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Research Article

A Critical Review to Investigate Chronic Fatigue Syndrome as Sleep Disorder

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Abstract

Introduction: Chronic fatigue syndrome is associated with marked fatigue and sleep disturbance specifically the non-restorative sleep. This has led to a though process among the Scientists to rule out possibility of association of CFS with Sleep Disorders. Researchers have tried to investigate the causal relationship between the two by virtue of multiple experiments, however consensus on the same still lacks.

Methods and Results: In current review, critical analysis of individual studies was conducted evaluating credibility of experiments leading to a final opinion pertaining to Chronic Fatigue Syndrome association with Sleep Pathology. Possible overlaps among different mechanisms were also identified to provide robust conclusion.

Conclusion: Current review suggests that Chronic Fatigue Syndrome and Sleep Disorders can be more of comorbid rather than having a causal relationship. Hence there is a mix type of evidence which tries to build relationship between the two but definite conclusion clearly demonstrating CFS as a sleep disorder cannot be reached.

Keywords: *Chronic Fatigue Syndrome; Sleep Disorders; Pathophysiology of CFS*

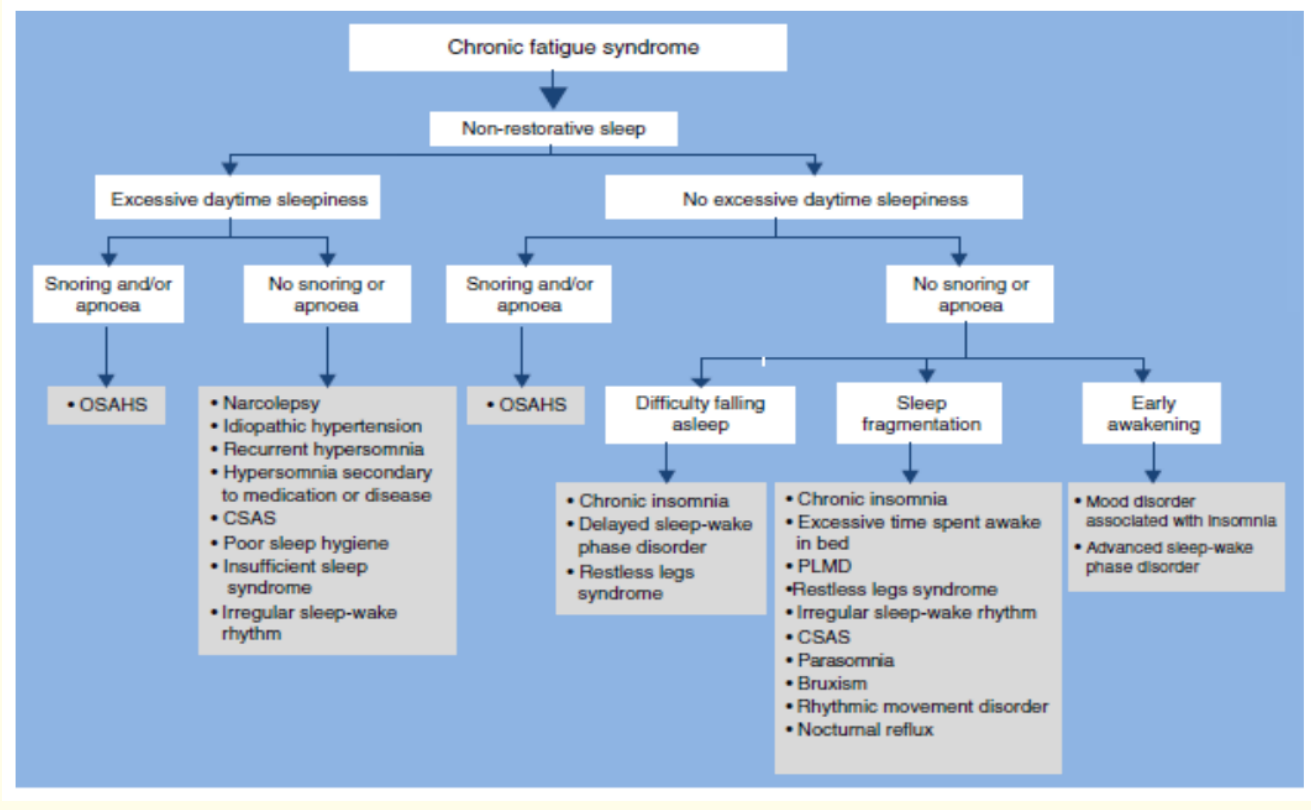
Abbreviations

CIS: Checklist Individual Strength; CFS: Chronic Fatigue Syndrome; DLMO: Dim Light Melatonin Onset; KSQ: Karolinska Sleep Questionnaire; MS: Multiple Sclerosis; MSLT: Multiple Sleep Latency Test; PLM: Periodic Limb Movement; PSG: Polysomnography; REM: Rapid Eye Movement; RLS: Restless Leg Syndrome

Introduction

Chronic fatigue syndrome is associated with marked fatigue and sleep disturbance specifically the non-restorative sleep. Based on subjective measures of sleep assessment, multiple studies have revealed that sleep disorders can be one of the etio-pathologic factor in development of CFS. However, similar symptoms are also found in different pathological conditions and may occur as a consequence of drug usage. Further, there is very limited evidence pertaining to objective assessment of sleep in CFS patients. Clinically CFS can be defined

as disorder in which more than 6 months of history of fatigue exists with no corresponding organic/physical or psychiatric pathology involvement. Fatigue can be defined as inability to initiate and maintain physical activity along with some psychological part including cognitive challenges. Similarly, excessive day time sleepiness can be explained as urge to sleep without any mental and/or physical fatigue. Non-restorative sleep is defined as getting up not fresh although sleep hours were sufficient