

Original Article

The Experience of Cancer-Related Fatigue and Chronic Fatigue Syndrome: A Qualitative and Comparative Study

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Abstract

*Cancer-related fatigue (CRF) is a common and disabling symptom complex reported by survivors. This study aimed to better understand the manifestations of CRF in women treated for breast cancer, and to compare them with those of women diagnosed with chronic fatigue syndrome (CFS). Women with CRF persisting 6 months after treatment for early stage breast cancer, and women with CFS participated in separate, audiotaped focus groups. Transcripts of the sessions were analyzed using the NUD*IST software, and interpreted using grounded theory. Twenty-eight women participated, 16 with CRF and 12 with CFS. Analysis of transcripts from both groups revealed a similar core set of symptoms, featuring fatigue, neurocognitive difficulties, and mood disturbances. Women with CFS reported additional symptoms including musculoskeletal pain and influenza-like manifestations. Both groups suffered disabling behavioral consequences of the symptom complex. Qualitatively, CRF appears closely related to CFS. These findings raise the emergent hypothesis of a conserved neurobehavioral symptom complex, which results from diverse triggering insults. J Pain Symptom Manage 2007;■■:■■-■■. © 2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Cancer-related fatigue, chronic fatigue syndrome, fatigue, neurocognitive disturbance, mood disorder, sleep disorder

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Background

The combination of surgery and adjuvant treatment for early stage breast cancer is associated with a 90%–95% cure rate.¹ Cross-sectional studies consistently record a high prevalence of prolonged fatigue often persisting many years after successful treatment for cancer.^{2–4} Recent prospective studies in both testicular cancer and Hodgkin's disease survivors also identified high rates of fatigue lasting

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months to years after treatment.^{5–7} Such fatigue syndromes are under-recognized by physicians and underreported by patients.^{8,9}

Cancer-related fatigue (CRF) has been proposed as a separate diagnostic entity in the International Classification of Diseases 10th Revision-Clinical Modification.¹⁰ These criteria emphasize the complaint of fatigue, accompanied by reported disturbances in cognitive performance and sleep, as well as loss of motivation. These manifestations should be causing functional impairment and be unexplained by comorbid psychological disorder (see Table 1). These components are very similar to the diagnostic criteria for the more prevalent disorder, chronic fatigue syndrome (CFS).¹¹ As CFS commonly follows from acute infections such as glandular fever,¹² the criteria also emphasize occurrence of additional symptoms including sore throat, headaches, and joint pain.

The focus group methodology is commonly used to assist in developing a systematic record of poorly characterized illnesses in health sciences research.¹³ The facilitated interaction between participants with shared experiences is a key component.¹⁴ This study describes the characteristics of the unexplained fatigue state following successful treatment for early stage breast cancer (termed here postcancer fatigue [PCF]), and compared those characteristics with those of women diagnosed with CFS. The findings raise the suggestion that both fatigue states represent relatively stereotyped

manifestations of the host response to a traumatic insult.

Method

The sampling method for this focus group study was systematic nonprobability (i.e., purposive) sampling¹⁵ with subjects chosen because they reported the phenomenon under investigation—a prolonged and unexplained fatigue syndrome. Women were screened for prolonged fatigue using the SPHERE questionnaire,¹⁶ which assesses a wide range of somatic and psychological symptoms commonly reported in medical and psychiatric settings. Reliability and construct validity of the instrument in identification of prolonged fatigue states have been demonstrated,¹⁷ including in women following adjuvant treatment for breast cancer.¹⁸

Twenty-four consecutive women, who attended outpatient clinics in the Department of Medical Oncology at the Prince of Wales Hospital, Sydney, Australia and who reported prolonged fatigue after completing treatment for cancer were approached. For inclusion, these women were required to meet study criteria for PCF, that is, the symptom complex met the diagnostic criteria for CRF,¹⁰ and the symptom complex had been present for at least six months after completion of adjuvant treatment for early stage breast cancer (i.e., Stage I or II). Women were excluded if their

Table 1
Diagnostic Criteria for CRF¹⁰

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- A. Six (or more) of the following symptoms have been present every day or nearly every day during the same two-week period in the past month, and at least one of the symptoms is significant fatigue.
- Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
 - Complaints of generalized weakness or limb heaviness
 - Diminished concentration or attention
 - Decreased motivation or interest to engage in usual activities
 - Insomnia or hypersomnia
 - Experience of sleep as unrefreshing or nonrestorative
 - Perceived need to struggle to overcome inactivity
 - Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
 - Difficulty completing daily tasks attributed to feeling fatigued
 - Perceived problems with short-term memory
 - Postexertional malaise lasting several hours
- B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.
- D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatisation disorder, somatoform disorder, or delirium.
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treating oncologist indicated that they had evidence of significant comorbid medical (e.g., anemia, cardiac, or endocrine disease) or psychiatric (e.g., psychotic disorder, substance abuse) conditions that could explain the fatigue state.

