Aspects of Diurnal Rhythmicity in Pain, Stiffness, and Fatigue in Patients with Fibromyalgia

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ABSTRACT. ***Objective.*** To determine diurnal rhythm characteristics of pain, stiffness, and fatigue in self-ratings performed by patients with fibromyalgia (FM).

Methods. Twenty-one women with FM made self-measurements of pain, stiffness, and fatigue on 100 mm horizontal visual analog scales at 6 prespecified timepoints at home for 10 consecutive days. Linear and multiple regressions were performed on the original data and the 24-hour means vs FM classifiers (age, disease duration, tender points, dolorimetry score, Fibromyalgia Impact Questionnaire score), respectively. Data were analyzed for 24-hour and 7-day time-effects by ANOVA and for diurnal and weekly rhythms by the cosinor technique.

Results. Individual ratings for pain, stiffness, and fatigue correlated highly with each other throughout the day and over the days of the week. Of the FM classifiers, dolorimetry score was found to be inversely related to the pain, stiffness, and fatigue scores. For the group of subjects with a low dolorimetry score (< 2.25 kg), a significant diurnal rhythm was found in each self-rated variable, with greater pain, stiffness, and fatigue observed in the morning and least in the late afternoon. No rhythm in pain or stiffness was observed in those subjects with a higher threshold for pain (dolorimetry score > 2.25 kg), while fatigue showed the same significant diurnal pattern as in the first group. For the group as a whole, the possible presence of a weekly variation was found with ratings for pain, stiffness, and fatigue higher on Sunday and Monday and lower on Friday.

Conclusion. Ratings of pain, stiffness, and fatigue in FM are significantly correlated, and show diurnal and possibly weekly rhythmicity, especially when pain threshold is low (dolorimetry score < 2.25 kg), and are thus predictive of each other over these time spans. This has important implications for scheduling activities of daily living, for measurement in clinical trials, and possibly for timing the administration of medications. (J Rheumatol 2004;31:379–89)

Key Indexing Terms:
FIBROMYALGIA PAIN DIURNAL RHYTHM STIFFNESS FATIGUE

Diurnal variation is common in biologic systems. Plants, animals, and humans display rhythmic variation at various levels from cell to entire organism. Rhythms that cycle roughly once per day are called circadian (or diurnal) rhythms[1], those of higher or lower frequency being respectively termed ultradian and infradian rhythms. A number of investigators have reported diurnal variations in clinical and laboratory variables in patients with either inflammatory or degenerative disorders of the musculoskeletal system[2-28]. Most often, these investigators have used traditional statistical models[29]. For some years, however, statistical methods based on least-squares and cosine-vector techniques, which permit the use of real-time data, have been used successfully by chronobiologists in mapping the absolute and relative timing of different biologic rhythms[30-33]. We have used such techniques in successfully identifying diurnal rhythms in rheumatoid arthritis pain, stiffness and manual dexterity[2], in pain in knee osteoarthritis (OA)[3], and in pain, stiffness and manual dexterity in hand OA[4]. These effects appeared intrinsic to the disorders, and were not explained by drug ingestion (analgesic or nonsteroidal antiinflammatory class agents) or fluctuations in climate (Environment Canada Statistics). Diurnal characteristics for these studies and more than 100 variables found in the literature that are pertinent to immune function and disease have been recently summarized[34]. The identification of such rhythms has important implications for patients with respect to planning their daily activities and in developing individual therapeutic programs with respect to diurnal variability, which therefore may be more effective (so-called chronotherapy regimens).

For similar reasons, evaluation of the time profile of symptoms in fibromyalgia (FM) has implications for patient management and activity planning. In particular, if significant diurnal variation does exist in pain, stiffness, and

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fatigue, it may be possible to develop drug therapy regimens tailored to the requirements of individual patients. Further, knowledge of diurnal variation in FM might permit patients to plan their activities around predictable fluctuations in their physical functioning. Reports suggest the variable presence (pain, fatigue, alertness)[35,36] or absence (pain, stiffness)[36] of diurnal variation in FM symptoms. We reevaluated this controversy in outpatients with FM who performed self-ratings of pain, stiffness, and fatigue 5 or 6 times each day over 10 consecutive days and whose data were analyzed for daily and/or weekly rhythmicity.

