	31.78 (12.41)b	29.28 (16.42)c	4.64	p<.004
% REM (of TST)	6.11 (4.58)abc	15.16 (5.47)ad	17.19 (5.57)be	9.65 (6.35)cde	26.46	p<.001
% WAKE (of TSP)	60.32 (21.09)abc	25.75 (11.61)ade	11.03 (6.16)bdf	75.26 (22.92)cef	271.62	p<.001

Notes
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

First Phenotype

The first phenotype comprised 14 patients with the longest Sleep Onset and REM Latencies 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 REM latencies, 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 all three other phenotypes.

Third Phenotype

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The third phenotype comprised 146 patients with the highest Total Sleep Time and percentage of REM. Additionally, this group demonstrated the shortest Sleep Onset and REM Latencies, lowest wake after sleep onset and percentages of wake time and Stage 1 sleep, and the lowest number of awakenings. Statistically, Total Sleep Time, percentage wake, and wake after sleep onset differentiated this phenotype from each of the others.

Fourth Phenotype

The fourth phenotype comprised 24 patients who demonstrated the highest wake after sleep onset, percentages of wake and Stage 1 sleep, and the highest number of awakenings. This group were also the lowest in terms of Total Sleep Time, number of arousals per hour, and percentage of SWS. Statistically, only wake after sleep onset and percentage of wake differentiated this group from each of the others.

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 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 a Primary Sleep Disorder (sleep apnoea or PLMD) is important and underscores the need to assess for Primary Sleep Disorders (PSDs) in CFS populations. As recommended treatment strategies for some PSDs differ considerably from those for CFS (e.g. 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

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carers may be helpful for diagnosis sensitivity as they are likely to be aware of nocturnal breathing disturbances (i.e. 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 comparing percentages of each sleep stage in 'normal' adult sleepers (i.e. ≤5% wake, between 2-5% stage 1, between 45-55% stage 2, between 13-23% SWS, and between 20-25% REM[53]) to the present sample this group fall outside the range on all these variables. The present sample are spending more time awake and in the lighter stages of sleep (stage 1 and 2 sleep), and less time in deeper sleep stages of sleep (i.e. stage 2 sleep and SWS) and in REM. Further, using the quantitative benchmarks of sleep disturbance outlined by Edinger[54] it can be seen that where sleep efficiency and sleep latencies appear to be on the cusp of 'normal' sleep in the present sample (85% sleep efficiency is considered normal and a sleep latency of ≥30 denotes a sleep problem), wake after sleep onset appears to be almost twice as long as is considered problematic (≥30 minutes 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 dendogram identified two groups partially related (i.e. groups one and four) and two that were largely independent (i.e. groups two and three). This configuration was confirmed by the ANOVA showing statistically significant differences in sleep continuity and architecture variables between the groups. That said, where statistical significance and relative characterisation (e.g. 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)

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or therapeutic interventions (i.e. 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 to nitrazepam, and lormetazapam appears better in reducing sleep latencies than zoplicone[55]. As such tailoring treatment options to the presenting sleep problems in this population is likely to be more effective (Table 3).

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 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 High amounts of Stage 2 Sleep	No difficulties in getting off to sleep and few awakenings but feelings or evidence of a 'restless' nights sleep
3	High Total Sleep Time Low amounts of time awake during the night Low number of wake periods during the night	High amounts of REM Sleep Short Sleep Onset Latency Low number of Awakenings Short REM Latencies 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 Highest amounts of time awake during the night	Low Total Sleep Time Low number of arousals per hour during the night 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.