A comparison group of 20 women with CFS was approached, from the practices of two specialist physicians in the same hospital—one in infectious diseases and one in immunology. Women were included if they had received a diagnosis of CFS in accordance with the international diagnostic criteria.¹¹

Women were excluded if they were unable to converse fluently in English. The institutional ethics committee approved the study, and written informed consent was obtained from all subjects before participation.

Focus Groups

Women with PCF and CFS participated in separate focus groups. Each woman participated in one focus group with three to six participants. Authors (BB and DG) acted as facilitators. The predetermined framework for the sessions was based on a series of brief, open-ended questions relating to symptoms and their consequences. After introductions and outline of the purpose of the group, the opening question (aimed at identifying illness characteristics that participants had in common) was “Describe any problems or symptoms you have had since finishing treatment...” (or “since the onset of illness...” for women with CFS). Then followed questions seeking to encourage participants to interact and discuss their experiences. For example: “Would you explain to me what it (the symptom) meant for you?” or (to encourage participation) “Could you explain what your own experiences have been like?” The sessions were continued until no new information was obtained—that is to “saturation.” The session was closed with a summary question by the moderator such as “Have we missed anything?”

All sessions were recorded on audiotape. The focus groups were conducted in a relaxed atmosphere (e.g., refreshments were provided) and participation “ground rules” were stated at the outset, emphasizing that there were no right or wrong answers, and highlighting privacy and confidentiality. The data collection process was interactive in that

information gleaned from one focus group was used to inform the process for the subsequent group within the two diagnostic categories (i.e., PCF and CFS).

Following each session, tapes were transcribed verbatim. All identifying characteristics were removed from transcripts and fictitious names substituted.

Data Analysis

An approach consistent with the grounded theory tradition¹⁹ was chosen for the analysis.¹³ Grounded theory research seeks to produce rich descriptions and theoretical explanations of the phenomenon under investigation. Analysis commenced as soon as possible after each group was completed. Transcripts were imported into the NUD*IST software program (Non-numerical Unstructured Data Indexing, Searching, and Theorising),²⁰ which facilitates the organization and analysis of qualitative data.

The coding and categorization were performed by BB. At each stage of the analysis, the coding schema was developed by consultation and discussion with an experienced oncologist (DG) and a highly experienced clinical researcher in relation to fatigue syndromes (AL).

Data analysis was a multistage process. First level of analysis, *coding of symptom concepts*, entailed a thorough word-by-word, line-by-line examination of transcripts to identify and label the experiences described. It was aimed at capturing each woman’s own meaning, and generated a large number of preliminary concepts. This process also involved continued comparisons when identifying, clarifying, and differentiating the concepts. Initial data reduction was achieved by grouping together very closely related descriptions of individual symptoms provided by subjects within each session. Second level of analysis required *interpretation of the data*. Preset classification schemes were avoided. Clusters of coded symptom concepts, very similar in meaning or which consistently co-occurred, were categorized into more abstract level notions. Additionally, elements describing symptoms were separated from the behavioral consequences of the symptom or symptom cluster. Categories were then linked based on their properties. For the third level of analysis *axial coding*, data were repeatedly

and exhaustively reexamined and compared to ensure that no concepts had been omitted and no categories overlooked or inappropriately merged (i.e., that saturation had been reached). The aim of axial coding was to inform a model of the symptom paradigm for each illness.

Results

Focus Groups

Sixteen of 24 eligible women with PCF (67%) agreed to participate. Twenty women with CFS¹¹ were approached and 12 agreed to participate (60%). The women who refused or were unable to participate, predominantly did so because they reported that they were “too fatigued” to travel to the hospital. Women who were approached but did not participate did not differ significantly in age or illness characteristics (data not shown). A total of seven groups (three PCF and four CFS), each comprising three to six women, were conducted with each session lasting 60–90 minutes. The characteristics of the women in both groups are displayed in Table 2. Women with CFS were younger ($P=0.005$) than those with PCF, and had on average been symptomatic longer (88 months vs. 21 months, $P=0.05$).