MATERIALS AND METHODS

Study design. A quasi-experimental one-group repeated-measures design was used, patients being followed for 10 consecutive days and performing self-measurements at home at prespecified time-points. All patients slept at night, with the average bedtime at 12:30 a.m. and waking at 7:30 a.m. The study was approved by the University of Western Ontario Review Board for Research Involving Human Subjects.

Patients. Twenty-one outpatients fulfilling the American College of Rheumatology (ACR) classification criteria for FM were assessed[37]. English-speaking female patients aged 20–50 years who were symptomatic (i.e., pain, fatigue, stiffness) for at least 3 months all provided informed consent. The following exclusion criteria were applied to patients: (1) starting physiotherapy in the next 10 days; (2) unable to comprehend the visual analog measurement scales (VAS); (3) unavailable to perform self-measurement for the next 10 days; (4) requiring a planned change in therapy in the next 10 days; (5) having comorbid condition causing pain, stiffness, or functional disability; (6) having symptoms precipitated by motor vehicle accident; and (7) who were pregnant or lactating females, and males.

Method. At baseline, the following information was collected: age, disease duration, ACR classification criteria, Fibromyalgia Impact Questionnaire (FIQ)[38], number of tender points, dolorimetry score[39], and current medications (drug dose and dosing schedule). The FIQ is a 10-component 19-item questionnaire developed to assess the influence of FM on various health dimensions[38]. Dolorimetry was conducted using a 9-kg Chatillon dolorimeter (John Chatillon and Sons, Kew Gardens, NY, USA) applied in a standardized fashion[39] at 18 different trigger points. Patients self-measured pain, stiffness, and fatigue at the following target time-points each day: wake-up, 10:00 a.m., 2:00 p.m., 6:00 p.m., 10:00 p.m., and bedtime. Patients were specifically instructed to look at a watch or clock and record the actual time at which they performed self-measurement, since it was unlikely that over the 10-day period the measurements would be performed exactly at the specified times. The collection of real-time data was critical to the success of the analysis because of the potentially dynamic fluctuation that could occur in the 3 variables.

VAS questionnaires were used for self-measurement and subjects were instructed to rate the severity of each item at the exact moment of measurement. Pain was self-rated on a 100 mm horizontal VAS with end markers and terminal descriptors (left = no pain, right = most severe pain I have ever had). Stiffness was self-rated on a 100 mm VAS with end markers and terminal descriptors (left = no stiffness, right = most severe stiffness I have ever had). Fatigue was self-rated on a 100 mm VAS with end markers and terminal descriptors (left = no fatigue, right = most severe fatigue I have ever had).

Subjects were instructed to complete the questionnaire at or near the time points indicated, and, in any event, record accurately the actual clock time at which the observation was made. Subjects waking after 10:00 a.m. or going to bed before 10:00 p.m. would sometimes have less than the 6 designated observation points per day. All data recorded were referenced to real-time date and clock hour. In addition, patients were requested to note at the end of each day the time, dose, and brand of any analgesics taken for any purpose during that day.