enough to provide physical and mental rest. Typically, primary complaint in non-restorative sleep can be associated with cognitive, musculoskeletal pain, headache and other psychiatric symptoms. Recently other symptoms like sleep fragmentation, delay in falling asleep and excessive day time sleeping are also added to rule out the diagnosis of CFS. Having so much similarity in symptoms with other sleep disorders it is difficult for differential diagnosis. Hence it is important to have a holistic approach and other diseased conditions including primary sleep disorders should be excluded while considering CFS patients (Flowchart 1).



Flowchart 1: *Describes different types of Sleep disorders and their association with chronic fatigue syndrome. We can find overlapping between symptoms of Sleep disorders and CFS.*

The key research question here is to rule out association between CFS and sleep disorders. Further, to evaluate whether sleep disorders are etio-pathological factors to cause CFS or not. For the purpose of evaluation original research work was reviewed and critically analysed. Both subjective and objective measures of sleep derangement assessment were observed and comparison between the two was undertaken.

In a case control study, 12 CFS and 12 healthy subjects were enrolled. Both subjective (sleep diaries) and objective measures (home based one-night PSG) were taken into consideration. It was observed that patients with CFS spent more time in bed as compared to

healthy controls (P < 0.001). Further, CFS group had decreased sleep efficiency (P < 0.005) and much more difficulty in initiation of sleep (P < 0.003) when compared with healthy subjects [1].

Although these results indicate association between sleep disorders and CFS, but results cannot exclude bias as outcomes were based on subjective assessments like sleep diaries. Being a case control study, a greater number of subjects would have been instrumental to provide evidence of CFS being a sleep disorder.

Krupp., *et al*. 1993 investigated sleep related challenges and fatigue symptoms in CFS patients (n = 72) and compared them with MS patients (57) and healthy subjects (n = 40). Both subjective and objective measures were observed in this study. CFS patients contributed to clinically significant fatigue and sleep disturbances based on sleep diaries. Sixteen patients completed overnight PSG as well.

PSG findings were suggestive of significant percentage (62.5%) of CFS patients with comorbid sleep disorders, later included periodic limb movement, excessive day time sleep, sleep apnoea and one patient with diagnosed narcolepsy (Krupp., *et al*. 1993). Current study enrolled good number of subjects and provided evidence on co-existence of sleep disorders and CFS.