Analysis of Transcripts—PCF Groups

Where possible the women’s own words were used initially to label the phenomenon

or symptom being described. For the purposes of analysis and presentation, these descriptions were uniformly modified to the present tense: “*I am very tired*”; “*my brain’s gone*”; “*I have no energy...*”; “*...now I’m lost for the word*”. In this preliminary round, 86 symptoms relating to the experience of PCF were identified. Where synonyms or very closely related symptoms were described, these were grouped together and identified as describing the same symptom—for example, “*I lose concentration...*,” “*I seem more absent-minded,*” and “*I can’t fully concentrate on anything*”.

These 86 coded symptoms were sorted into four categories that were supported following continued reexamination of the data. The categories identified (see Fig. 1) were 1) *fatigue*, which included “abnormal tiredness” implying exaggerated fatigue after activity; “lack of energy” implying fatigue at rest; and “unrefreshing sleep” describing the sense of awakening from sleep without renewed energy; 2) *neurocognitive impairment*, including difficulties with “memory” particularly short-term memory; and “attention” notably inability to sustain mental activity; and with “verbal fluency” including a sense of increased hesitancy in finding the words and sometimes feeling “lost for the word”; 3) *mood disturbance* components, including feelings of “sadness,” “frustration,” and “worry”; and 4) the final category included “*miscellaneous symptoms*”—for instance those associated with menopause such as hot flushes, or (as one woman reported) the onset of classical migraine headaches.

The behavioral impact of the symptoms was identified as a second categorization schema—these fell into three domains including 1) *physical*: “*I can only do a handful of things - I know I used to be able to do...*,” “*...I used to jump fences. I can’t jump fences any more...*”; 2) *psychological*: “*worrying that something had gone wrong*” (i.e., that the disease had progressed or that the treatment had not been effective), “*I am totally in fear the whole time,*” and “*I feel this need to cry...*” These descriptions also included more pervasive manifestations, suggesting underlying anhedonia such as “*...I think I can’t be bothered doing it. I have no inspiration to do that at all...*,” “*You just lose interest*”; and 3) *social consequences*, such as “*I feel I can only cope with going to work and not doing all the other things that I did before,*” “*I can’t even read a newspaper. I’ve not*

Table 2
Characteristics of the Women with Prolonged Fatigue Participating in the Focus Groups

Illness characteristics	Subject Groups	
	PCF ($n=16$)	CFS ($n=12$)
Mean age (years) (range)	56 (43–71)	44 (31–67) ^a
Time posttreatment (CRF) or time since diagnosis (CFS) (months)	21 (6–48)	88 (30–500) ^b
Breast cancer treatment		
Mastectomy, % (n)	63 (10)	
Lumpectomy, % (n)	37 (6)	
Chemotherapy, % (n) ^c	100 (16)	
Radiotherapy, % (n)	69 (11)	
Tamoxifen, % (n)	50 (8)	

^a $P=0.005$.

^b $P=0.05$.

^cIncludes women who received combined chemotherapy and radiotherapy.