Statistical analysis. Chronograms were constructed for each data series in order to view the individual data for patterns, trends, and outliers. No data were excluded from analysis. Descriptive statistics were used to summarize the arithmetic mean, the lowest and highest data values, and the range between these (range of change, ROC). Individual data series were converted to a percentage of the mean value before constructing overall waveforms for diurnal (about 24-hour) and weekly (about 7-day) frequencies for the 3 variables of interest. Time-series analyses were performed using both original units and values as percentages of mean. A one-way analysis of variance (ANOVA) was used to test grouped data for a time effect at 24 hours and 7 days. Each individual series was analyzed for diurnal rhythmicity by the least-squares method of fitting of cosines (single cosinor method)[30-32] with periods in the expanded diurnal range between 14 and 34 hours[33] with 0.1 hour between trial periods. Rhythm characteristics at precisely 12:00 midnight were summarized for the group by population mean cosinor analysis[31]. Rhythm detection was considered statistically significant if $p \leq 0.05$ from a zero-amplitude test and borderline significant if $p \leq 0.10 > 0.05$. Rhythm characteristics estimated from the single cosinor procedure include the mesor (middle of the fitted cosine, representing a rhythm-adjusted mean that differs slightly from the arithmetic mean, when data are collected at uneven intervals), the amplitude (the distance from the mesor to the peak or trough of the fitted cosine), and the acrophase (peak of the fitted cosine with reference to local midnight). As has been our common practice in evaluating rhythmic variation in other disorders[2-4], and as specified a priori in the study protocol, we discarded the first 3 days of data to eliminate any learning effect that patients may have encountered in making responses on VAS. Similar analyses were performed using the trial period of 168 hours (7 days) to test for any weekly time-effect. An inventory of classifiers[37,38] was created in order to identify subgroups in the data. A multiple regression was performed to determine if any of the 5 FM classifiers (disease duration, age, number of tender points, dolorimetry, and FIQ score) served as predictors of the 24 h mean self-rated scores of pain, stiffness, and fatigue. Analyses for circadian time-effect were rerun after subgrouping the subjects according to findings from the multiple regression.

RESULTS

Twenty-one females with FM, of mean age 34.3 years (range 20–48 yrs), participated in the study. FM classifiers are listed for each subject in Table 1. Self-ratings of questionnaires were completed during January, February, and March, with subjects starting their data collection on different days of the week [most (n = 15) started on a Monday, 2 on Wednesday, and one on a Tuesday, Friday, Saturday, or Sunday]. No participant was involved in night or shift work in the period of the study or indulged in transmeridian travel during the course of the study. Multiple regression revealed a significant correlation between the Dolorimetry Score at $p < 0.001$ and each of the 24 h mean ratings for pain, stiffness, and fatigue (Figure 1), suggesting that the intensity of pain perception measured by dolorimetry was inversely related to the overall magnitude of the self-ratings. No other classifier (age, disease duration, tender points, FIQ score) was predictive of self-rated scores. In addition, a correlation of all 1206 raw values of the self-ratings revealed a highly significant ($p < 0.0001$) relationship among variables, suggesting that a rating of pain could serve as a predictor of a similar level for stiffness or fatigue, etc. (Figure 2).

Table 1. Subject age and disease characteristics.

Subject	Age, yrs	Disease Duration, yrs	Tender Points	Dolorimetry Score	FIQ Score
1	42	3	16	2.23	57
2	32	3	16	2.63	63
3	41	5	12	3.44	55
4	25	2	15	2.56	59
5	33	4	17	2.87	69
6	28	3	18	1.09	76
7	41	5	13	3.29	64
8	35	6	15	1.12	79
9	36	3	16	1.36	58
10	38	4	13	2.74	61
11	43	2	16	1.20	74
12	23	3	12	1.89	60
13	20	1	14	2.47	53
14	29	5	13	2.38	49
15	28	6	18	0.92	75
16	30	3	18	1.36	60
17	35	4	17	1.83	63
18	34	3	15	1.14	67
19	43	5	14	1.67	72
20	48	6	15	1.99	57
21	37	3	16	2.48	46

FIQ: Fibromyalgia Impact Questionnaire[38].