Buchwald., *et al*. 1994 studied sleep patterns in CFS patients (n = 37) to rule out presence of Sleep disorders using overnight PSG.41% of CFS subjects had presented with multiple sleep latency and 81% percent had been diagnosed with at least a single sleep disorder. In sleep disorders primarily, sleep apnoea was diagnosed, and other cases were of idiopathic insomnia. Whereas in non CFS group (n = 22) none presented sleep disorders. This study provides evidence pertaining to co-existence of CFS and sleep disorders, however does build up causal relationship between the two. Study also provides a direction to rule out overlapping symptoms between CFS and sleep disorders in context with understanding the causal association.

Another research group studied type and frequency of sleep problems in patients with CFS (n = 13) and compared it with control group of fibromyalgia. (n = 50). Pearson's correlation was calculated for each groups corresponding to symptoms like fatigue and sleepiness. Results revealed significant correlation between CFS and sleep problems (r = .63, P < 0.01). Further CFS group was also found to have significantly greater concerns related to sleep as compared to fibromyalgia group. Main concern with study design here was utilization of subjective measures for assessments and overall sample size was too low to extrapolate results to CFS population [2].

In a four-arm study [3] evaluated relationship between CFS and sleep disorders in over 200 subjects. Out of these 68 CFS patients were without any history of depression while 59 CFS patients were diagnosed with depression. Other arms of study comprised of patients with depression with no CFS (38) and 45 healthy subjects.

In CFS without depression 36% of patients had difficulty in sleep initiation, 48% reported more than 2 times waking, 60% felt waking up not fresh. Snoring, kicking and restless legs were reported by 16%, 15% and 28% respectively in this group. Similar kind of finding was observed in patients with CFS and depression. When these findings were analysed in healthy controls the impact was on much lesser percentage. Further, patients with only depression had lesser percentage of sleep issues. Similar case control study was done by Sharpley and his team (n = 40, 20 CFS and 20 healthy subjects). Sleep diaries were used as subjective measure and home-based PSG as objective measure. Though CFS patients reported poor quality sleep, longer duration in bed (P < 0.01) and lesser sleep efficiency (P < 0.03) on subjective measures.

However, sleep diary subjective findings did not correspond to PSG findings except in one CFS patients. Hence, this makes it a limited evidence to prove CFS to be a sleep disorder [4].

In a study conducted by Watson and team, 11 pair each of monozygotic twins with and without CFS were compared for subjective and objective measures of Insomnia. Multiple parameters like total sleep time, arousal number and index, hypnogram awakenings, sleep efficiency, REM sleep latency and sleep latency were observed using overnight PSG. For subjective measures of Insomnia, 175-point Sleep disorder questionnaire was used with focus on subjective aspects of sleep [5].

PSG recordings revealed that total sleep time, awakenings, sleep efficiency, REM sleep latency and sleep latency were not statistically different in CFS versus healthy group REM percentage was found to be increased in the CFS group (P < 0.05) (Table 1).

Measures	CFS Twins Mean (95% CI)	Healthy Twins Mean (95% CI)	Intraclass Correlation
Total sleep time (hours)	6.3 (5.9 - 6.7)	6.3 (6.0 - 6.8)	0.74
Arousal number	111.7 (84.3 - 139.0)	116.1 (88.7 - 143.4)	0.61
Arousal index (arousals/hour of sleep)	17.9 (13.6 - 22.3)	18.6 (14.2 - 22.9)	0.71
Hypnogram awakenings	25.9 (20.7 - 31.1)	27.1 (21.9 - 32.4)	0.63
% Stage 1	8.3 (5.4 - 11.3)	9.0 (6.1 - 12.1)	0.72
% Stage 2	44.9 (41.4 - 48.4)	49.0 (45.5 - 52.5)	0.21
% Stage 3-4	19.1 (15.4 - 22.9)	17.5 (13.7 - 21.3)	0.72
% Stage REM[1]	27.7 (24.6 - 30.7)	24.4 (21.3 - 27.5)	0.65
Sleep efficiency	88.3 (83.4 - 93.1)	88.6 (83.7 - 93.4)	0.69
REM sleep latency (min)	63.5 (41.1 - 86.0)	88.0 (65.5 - 110.5)	0.13
Sleep latency (min)	13.6 (7.8 - 19.4)	10.6 (4.8 - 16.4)	0.15

Table 1: *Objective Sleep Measures using PSG in CFS versus healthy twins [5].*
CFS: Chronic Fatigue Syndrome; CI: Confidence Interval; REM: Rapid Eye Movement.
[1]p ≤ 0.05.