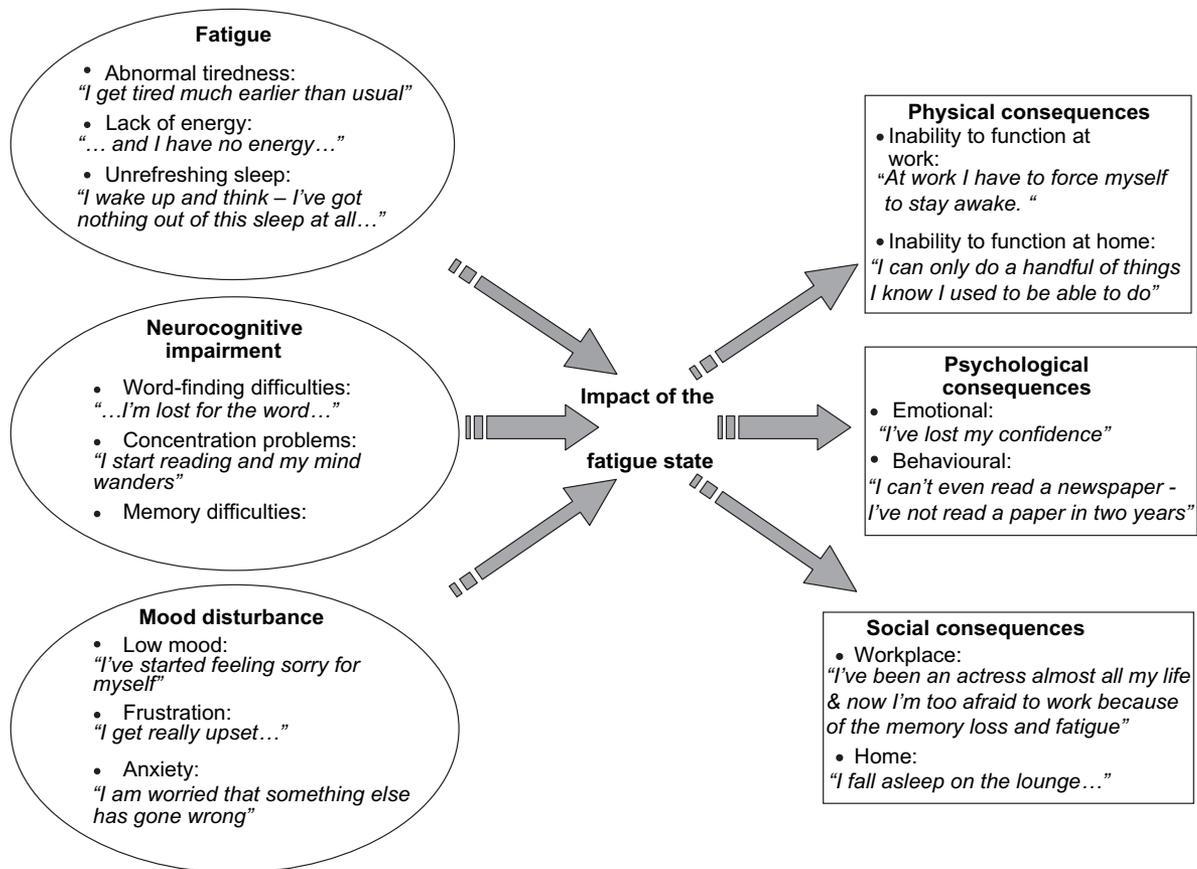


Fig. 1. Characteristics of PCF—analysis of focus group transcripts.

read a newspaper in two years...." All women with PCF reported that the prolonged course of illness was a totally unexpected occurrence "because nobody warned me it would take me so long to even start to feel better." For many women both social and economic consequences were profound. "I get lots of nice social invitations...but I refuse a lot ...I just have to miss out." "I forget many things, I start doing one thing and then forget what it was and end up doing something else." "It's a disempowering thing, because you're not on deck when everything is happening in the family and at work. At work you have to force yourself to stay awake of course." "At times I believe I'm living in a body 15 years older than it need be..." "But I haven't really got right back into life. I don't work."

Analysis of Transcripts—CFS Groups

Data from the CFS groups were analyzed using the same three level process. The initial coding identified 80 symptoms. Interestingly, a number of very similar constructs emerged,

with women using many almost identical descriptors to those used by the women with PCF (see Fig. 2). For example, in describing the feeling of fatigue "...it is such an effort to do that simple task...", "I feel like I have run a marathon...", "the body is so tired, heavy," "just complete lethargy and no energy." Unrefreshing sleep was also a ubiquitous complaint: "I guess I don't remember when I last woke up in the morning and actually felt refreshed," "When you wake up you feel like you haven't slept." Similarly, neurocognitive symptoms were described as "it's really hard you know...to remember words," "I am often searching for the right word." Although the categories comprising "fatigue," "neurocognitive impairment," and "mood disturbance" were essentially indistinguishable between the two groups, women with CFS also commonly reported an additional category of somatic symptoms. Many were of a musculoskeletal nature: "I also get really bad muscle pains when I lay in bed," "I wake up stiff and achy...like you've run