Diurnal characteristics for each self-rated variable are presented in Table 2, where subjects are divided by dolorimetry scores. There were 12 subjects with a score < 2.25 kg and 9 subjects with a score > 2.25 kg [close to halfway (2.20 kg) between the lowest and highest individual scores]. The cut-point of 2.25 kg was not specified a priori. A relationship between dolorimetry score and self-report score was initially suggested by the multiple regression analysis, after which it was recognized that the 2.25 kg cut-point defined a threshold above which diurnal rhythmicity could no longer be detected in that grouping of subjects. Each grouping of subjects showed a range of change from lowest to highest ratings of about 50, which was half the distance on the 0–100 mm scale. More subjects with a low dolorimetry score showed significant diurnal rhythms for pain (8/12 vs 2/9) and stiffness (7/12 vs 4/9), and the same was observed for fatigue (4/12 vs 4/9) (Table 2). Summarizing all subjects as a group, the ANOVA detected a significant time-effect, and population mean cosinor revealed a significant diurnal rhythm only for rating of fatigue (Table 3). When subgrouping the subjects by dolorimetry score, a significant time-effect and diurnal rhythm was found for pain, stiffness, and fatigue for those subjects in the low score group (< 2.25 kg) and only for fatigue in the high score group (> 2.25 kg) (Table 3). For pain and stiffness in the low dolorimetry score group, self-ratings were highest in the morning and lowest in the early evening (Figure 3) and were fairly flat for the high score group (Figure 4). Both groups showed similar diurnal variations in fatigue, with higher rating in the early morning and before bedtime, and lowest ratings in the afternoon.

The waveform of a time series may often be more accurately approximated by the least-squares fit of a multiple-component cosine model[31,32] involving a concomitant fit of 2 or more components (i.e., 24 hours plus 12 or 8 or 6 hours, etc.). Thus, each time series was additionally tested for rhythm by the fit of a 12 h single cosine and a 24 h/12 h composite cosine model. However, neither the 12 h nor 24 h/12 h model was significant for any of the 3 self-rated variables for any subject or for the group overall. Thus, results from testing for a 12 h rhythmic component are not reported.

Graphs of individual data for each variable for each subject showed that some subjects showed clear diurnal patterns, and some were quite erratic or flat, while others showed prominent weekly patterns. Chronograms shown in Figure 5 reveal a diurnal rhythm as the prominent feature for one subject (left) and a weekly component as the prominent rhythm for another (right). For the group as a whole, a weekly (7-day) rhythm was detected in each self-measured variable when using the last 7 days of each subject's data series (Table 4). The overall weekly amplitudes of about 6% suggested at least a 12% change in levels of self-ratings throughout the week. On average, pain, stiffness, and fatigue were all rated higher near the beginning of the week (on Sundays and Mondays) and lower near the end of the week (on Fridays) (Figure 6).