Based on subjective measures, statistically significant Insomnia was reported. (p < 005) by CFS group. (Table 2). Use of medication for sleep, difficulty in initiation of sleep, wakefulness, restlessness and disturbed sleep were reported more in the CFS group [5].

Subjective Measures	CFS Twins (% yes)	Healthy Twins (% yes)	P value
I wake up often during the night	81.8	31.8	≤ 0.001
My nights sleep is often restless and disturbed	81.8	19.1	≤ 0.001
I feel that my sleep is abnormal	86.4	9.5	≤ 0.001
I have trouble getting to sleep at night	72.7	22.7	≤ 0.001
I have been unable to sleep at all for several days	18.2	0.0	≤ 0.05
I feel that I have insomnia	31.8	4.8	≤ 0.01
I often have a poor nights sleep	86.4	27.3	≤ 0.001
I take a prescription drug to help me sleep	61.9	0.0	≤ 0.001

Table 2: *Subjective sleep measures using sleep questionnaire CFS versus healthy twins [5].*
Twins answering disagree or never or rarely were combined into a single "no" group; twins answering sometimes, usually, or true or always were combined into a single "yes" group. All statistical tests are signed-rank tests.

Key finding here is the subjective measures of Insomnia endorsed by CFS group was not found to be aligned with objective findings in PSG recordings. An important aspect of this study is increase in percentage of REM sleep in CFS group which somehow indicates the association of CFS and sleep pathophysiology. However, it cannot be concluded that whether this increase in REM pressure is secondary to CFS or vice versa. Hence, there is an evidence between association of CFS and sleep pathology however CFS cannot be termed as a Sleep disorder based on the current limited evidence.

Fossey., *et al*. [6] worked on CFS patients to rule out association between CFS and sleep disorders. Group enrolled 37 CFS patients with control groups comprising of healthy subjects (n = 17) and patients with narcolepsy (n = 24). Subjective parameters of assessment

included sleep questionnaires, diaries and detailed clinical history of patients. ESS (Epworth Sleepiness Scale), fatigue severity scale, Stanford Sleepiness Scale, and Chalder Fatigue Questionnaire were also used in the assessments. Overnight PSG monitoring was also undertaken. It was observed that CFS group had higher prevalence of sleep disorders as compared to healthy control group (chi square test $p < 0.005$).

Although current study demonstrates co-existence of sleep disorders and CFS however there is no evidence of causal relationship between the two. Further, sample size was also very less and hence power of study parameters would also be impacted accordingly.

Shift workers develop a set of pathologies secondary to sleep derangement. Hossain and his team investigated whether Shift workers tend to develop chronic fatigue based on the sleep pathology**.** They conducted a cross sectional study comprising of patients with chronic fatigue (n = 21) and with no fatigue (n = 21). It was observed that patients with chronic fatigue had statistically significant sleep pathology as per PSG as compared with controls. (Fisher's exact test $P < 0.0001$) This study provides evidence pertaining to involvement of sleep pathology in genesis of chronic fatigue in shift workers. However, these results cannot be translated to CFS patient's population (Hossain., *et al*. 2002).

In a population-based study on CFS patients (n = 43) and healthy controls, based on overnight PSG and multiple sleep latency test, when CFS patients were rolled out for sleep apnoea, frequency of apnoea was found to be higher in CFS ($p = 0.003$). However during clinical assessment difference in apnoea frequency was found to be not appealing. Hence, this study does not provide any strong evidence proving CFS being a sleep disorder. Further, there were no changes in sleep architecture in CFS group versus controls (Reeves., *et al*. 2006).

