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Sub-typing Daily Fatigue Progression in Chronic Fatigue Syndrome

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Abstract

Background—Activity logs involve patients writing down their activities and symptoms over one or more days.

Aims—The present study sought to classify daily fatigue patterns among patients with chronic fatigue syndrome (CFS) using activity logs.

Method—Fatigue intensity was self-reported every 30 minutes in a sample of 90 patients with CFS over one day. A cluster analysis using fatigue intensity, variability, and slope was conducted.

Results—Three clusters emerged involving patients with different trajectories. One group evidenced high fatigue intensity, low variability, and fatigue intensity stayed the same over time. A second group had moderate fatigue intensity, high variability, and fatigue intensity decreased over time. A third group had moderate fatigue intensity, high variability, but fatigue intensity increased over time. The three clusters of patients differed on measures of actigraphy, pain, and immune functioning.

Conclusions—Activity logs can provide investigators and clinicians with valuable sources of data for understanding patterns of behavior and activity among patients with CFS.

Keywords

Activity Logs; Daily Fatigue; Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a highly incapacitating illness characterized by a loss of stamina or endurance. Measurement of activity and CFS symptoms continues to pose a challenge for researchers (Jason & Choi, 2008). Questionnaires have been the preferred instruments in assessing patterns of behavior, physical activity, and fatigue (Paffenbarger, Blair, Lee, & Hyde, 1993), but questionnaires are vulnerable to recall bias and other threats to validity compared to electronic monitoring devices (Cartmel & Moon, 1992).

Patterns of behavior have also been assessed through activity logs. The National Institutes of Health Activity Record (ACTRE) is an example of a daily self-administered log of the quantity and intensity of an individual's physical activity and subjective experiences associated with the activity (Gerber & Furst, 1992). Hawk, Jason, and Pena (2007) found the ACTRE differentiated patients with CFS, Major Depressive Disorder (MDD) and controls. Those with CFS spent more time resting, performing low intensity activity, and experiencing fatigue than the other groups. Using the ACTRE, Jason et al. (2009) found a positive association between time spent feeling fatigued and time spent in pain, and a negative relationship with time spent in meaningful activities.

Useful information on dimensions of fatigue based on daily fatigue patterns may be gained from activity logs. Theoretically, there are three dimensions that can be assessed over a given timeframe including intensity (i.e., average fatigue severity), variability (i.e., magnitude of fatigue fluctuations), and slope (i.e., increases or decreases in fatigue severity). Yet, most fatigue measures only capture the overall amount of fatigue experienced without assessing the variability of fatigue over time (Jason et al., 1999). For example, someone with a very high level of fatigue that is stable might be more debilitated than someone with fluctuating patterns who experiences both high and moderate/low fatigue over the course of the day. Patterns of fatigue might also increase or decrease over the day, which may have implications for structuring daily activities.

Activity logs might allow investigators to better understand fatigue intensity, variability and slope over the course of a day. The purpose of the current study is to examine the utility of the ACTRE in sample of patients with CFS and determine if there are different clusters of patients in terms of their daily fatigue trajectories. We hypothesized that these clusters would be related to measures of immune functioning, activity, and impairment.

Method

Participant Recruitment

Participants were recruited for a non-pharmacologic treatment trial for CFS (citation omitted for peer review) from physician referrals, advertisements in local newspapers, and announcements at local CFS support group meetings. One hundred and fourteen individuals were recruited. Participants were required to be at least 18 years of age, not pregnant, able to read and speak English, and considered to be physically capable of attending the scheduled sessions. Participants met the Fukuda et al. (1994) criteria for CFS, stating individuals must experience fatigue and four of the following eight symptoms over six months: sore throat, tender lymph nodes, memory or concentration difficulties, post-exertional malaise, unrefreshing sleep, headaches, muscle pain, and joint pain. Medical and psychiatric examinations were performed to rule out exclusionary conditions (see [citation omitted for peer review] for more details). Fibromyalgia diagnoses were established during the medical examination based on the Wolfe et al. (1990) criteria.