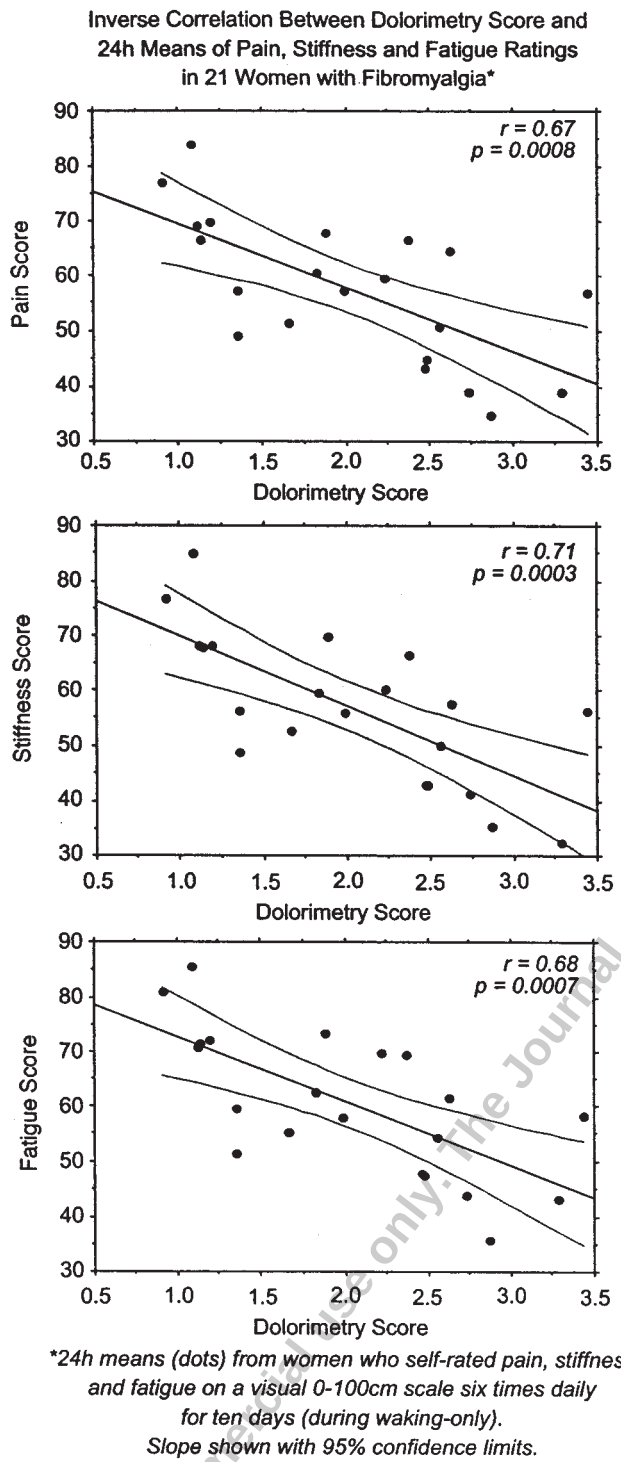

Figure 1. Inverse correlation between dolorimetry score and 24 h means of pain, stiffness, and fatigue ratings in 21 women with FM who self-rated pain, stiffness, and fatigue on a 100 mm VAS 6 times daily for 10 days during waking-only.