Post-cancer fatigue	Chronic fatigue syndrome
<p>Fatigue</p> <ul style="list-style-type: none"> ● Abnormal tiredness: "I'd get tired much earlier than usual" ● Lack of energy: "and I have no energy..." ● Unrefreshing sleep: "I'd wake up & think...I've got nothing out of this sleep at all..." 	<p>Fatigue</p> <ul style="list-style-type: none"> ● Abnormal tiredness: "I am so tired & heavy that I can't stand." ● Lack of energy: "complete lethargy & no energy..." ● Unrefreshing sleep: "But I never wakeup fresh, not like I used to..."
<p>Neurocognitive impairment</p> <p><i>Impaired: –</i></p> <ul style="list-style-type: none"> ● Verbal fluency: "...I'm lost for words..." ● Concentration: "I start reading & my mind wanders..." ● Memory : "I have no memory..." 	<p>Somatic</p> <ul style="list-style-type: none"> ● 'Flu-like symptoms: "...constantly feel like I am getting the flu all the time." ● Musculo-skeletal: "... muscle heaviness and aches and pains..." ● Abnormal sensitivities: "I seem to be a lot more sensitive to so much more foods." "like me with the smell..."
<p>Neurocognitive impairment</p> <p><i>Impaired: –</i></p> <ul style="list-style-type: none"> ● Verbal fluency: "Its really hard - you know - to remember words." ● Concentration: "You read one sentence over & over again." ● Memory: "...brain won't work, I can't remember anything." 	<p>Mood Disturbance</p> <ul style="list-style-type: none"> ● Low Mood: "I've started feeling sorry for myself..." ● Frustration: "... I get really upset..." ● Anxiety: "I am worried that something else has gone wrong"
<p>Mood Disturbance</p> <ul style="list-style-type: none"> ● Low Mood: "...it does depress me..." ● Frustration: ". The most frustrating thing.... is I want to be doing things and I can't" ● Anxiety: "and then developing anxiety about not coping..." (with work) 	

Fig. 2. Comparison of the characteristics of PCF and CFS—analysis of focus group transcripts.

around the block all night,” “I have the most incredible pain in my joints.” A small number of women with CFS also reported that they constantly felt as though they were “...getting the flu all the time...,” while others described heightened sensitivity to light, noise, or odors (e.g., perfumes) “My sense of smell has become incredibly heightened. I have discovered baby powder is something that makes me feel really, really ill.”

Closely analogous to the descriptions of the women with PCF, the women with CFS also reported physical, psychological, and behavioral consequences of fatigue: “I have no energy and I can’t wait to get home from work. It’s sad because I never used to be like that”; “I go to bed at 8 o’clock, half past 7 maybe...because I can’t stay up any longer”; “Last year I would have gone out about four times, and I’m single, so that’s a great life isn’t it!”; “I took time off because I realised that I was doing a very poor job in the classroom”; “I think one of the most frustrating things was that I wanted to be doing things and I just couldn’t...”; “I found I was often searching for the word. I couldn’t actually find the word I wanted ... which being an English teacher was somewhat of a problem!”

Discussion

Prolonged fatigue states following cancer treatment have been documented to cause substantial reductions in quality of life and functional status.^{8,9,21} In common with other fatigue syndromes, such as postinfective fatigue²² and CFS,^{11,23} the underlying mechanisms of the illness are unknown. A fundamental question is whether these illnesses share clinical characteristics and potentially therefore pathogenic mechanisms.

This report describes the spectrum of symptoms in the unexplained fatigue state after otherwise successful treatment for early stage breast cancer. Somatic, neurocognitive and affective symptoms were described, which led to significant negative physical, psychological, and social consequences. Earlier studies using^{24,25} unstructured interviews were focused on subjects still on treatment. The study reported here is the first to use the focus group methodology to provide an empirical description of PCF in cancer survivors. In both CRF²⁶ and CFS,¹¹ the diagnosis is currently made on the basis of criteria derived by expert

consensus rather than empirically derived datasets. It is generally reassuring to note that the 11 symptom criteria listed in the case definition for CRF¹⁰ were disclosed by women in this study. For instance, as expected, the complaint of fatigue was prominent in the sessions, and was consistent with the various descriptors in the case definition (“...disproportionate to any recent change in activity level”; “post-exertional malaise lasting several hours”). Most women described the fatigue state as being excessive in relation to the relatively limited physical activity undertaken and protracted in course. Similarly, impairments in concentration and short-term memory were commonly reported and are included in the case definition. One commonly reported neurocognitive disturbance, which is not a component of the definition, was difficulty with word finding. The case definition for PCF also lists a “perceived need to struggle to overcome inactivity” as one of the 11 symptoms. This phenomenon, which is suggestive of motivational loss was not described by the participants—instead the women generally reported that they struggled to overcome the limitations on physical and cognitive activity imposed by the fatigue state, which is more consistent with another element of the definition, “difficulty completing daily tasks attributed to feeling fatigued.” This finding suggests that modification of the former element of the diagnostic criteria should be considered.