Similar population-based study was conducted by Majer and his team in which 35 CFS patients were recruited and compared with 40 healthy controls. Key focus of study was to evaluate difference in perception of Sleep derangement in CFS patients based on subjective and objective measures of sleep. For subjective measures, group used sleep questionnaires and for objective assessment, PSG and multiple sleep latency tests were used. Most CFS patients complained about sleep disturbance and other sleep related concerns. However, when these were mapped with PSG and MSLT recordings there was no evidence of derangement in sleep pathology in CFS. This study clearly highlights perception of CFS patients versus evidence-based assessment have two different points of view. There is need to investigate psychological and psychiatric assessment of CFS patients (Majer., *et al*. 2007).

CFS patients also presented with challenges pertaining to sleep like Insomnia and non -restorative sleep. Research group focused on slow wave activity change secondary to delay in sleep in monozygotic twins with clinical established CFS (n = 13) as compared to non CFS group (n = 13). Study procedure comprised of 4 hours delayed sleep and monitoring with PSG on the 3rd night. 1st night was for adaptation and 2nd night was taken as baseline. For quantification of slow wave activity, power spectral analysis was done [7].

At baseline SWA (slow wave activity) power analysis for both groups was similar. Post 4 hours sleep delay CFS group had lower SWA power as compared to non CFS twins. Figure 1 indicates power analysis of SWA in NERM 1 - 4 phases in CFS and healthy twin groups. It was observed that in NREM 1 stage CFS twins had less than 120% of SWA accumulation when compared with healthy group (140%) with respect to baseline measurements. In NREM stage 4 slow wave activity was observed to be higher (blunt) in CFS twin group as compared to control (Statistically significant $p < 0.005$) (Figure 1). Further PSG recordings indicated shorter sleep latency in the CFS twin group post 4 hours sleep delay as compared to healthy group ($P = 0.001$). These findings are suggestive of association of CFS and the derangement in the slow wave activity in diseased group, however these two conditions can be comorbid rather than having a causal relationship. One of the major limitations of study was duration of sleep delay i.e. 4 hours which should have been more to predict association between CFS and SWA in a better way.

Creti., *et al.* [8] compared findings of PSG, actigraphy and sleep related self-reporting questionnaires in 49 CFS patients. There was significant difference in findings pertaining to sleep disturbance and architecture in PSG, Actigraphy versus subjective measures. Sleep derangement reporting in self-reporting questionnaires did not correspond to findings of PSG and Actigraphy.