Materials

The CFS Questionnaire was used to collect demographic and symptom data. This instrument evidenced good psychometric properties when administered to those with CFS, MDD, and controls (Hawk, Jason, & Torres-Harding, 2006). The CFS Questionnaire was used to assess the severity of the eight Fukuda et al. (1994) CFS symptoms. Participants self-reported the intensity of each symptom they endorsed on a scale of 0 to 100, where 0 = no problem and 100 = the worst problem possible.

The Structured Clinical Interview for DSM-IV (SCID; First Spitzer, Gibbon, & Williams, 1995) was used to establish Axis I psychiatric diagnoses and rule out exclusionary psychiatric disorders. In a psychodiagnostic study, Taylor and Jason (1998) validated the use of the SCID among patients with CFS.

The ACTRE is a daily self-administered log of physical activity and symptoms. Respondents log their activities every half-hour over the course of two days. The type (e.g., sleeping, work, etc.) of activity is rated. Respondents answer seven questions on four-point scales for every activity to assess whether the activity is associated with pain, fatigue, or perceived as difficult to perform, meaningful, enjoyable, or well done. Need for rest is also assessed every half-hour.

Using the ACTRE, clinicians are able to obtain a comprehensive profile of functioning as well as areas of dysfunction (Gerber & Furst, 1992). In a validation study, Gerber and Furst demonstrated that the ACTRE has adequate psychometric properties as a measure of activity and functional status in a population with a chronic disabling condition. The ACTRE is significantly correlated with other measures of fatigue (Gerber & Furst, 1992).

For this study, ACTRE data for one day were used to evaluate patterns of fatigue over the course of the day. Fatigue is rated on a four-point scale in response to the question, "At the beginning of this half-hour I felt fatigue," with 1 = not at all; 2 = very little; 3 = some; and 4 = a lot. Fatigue ratings were only counted when participants were awake, as fatigue ratings were invalid when asleep. Only ratings between the hours of 8:00am and 10:30pm were used because these timepoints encompassed the greatest portion of the sample when awake. Participants' mean, standard deviation, and slope of fatigue ratings were computed.

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; Ware & Sherbourne) was used to assess health-related functioning. The SF-36 contains eight subscales: Physical Functioning, Social Functioning, Role-Physical, Role-Emotional, Bodily Pain, General Health, Vitality, and Mental Health. A higher score indicates less impact of health on functioning. The SF-36 has demonstrated good psychometric properties (McHorney, Ware, & Raczek, 1993).

Krupp, LaRocca, Muir-Nash, and Steinberg's (1989) Fatigue Severity Scale (FSS) was used to measure fatigue severity in terms of behavioral consequences of fatigue. This scale includes 9 items rated on 7-point scales, with higher scores indicating more severe fatigue. The FSS was normed on a sample of individuals with multiple sclerosis, systemic lupus erythematosus, and healthy controls (Krupp et al., 1989).

The Brief Pain Inventory (BPI; Cleeland & Ryan, 1994) was administered to measure intensity of pain (pain severity) and interference in functioning due to pain (pain interference), with higher scores indicating worse pain. This measure exhibits adequate levels of reliability to assess pain in non-cancer samples, with coefficient alphas of .70 and above. It also evidences good concurrent validity with other generic pain measures, and has been shown to be sensitive to changes in pain status over time (Keller et al., 2004).

The Pittsburgh Sleep Quality Index (PSQI) was developed to measure sleep quality in psychiatric research (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This index measures sleep disruptions and sleep quality. Global PSQI scores range from 0 to 21, with higher scores indicating worse sleep quality.

Participants wore an actigraph (Tryon & Williams, 1996) on the waist for a one-week period. Actigraphy data were collected using an accelerometer to measure movement intensity. An 8-bit analog-to-digital (A/D) converter quantifies these measurements into units of positive or negative acceleration every 0.1 second, and final counts are recorded as 1.664 milli-g/count. The average of 600 A/D counts was stored every minute. Average daily actigraphy counts were used in this study.