An important feature of the descriptions provided by women with CRF was the element of mood disturbance. This is noteworthy as fatigue may be the presenting complaint of primary psychiatric disorders, including major depression and anxiety.^{27,28} Up to 47% of patients with cancer experience major depression during or after adjuvant treatment,²⁹ although in the presence of a physical disorder, such psychiatric illness is often hard to formally diagnose (as symptoms such as fatigue overlap between the diagnostic criteria).^{29,30} Although the women with CRF in this study were excluded if an alternative medical or psychiatric disorder could explain the fatigue state, it is readily apparent that symptoms of mood disturbance were prevalent. This finding argues against the arbitrary exclusion of patients with major depression from the diagnosis of CRF—instead a more sophisticated

consideration of the symptom of depressed mood, and the possibility of comorbid major depression as a syndromal diagnosis in conjunction with the fatigue state is warranted.

Another prominent element of the mood disturbance in women with PCF was the fear (and associated anxiety) that the ongoing illness may be a consequence of tumor recurrence. In turn, this appeared to be related, at least in part, to the discrepancy between the illness experience and the expectations provided by the health care team, which suggested that following the end of adjuvant treatment, they would rapidly feel better. This observation points to the need for a better recognition of the prevalence of CRF in the medical oncology setting.

The symptom domains reported by women with CFS were remarkably similar to those described by women with CRF. Often women used almost identical phrases to describe the individual symptoms. The core symptom of fatigue, in particular, was described uniformly by the two groups. Women with CFS did report additional somatic symptoms including those designated as being influenza-like, as well as musculoskeletal pain. This finding suggests shared illness mechanisms in the two conditions. Several of the shared symptom domains have been subjected to formal testing for objective abnormality. For instance, studies of neuromuscular performance in patients with CFS indicate that the phenomenon of fatigue is attributable to a central (i.e., in the brain), rather than a peripheral (i.e., in the nerve or muscle) defect.³¹ No neuromuscular studies in patients with CRF have been reported. Regarding neurocognitive disturbance, a meta-analysis of 30 cross-sectional studies of formal testing of cognition in CRF and two recent prospective cohort studies have found generally consistent impairments of executive function, verbal memory, and motor function.^{32–34} Similar impairments have been demonstrated in patients with CFS.³⁵ However, in both contexts the majority of subjects do not demonstrate objective impairments in cognitive performance, highlighting the discrepancy in prevalence with the essentially universal symptom report.

A close relationship between fatigue and sleep disturbance was also evident in both subject groups. In healthy individuals, adequate

rest or sleep relieves physiological fatigue, resulting from physical exertion or sleep deprivation. However, women with PCF and CFS reported both hypersomnia (increased sleep requirements) and an unrefreshing sleep quality, but not other manifestations typical of primary sleep disorder such as daytime somnolence. Formal polysomnography in patients with CFS indicates that disturbances of sleep maintenance (e.g., frequent awakenings, restless legs) are prevalent, but primary sleep disorders are rare.³⁶ Formal sleep studies in patients with PCF have not been reported.

A limitation of this study is that the women studied were purposefully selected as having scored above a predetermined cut-off for fatigue states identified by questionnaire, and having met case definitions for PCF or CFS, including the requirement for exclusion of alternative explanatory medical and psychiatric disorders. Both stages of this prestudy evaluation may have influenced the type of patients included and consequently the outcomes of the analysis of symptom reports. Nevertheless, the findings suggest both shared, and potentially divergent mechanisms of disease. The pathogenesis of prolonged subjective fatigue states remains obscure, with the exception of acute infection, where such symptoms are believed to be immunologically mediated via the effects of proinflammatory cytokines on the CNS.³⁷ It has been hypothesized that similar mechanisms may be implicated in the pathogenesis of CRF³⁸ and CFS.³⁹

Further investigations of fatigue states in oncology and in other settings should take account of these phenotypic similarities.

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