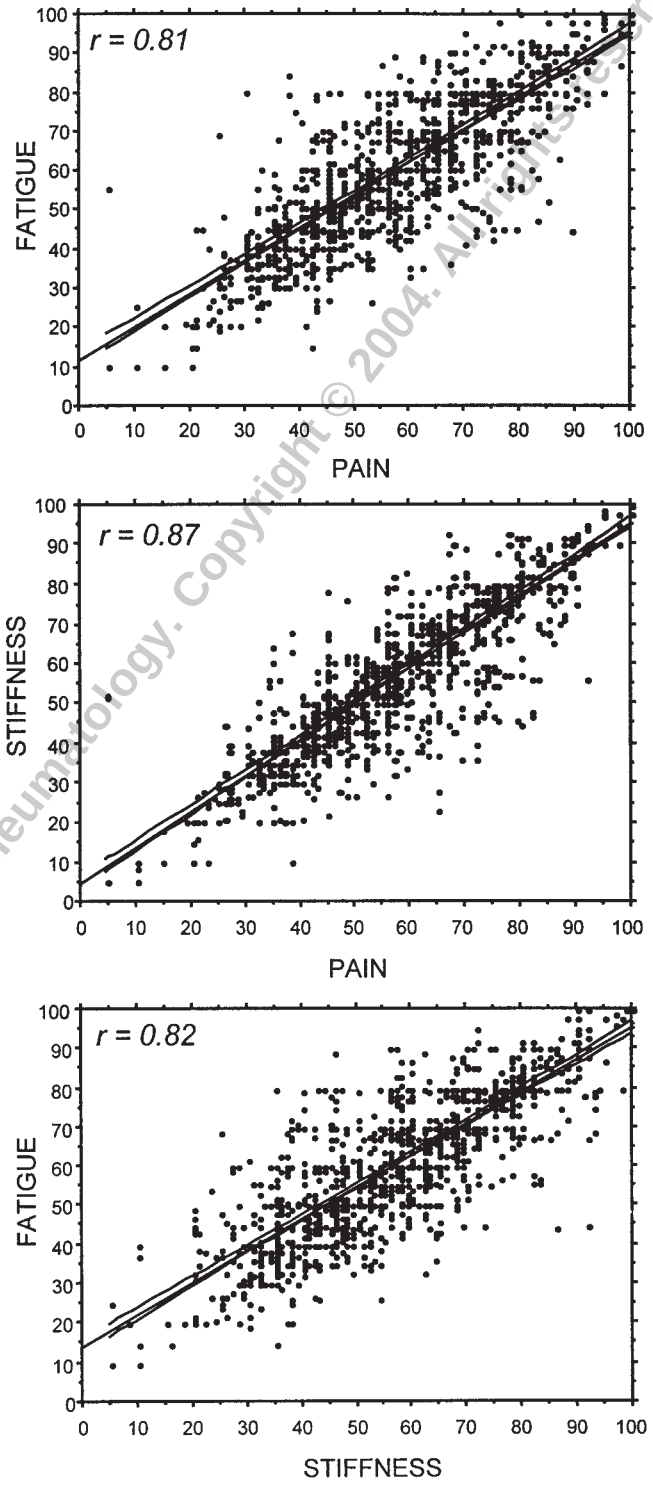

Figure 2. Positive correlation between single ratings of pain, stiffness, and fatigue in 21 women with FM. 1206 values were obtained from women who self-rated pain, stiffness, and fatigue on a 100 mm VAS 6 times daily for 10 days during waking-only.

DISCUSSION

Pain, stiffness, and fatigue are important measures in FM. We used conventional 100 mm visual analog scales to measure these variables in the assessment of patients with FM. The self-ratings of pain, stiffness, and fatigue may be altered by the presence of musculoskeletal or neurological

Table 2. Diurnal characteristics for ratings of pain, stiffness, and fatigue. Data obtained by self-measurement every 2–4 h during walking-only for 10 consecutive days. Subjects arranged by dolorimetry score.

Subject	Dolorimetry Score	N	Pain Rating Mean	Min	Max	ROC	±	Stiffness Rating Mean	Min	Max	ROC	±	Fatigue Rating Mean	Min	Max	ROC	±
Dolorimetry Score < 2.25																	
1	2.23	60	59.6	25	100	75	09:24h	60.4	25	100	75	11:32h	69.2	15	100	85	04:16h
6	1.09	50	84.0	63	100	37	09:36h	85.1	67	100	33	09:56h	85.1	58	100	42	06:36h
8	1.12	50	69.5	38	100	62	12:36h	67.5	36	100	64	23:20h	69.8	34	100	66	04:12h
9	1.36	60	48.5	30	67	37	07:20h	48.3	30	69	39	07:24h	50.3	32	67	35	05:16h
11	1.20	60	69.3	43	92	49	07:48h	67.8	45	92	47	08:44h	71.6	44	92	48	07:00h
12	1.89	51	67.5	45	90	45	05:48h	69.3	41	93	52	03:40h	72.7	35	98	63	02:52h
15	0.92	60	77.2	50	100	50	13:16h	76.9	37	99	62	12:08h	80.8	50	100	50	09:52h
16	1.36	60	57.1	35	80	45	08:44h	55.4	23	83	60	05:40h	58.8	24	84	60	03:20h
17	1.83	50	61.0	41	95	54	16:28h	59.6	28	98	70	19:32h	61.6	36	90	54	23:16h
18	1.14	60	66.4	50	92	42	12:20h	67.0	36	95	59	06:32h	70.8	50	98	48	04:16h
19	1.67	60	51.4	24	90	66	22:52h	52.1	25	92	67	01:20h	54.3	20	100	80	01:44h
20	1.99	60	56.6	33	89	56	08:08h	54.9	35	82	47	06:40h	57.3	30	78	48	03:56h
Mean	1.42		64.4	41.1	90.5	49.4		64.0	36.6	91.2	54.5		66.6	37.5	91.5	54.0	
SE	0.11		3.2	3.3	3.0	2.9		3.4	3.6	2.9	3.6		3.3	3.5	3.3	3.8	
Dolorimetry Score > 2.25																	
2	2.63	55	64.3	36	87	51	01:32h	58.5	27	84	57	17:32h	60.5	36	87	51	01:24h
3	3.44	60	56.8	26	85	59	11:20h	56.1	32	92	60	01:12h	57.7	33	98	65	01:32h
4	2.56	60	51.1	26	78	52	17:56h	50.2	28	79	51	20:00h	53.4	26	78	52	01:00h
5	2.87	60	34.9	15	58	43	19:00h	35.9	10	68	58	19:08h	35.9	10	70	60	22:00h
7	3.29	60	39.0	5	68	63	18:00h	32.1	5	65	60	02:44h	43.2	10	71	61	22:44h
10	2.74	60	38.6	5	78	73	07:16h	40.8	25	73	48	08:20h	43.2	27	77	50	03:32h
13	2.47	60	42.7	21	82	61	05:16h	42.4	16	80	64	03:48h	47.1	15	89	74	02:56h
14	2.38	60	65.9	45	90	45	23:56h	65.8	27	87	60	00:56h	68.9	42	90	48	23:56h
21	2.48	50	44.8	27	64	37	08:32h	43.4	31	68	37	09:48h	46.6	30	65	35	03:32h
Mean	2.78		46.7	21.3	75.4	54.1		45.8	21.8	76.5	54.8		49.5	24.1	79.8	55.6	
SE	0.14		3.7	4.6	3.9	4.2		3.9	3.6	3.4	3.1		3.6	4.1	4.1	4.2	