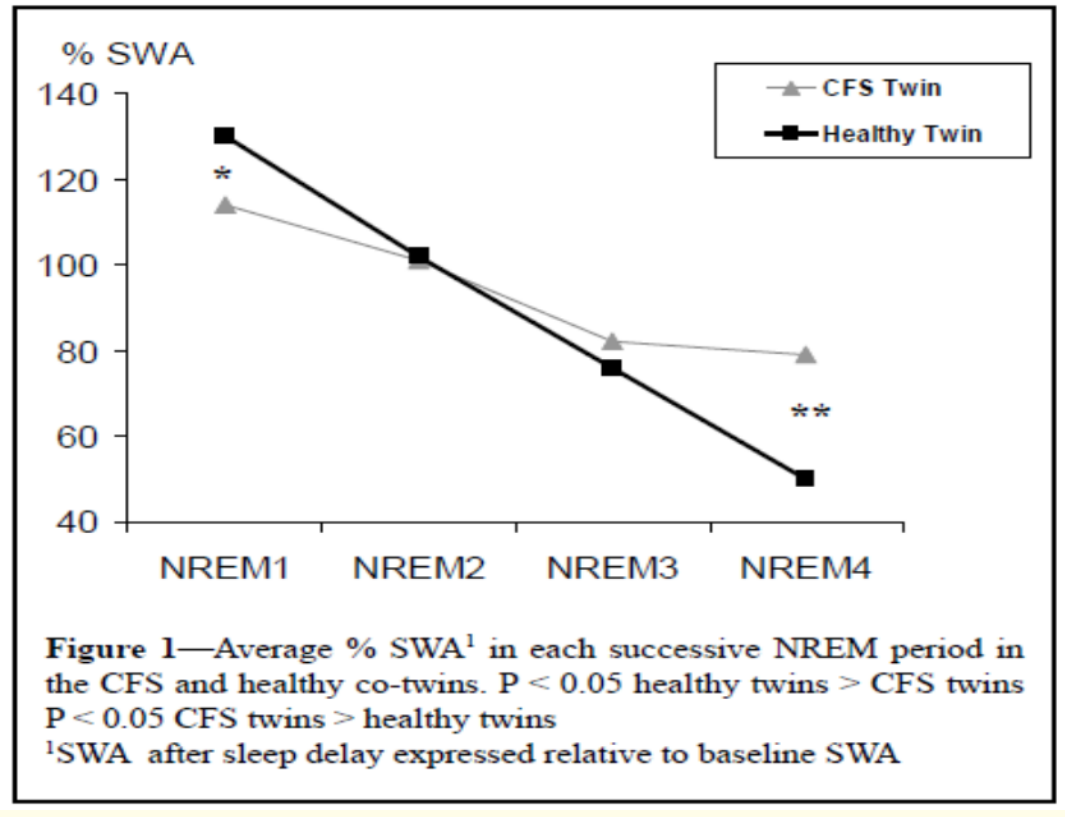


Figure 1: *Slow wave activity across NREM Stages 1-4 in CFS (n = 13) and healthy subjects (n = 13) [7].*

Spitzer., *et al.* [9] conducted a retrospective study on 118 patients with CFS and fibromyalgia to rule out association between sleep disorders and CFS. Group found that similarities between CFS patients and narcolepsy clinical presentation. Based on these similarities and clinical relevance to CFS and fibromyalgia patients were prescribed sodium oxybate. It was observed that out of 85 patients who received sodium oxybate, 74% presented lesser symptoms of fatigue later on.

Study provides evidences association between usage of sodium oxybate and improvement in symptoms in CFS and fibromyalgia patients. Being a retrospective study adds to limitation here, as there can be associated bias. Further, the study considers both CFS and fibromyalgia patients together however sleep derangement in both these disorders is not well defined. Focus of study has been more on pain and fatigue symptoms in CFS patients rather than core sleep disorder.

Rahman and his team conducted a case control study in which CFS patients (n = 15) and healthy subjects (n = 15) were compared on behavioral outcomes for 5 days. Symptoms of CFS include fatigue, poor cognition and sleep issues indicating some relationship with circadian dysregulation i.e. internal biological clock derangement. Both groups were provided self-reporting question logs which included symptoms related to sleep quality/issues, mood issues and cognition. Research group also used actigraphy for 5 days along with pain and heart rate recording overnight. Cortisol (salivary) levels were also recorded [10]. In CFS group, there were significant complaints of pain, disability and sleep disturbance. When compared with healthy group Cortisol levels, sleep duration and quality, actigraphy showed no difference in both groups. It was also observed that during night decreased heart rate had correlation with unrefreshing sleep. Current study investigated association of circadian rhythm abnormality with CFS however no strong evidence could be observed in this case.

This further emphasizes, though sleep related symptoms are present in CFS patients, it cannot be termed as a Sleep disorder due to lack of evidence. Being case control and self-reporting questionnaires bias is key limitation of the study. Further very low sample size was enrolled (n = 30) which also needs to be raised to a significant level in future studies.

Pederson., *et al.* [11] analysed sleep wake rhythm in 120 CFS patients and compared them with 39 healthy subjects. Subjective measures used in study were Karolinska Sleep Questionnaire (KSQ) and movement detection was done based on accelerometer. Results showed, CFS patients spent more time in bed as compared to healthy individuals. CFS patients also presented with rhythm derangement in sleep cycle. KSQ scores indicate more insomnia symptoms in CFS patients as compared to healthy group.