Flow cytometry was conducted on blood draws to assess immunological functioning. The details of the flow cytometry methods used in this study were described previously (citation omitted for peer review), and the methods followed were based on the CDC's recommendations for flow cytometric analyses (Centers for Disease Control and Prevention, 1997). Data for this study included the total number of CD8 positive cells, with lower counts indicating lower anti-viral immune responses (lower TH₁). We also inspected the total number of CD56 cells (including CD3+ and CD3-), with higher scores suggesting a more

cellular type (TH₁) response. TH₁ to TH₂ ratios were computed, and participants were classified as having either a TH₁ or TH₂ shift in immune response.

Statistical Analysis

Using average fatigue intensity rating over the day, standard deviation (a measure of variability), and slope (a measure of increasing or decreasing fatigue), hierarchical cluster analysis was employed to explore whether individuals with these three scores could be categorized into distinct clusters. The squared Euclidean distance measure was selected, which places individuals in clusters based on the distance between individuals and represents the sum of the squared differences across all of the variables. In combining cases into clusters, we used the agglomerative hierarchical clustering method. The method used to decide which cases should be combined at each step was the average linkage within groups method. When we examined a dendrogram, three homogeneous clusters emerged. In addition, when looking at the agglomeration schedule, coefficients indicated that there was a fairly large increase in the value of the distance measure, from a 4-cluster to a 3-cluster solution. Fifty-three individuals were included in Cluster 1, 17 were in Cluster 2, and 20 in Cluster 3. A series of one-way analyses of covariance (ANCOVA) were conducted to evaluate the effect of cluster membership on outcomes, controlling for gender. Bonferroni post hoc tests were used for comparisons between groups.

Results

Participants

Of the 114 participants enrolled in the original study (citation omitted for peer review), 24 were excluded from the analysis because they did not complete the ACTRE. Of the remaining 90 participants, the mean age was 44.16 (SD = 10.72), and 76 (84%) were females. There was a significant effect of gender, $\chi^2(2, N = 90) = 6.96, p = .03$; with women representing 87% of Cluster 1, 65% of Cluster 2, and 95% of Cluster 3. There were no significant differences between the clusters on other sociodemographic characteristics or illness duration.

Clusters

Figure 1 shows fatigue ratings over time for the three clusters. Descriptively, Cluster 1 had high fatigue intensity that was fairly stable and slightly increased over the day. Cluster 2 had the lowest intensity, high variability, and an overall decrease over the day. Cluster 3 demonstrated a similar pattern of intensity and variability to Cluster 2; however, fatigue increased over the day. Table 1 provides the means and standard deviations for fatigue intensity, variability, and slope; and for the outcomes. Significant overall effects were observed for intensity, $F(2, 86) = 99.26, p < .001$; variability, $F(2, 86) = 23.39, p < .001$; and slope, $F(2, 86) = 42.14, p < .001$. Post hoc tests revealed Cluster 1 had significantly more fatigue and variability than Clusters 2 and 3. Cluster 3 had a significantly higher slope than Clusters 1 and 2, and Cluster 1 had a significantly higher slope than Cluster 2.

Fatigue and Symptom Measures

There were no significant differences between the three clusters on the FSS, CFS Questionnaire fatigue intensity measure, the eight Fukuda et al. (1994) symptoms, or the PSQI. For the BPI, significant effects were revealed for both the pain severity, $F(2, 82) = 7.60, p = .001$, and interference $F(2, 82) = 4.98, p = .009$, scales. Cluster 1 had significantly more pain severity than Clusters 2 and 3, and Cluster 1 had significantly more interference than Cluster 2.

Physical Functioning and Actigraphy

For the SF-36, significant overall effects were found for Vitality, $F(2, 86) = 3.98, p = .02$, and Bodily Pain, $F(2, 86) = 5.11, p = .008$. Cluster 1 had significantly more impairment in Vitality than Cluster 3. In addition, Cluster 1 had significantly more impairment due to Bodily Pain than Clusters 2 and 3. A significant effect was revealed for actigraphy, $F(2, 78) = 4.80, p = .01$, and Cluster 3 had significantly higher scores than Cluster 2.