Another, albeit related, consideration is the presence within the final sample of PSDs for which PSG is either not routinely recommended or where stand-alone it is insufficient for a definitive diagnosis[52]. Most relevant to the present sample are insomnia disorder and hypersomnolence disorders. Interestingly, groups one and four appear to be characterised by insomnia-like symptoms (i.e. difficulties initiating sleep or maintaining sleep) whereas groups two and three appear to share overlapping characteristics with disorders characterised by poor sleep quality (Table 2). In relation to

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group three there is some overlap with hypersomnolence disorders (the term hypersomnolence will replace hypersomnia under the DSM-5) as 14 patients (9.59%) slept for nine hours or longer and eight patients (5.48%) demonstrated the main polysomnographically defined symptom of narcolepsy (i.e. a REM Latency of less than 15 minutes). For group two 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[56] 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 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 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 diagnostic criteria for insomnia[57] and 5% meeting diagnostic criteria for hypersomnia[58] the present data do not reflect this with 213 of the 239 (89.1%) participants, without apnoea or PLMS, meeting at least one quantitative criteria 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[45]. 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 one and two 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[45] sample also demonstrated an 'inverse first-night-effect' whereby they slept better on the first night compared to the second. This issue of the first-

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night-effect in CFS is further complicated by other studies which have shown no such effect in this population[31]. It is likely that inconsistencies in the first-night-effect reflect typical night-to-night variability[59-61] in addition to situation-specific factors, such as acclimating to a new environment, relating to the PSG on the first and second nights. What would be ideal, albeit expensive, is a PSG study over several nights (e.g. at least fourteen continuous nights are suggested for insomnia[62]) to ensure 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, ideally after ruling out PSDs, individuals should be interviewed about their sleep (usually over the last month) and provide 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 periodic limb movement 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.

Contributions – All authors (JGE, ZMG, VD, JLN, PdR, DD) were involved in the design of the study. PdR and DD conducted the study and JGE and ZMG analysed the data. The first draft was written by JGE, JLN, VD and ZMG and was edited by all authors. All authors approved the final version of the manuscript.

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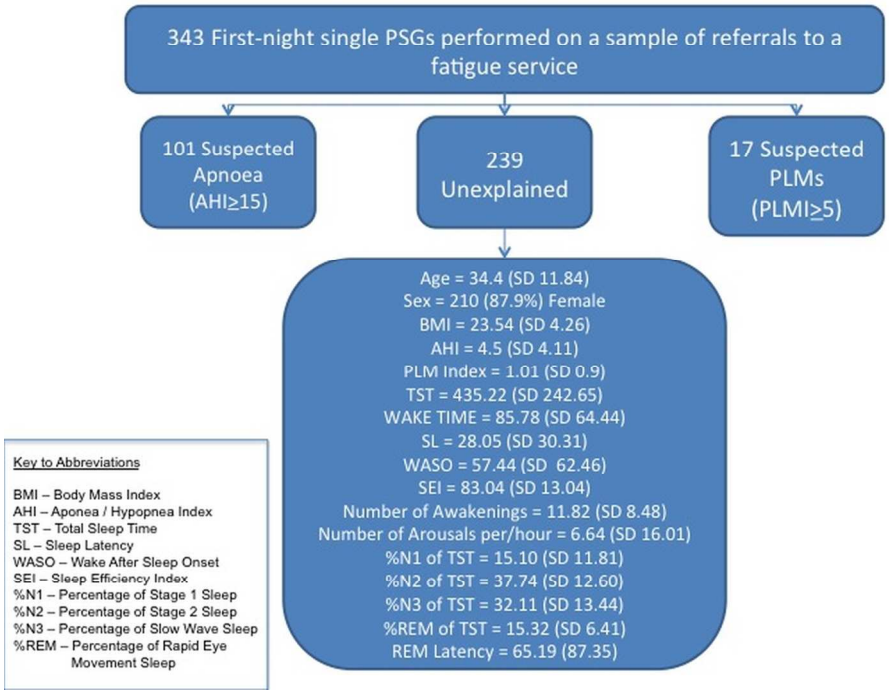
Figure 1: Study Overview



Study Overview
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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
X Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
X Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
X Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
X Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

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X Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
X Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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