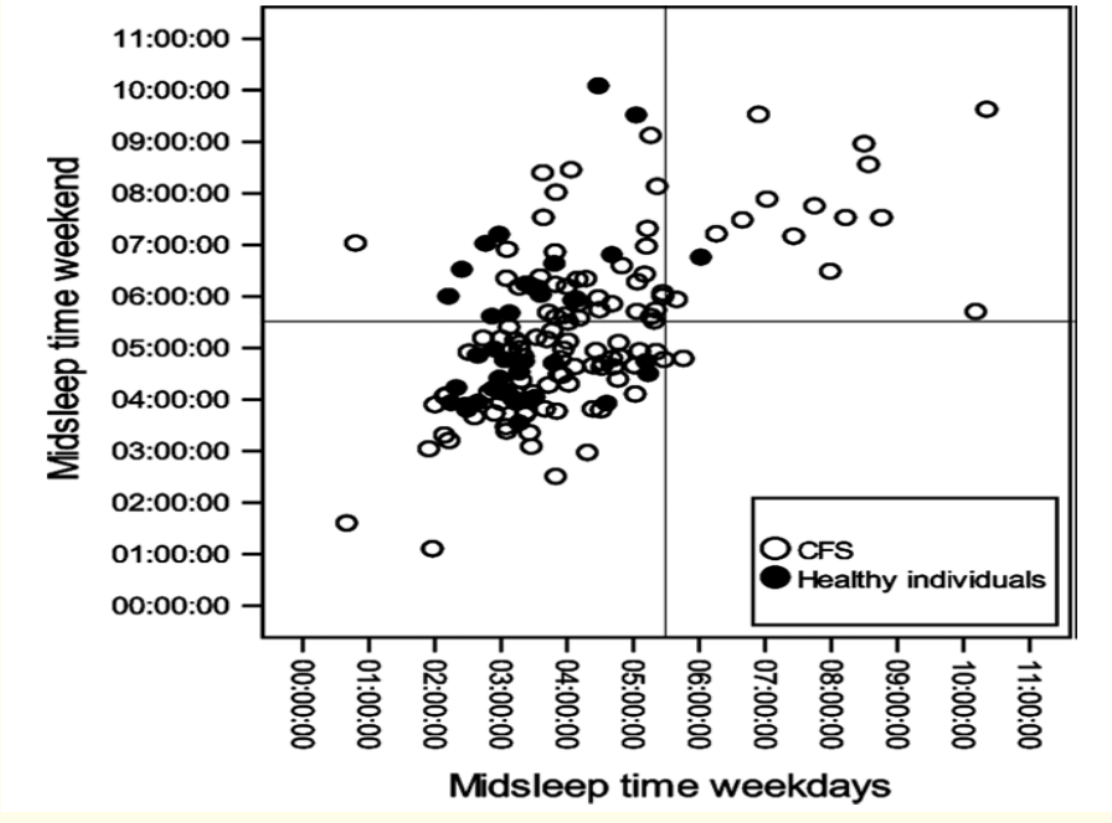


Figure 2: *Scatter plot in CFS versus healthy subjects. X-axis indicates midsleep time over weekdays. Y-axis indicates midsleep time over weekends. Right upper quadrant shows much more disturbed sleep rhythm in CFS group [11].*

Though this study provides good evidence of association between CFS and sleep disorder as 120 CFS subjects were recruited and there were statistically significant findings, the major drawback of study was the accelerometer sleep algorithm validation was not done prior to use.

Davidson., *et al.* [12] conducted a two year follow up study in which 15 patients with CFS were followed up and compared for subjective measures like Sleep diaries and questionnaires. Results suggested no significant change in subjective measures over period of 2 years. 7 patients also agreed to 2 night follow up PSG and it was observed that these patients had increased duration of NREM stage 1 ($P < 0.01$). Further, as per PSG finding 7 patients also had greater incidents of awakenings in one hour as compared to recordings done 2 years ago [12].

Although results indicate changes in objective measures like PSG scorings in CFS patients over the years however lesser number of patients (n = 7) does not substantially support evidence pertaining to CFS as a Sleep disorder. Epidemiological studies at a much larger sample size are required to be conducted to rule out causal relationship between Sleep disorder and CFS.

Pajediene., *et al.* [13] conducted a PSG based study in which 381 patients were screened for CFS and finally 78 patients underwent PSG study. These patients were evaluated for existence of sleep disorder which can be diagnosed based on PSG recordings. It was observed that 69.3% of patients who underwent PSG had one or more kind of sleep issue.41% of them were diagnosed as RLS while 40.3% had sleep apnoea. Some patients also reported periodic limb movement (8.9%).