Other Conditions and Biological Markers

There were no significant differences for current psychiatric diagnosis among the clusters. Chi-square analyses revealed a significant difference across clusters for fibromyalgia diagnosis, $\chi^2(2, N = 90) = 11.72, p = .003$. Those in Cluster 1 had a higher percentage of fibromyalgia than those in Cluster 2. A significant difference was found for TH₂ shift, $\chi^2(2, N = 90) = 9.48, p = .009$, with Cluster 1 showing a higher percentage showing a TH₂ shift than Cluster 3.

Discussion

The present study found three clusters of daily fatigue patterns among patients with CFS. Cluster 1 had the most fatigue, which was fairly stable over the course of the day, and this group experienced the greatest severity of pain. Cluster 2 had moderate levels of fatigue that decreased over the course of the day, with this group experiencing the lowest levels of pain. Cluster 3 had moderate levels of fatigue that increased over time, and this group experienced moderate levels of pain.

The finding that the more traditional measures of fatigue intensity, severity of the Fukuda et al. (1994) symptoms, and disability were not related to the three clusters was an unexpected outcome. Potentially, single assessments for intensity might not reflect the patterns of fatigue that occur over a day. Further, the amount of functional disability fatigue causes might not be represented in the fatigue patterns over a particular day. For example, a person might experience high levels of fatigue but continue to use all available energy to stay involved in work activities. Although this work activity might be necessary to survive economically and the level of functional impairment might not be evident, continuing to experience high levels of fatigue might result in later problems and impairments. Patients often talk about continuing to work for as long as possible until they are so functionally impaired that they can no longer maintain their employment.

The relationship of the clusters to the experience of pain was one of the more consistent findings. Cluster 1 had more fibromyalgia, more pain severity and interference, and more impairment due to bodily pain. It is certainly possible that the higher levels of pain within the members of this cluster led to lower vitality, and possibly higher fatigue ratings over the course of the day.

With regard to activity level, as measured by actigraphy, significant differences emerged between Clusters 2 and 3. The actigraphy measure indicated that Cluster 2, which had the lowest fatigue ratings that continued to decrease over the day, also had the lowest activity. In addition, Cluster 3 had moderate fatigue ratings that increased over the day had the highest activity ratings. Among a sample of people with CFS, Black, O'Connor, and McCully (2005) found that an average of a 28% increase in daily physical activity over four weeks resulted in worsening daily fatigue. It is possible that those who tended to be the most active had higher fatigue and those that were the least active had the lower levels of fatigue. Yet, Cluster 1 demonstrated the highest fatigue and the directionally middling activity level, and

it is possible those in Cluster 1 are particularly vulnerable to an adverse response to moderate levels of activity.

Those in Cluster 1 had a greater percentage of individuals with a Th₂ shift than Cluster 3. Hanson, Gause, and Natelson (2001) used neural-network classifiers to support this Th₂ shift among patients with CFS. In a non-pharmacologic intervention study, Jason et al. (2008) found those who improved had a Th₁ shift as indicated by the relatively expanded cytotoxic subsets (CD8, CD56), while non-improvers had a Th₂ shift. The current study further supports the contention that clinically distinct subsets of patients exist within the current definition of CFS. Such differences may explain some of the discrepant conclusions across CFS studies and highlight the need to define clinical subsets in CFS.

There were several limitations in the study. The data represent patterns of behavior for only one day, and as such, might not be representative of fatigue patterns over longer periods of time. In addition, it is unclear whether the one-day activity log data provided by participants is representative of their typical daily fatigue patterns. There is a need for more activity log data to be collected on larger groups of individuals for longer periods of time to attempt to replicate the findings in this study.

The present study used an activity log to examine patterns of fatigue for different clusters of patients diagnosed with CFS. These patterns were most closely associated with pain, and their lack of relationship to more traditional fatigue instruments suggests that they are measuring different dimensions of fatigue. Certainly, more research is needed, but this study suggests that activity logs can provide investigators and clinicians with valuable sources of data for understanding patterns of fatigue among patients with CFS.