This study shows promising results of association between CFS and Sleep disorders. Main concern in this study is no evidence on causal relationship between the two. There is high possibility that these two pathologic conditions share a common pathway and are more likely to be comorbid conditions rather than being an etio-pathological factor.

Discussion

Chronic fatigue syndrome is a complex disorder and so is sleep disorder pathophysiology. Over last two decades multiple studies (primarily observational) have been conducted to rule out association between CFS and sleep disorders. Concept under evaluation is whether CFS is a sleep disorder or not. Most studies considered subjective measures of sleep for ruling out sleep disorders in CFS patients (Table 3). CFS patients contributed to clinically significant fatigue and sleep disturbances based on sleep diaries, questionnaires and other subjective measures [1,3,5]. However, co-existence of sleep derangement based on subjective measures does not guarantee that CFS is a sleep disorder. Further, none of the studies investigated mechanism involved in genesis of sleep problems in CFS patients as available evidence is based on observations rather than interventional clinical studies. On the other hand, objective measures of sleep provided different picture with respect to CFS and sleep disorders as much of the evidence indicated poor association. In an observational study conducted by Majer., *et al*. 2007, PSG and MSLT indicated no sleep pathology in CFS. Another study indicated that CFS patients reported poor quality sleep, longer duration in bed ($P < 0.01$) and lesser sleep efficiency ($P < 0.03$) on subjective measures only [4]. As per Creti., *et al.* [8] sleep derangement reporting in self-reporting questionnaires did not correspond to findings of PSG and Actigraphy.

Contrarily, some scientists also reported evidence pertaining to sleep derangement in CFS based on objective measure like PSG and actigraphy. Patients with chronic fatigue had statistically significant sleep pathology as per PSG when compared to controls (Fisher's exact test $P < 0.0001$) (Hossain., *et al*. 2002). Another study provided evidence pertaining to REM percentage increase in CFS group ($P < 0.05$) [5]. As per Fossey., *et al*. [6] CFS patients had higher prevalence of sleep disorders as compared to healthy control group (chi square test $p < 0.005$). One of PSG evaluation CFS group showed higher frequency of apnoea than controls ($p = 0.003$) (Reeves., *et al*. 2006).

Hossain., *et al*. 2002 studied association between CFS and sleep disorders in shift workers. Team investigated whether shift workers had tendency to develop chronic fatigue based on sleep pathology. They conducted cross sectional study comprising of patients with chronic fatigue (n = 21) and with no fatigue (n = 21). It was observed that patients with chronic fatigue had statistically significant sleep pathology as per PSG when compared with controls (Fisher's exact test $P < 0.0001$). This study provided evidence pertaining to involvement of sleep pathology in genesis of chronic fatigue in shift workers [14-20].

Conclusion and Future Considerations

CFS is a complex disorder and requires significant expertise for diagnosis as symptoms overlap with other sleep disorders. Differential diagnosis is key aspect to be taken into consideration for CFS for which subjective and objective measures as Sleep diaries, PSG, actigraphy and MSLT etc. can be utilized. Till now studies have demonstrated significant difference in findings of subjective versus objective measures of sleep assessment. On one side where, subjective measures indicate association between CFS and sleep disorders and to some extent causal relationship between the two especially conditions like shift workers. However, various scientific groups have observed that subjective findings could not be translated to objective findings based on PSG, actigraphy results. Hence, there is disparity among researchers regarding association between CFS and sleep disorders. Overall there is limited evidence to conclude that chronic

fatigue syndrome is a sleep disorder. Current research suggests that these two conditions can be more of comorbid rather than having a causal relationship. Hence there is a mix type of evidence which tries to build relationship between the two but definite conclusion clearly demonstrating CFS as a sleep disorder cannot be reached.

Differential diagnosis of CFS, clarity of symptomology, interpretation and linkage of subjective versus objective measures of sleep is required to make final recommendations in this subject matter. Functional imaging and other novel techniques need to be employed to find relationship between the two.

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