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Figure 1.
Mean Fatigue Ratings Every Half Hour Between 8:00am and 10:30pm Among Three Clusters

Table 1

Descriptive Statistics for Outcomes for Three Clusters

	Cluster 1 n = 53	Cluster 2 n = 17	Cluster 3 n = 20	p
	M (SD)	M (SD)	M (SD)	
Cluster Variables				
Mean Fatigue ^I	3.34 (0.33) ^{a,b}	2.17 (0.44) ^a	2.43 (0.28) ^b	< .001
Standard Deviation Fatigue	0.43 (0.25) ^{a,b}	0.75 (0.21) ^a	0.79 (0.20) ^b	< .001
Slope Fatigue	0.17 (0.36) ^{a,b}	-0.49 (0.24) ^{a,c}	0.49 (0.26) ^{b,c}	< .001
Fatigue Severity Scale ^I	6.07 (0.88)	6.13 (0.62)	6.12 (0.72)	.84
Symptom Severity ^I				
Fatigue	75.28 (14.64)	77.32 (16.97)	66.78 (19.11)	.10
Sore Throat	22.59 (24.54)	16.32 (21.54)	26.25 (31.66)	.53
Tender Lymph Nodes	25.90 (29.32)	20.88 (32.37)	34.21 (32.29)	.71
Muscle Pain	63.81 (28.53)	42.35 (31.43)	61.48 (26.63)	.09
Joint Pain	51.57 (37.18)	33.24 (34.28)	41.00 (34.86)	.23
Memory/Concentration Problems	63.91 (20.46)	63.24 (28.77)	61.13 (26.30)	.92
Unrefreshing Sleep	79.04 (20.82)	80.84 (20.69)	78.76 (14.93)	.95
Headaches	54.95 (32.87)	35.03 (28.17)	61.71 (31.18)	.10
Post-Exertional Malaise	78.46 (14.37)	74.12 (19.38)	70.53 (23.74)	.22
Brief Pain Inventory ^I				
Severity	4.82 (2.12) ^{a,b}	2.80 (2.18) ^a	3.16 (2.05) ^b	.001
Interference	5.06 (2.90) ^a	2.56 (2.54) ^a	3.55 (2.90)	.009
Sleep (PSQI) ^I	8.04 (2.49)	8.18 (2.30)	7.00 (2.71)	.23
SF-36 ²				
Vitality	15.00 (14.54) ^a	18.82 (11.93)	25.75 (15.67) ^a	.02
Social Functioning	36.08 (23.60)	47.79 (21.30)	45.00 (26.41)	.13
Physical Functioning	40.94 (23.43)	54.41 (26.39)	51.00 (19.24)	.08
Role-Physical	4.72 (12.07)	2.94 (12.13)	6.25 (13.75)	.68
Bodily Pain	34.34 (20.69) ^{a,b}	50.47 (23.18) ^a	47.90 (19.06) ^b	.008
General Health	30.99 (18.61)	39.47 (18.68)	30.10 (14.30)	.27
Role-Emotional	57.23 (43.55)	43.14 (45.28)	60.00 (38.39)	.48
Mental Health	64.60 (18.24)	64.71 (17.85)	63.60 (15.24)	.98
Actigraphy Counts	153.23 (56.68)	125.04 (48.50) ^a	184.02 (48.99) ^a	.01
	n (%)	n (%)	n (%)	
Other Conditions				
Current Psychiatric Disorder	18 (34.0)	6 (35.3)	8 (40.0)	.89
Fibromyalgia	26 (49.1) ^a	1 (5.9) ^a	5 (25.0)	.003
Biological Markers				
TH ₂ Shift	26 (49.1) ^a	6 (35.3)	2 (10.0) ^a	.009

Notes: Similar letters across rows indicates a significant difference at the $p < .05$ level;

¹ Lower scores are better;

² Higher scores are better