All data for each subject analyzed for diurnal rhythm by the least-squares fit of a 24.0 h cosine to calculate acrophase, ± (highest point of fitted cosine, referenced from 00:00 h); these values underlined if p = 0.05 for rhythm detection by zero-amplitude test for any period in diurnal domain of 20–28 h. N: total ratings/subject. ROC: range of change from lowest to highest rating.

disease. However, the patients in this study had no clinical evidence of neurological disease, and thus daily and weekly changes in the ratings are likely attributable to the presence of FM disease.

We mapped daily changes in pain, stiffness, and fatigue in patients with FM. Individual ratings of pain, stiffness, and fatigue were all highly significantly correlated with each other, suggesting that over 24 hours and even over 7 days, the level of one variable can predict the level of the others (e.g., stiffness can predict pain or fatigue and vice versa). In a recent study using single time-unqualified ratings, pain was also found to be a predictor of stiffness and tiredness in FM[40]. In our study, multiple regression identified the dolorimetry score as a significant predictor of levels of pain, stiffness, and fatigue ratings. In addition, the group of subjects with a lower score (e.g., greater sensitivity to pain) showed significant diurnal rhythms in each variable, while the group with a higher threshold of pain (dolorimetry score > 2.25 kg) failed to show a significant diurnal rhythm for pain and stiffness. The data suggest that the level of pain and stiffness throughout the day are, in part, predictable in those subjects that have a higher sensitivity to pain, while fatigue may reflect the usual pattern observed in healthy subjects rating their level of vigor[30]. The explanation for the observed variation cannot be addressed from our study. Neuroendocrine deficiencies have been implicated in FM, and a significant correlation between dehydroepiandrosterone sulfate (DHEAS) and pain has been reported in women with FM[41]. However, correlation does not establish a causal relationship, the significance of the observed relationship did not persist after adjustment for body mass index, and the study design did not permit identification of any relationship that might exist between fluctuations in DHEAS and diurnal variation in pain intensity. Nevertheless, the relationship between neuroendocrine and/or metabolic factors and variations in symptom intensity in FM merits further study, as does the relationship between psychosocial variables and variations in symptom severity.

The diurnal variation in fatigue observed in this study in

Table 3. Group circadian rhythm characteristics for ratings of pain, stiffness, and fatigue by women with FM. Data obtained by self-measurement every 2–4 h during waking-only for 10 days. Each series analyzed for time-effect by ANOVA and for circadian rhythm by the least-squares fit of a 24.0 h cosine. Circadian characteristics (M,A,Ø) summarized by population mean cosinor analysis.

	Units analyzed: Original									Percentage of Mean						
Time-effect:	ANOVA, Cosine Period = 24.0 h									ANOVA, Cosine Period = 24.0 h						
Variable	N	F	p	p	M ± SE	A ± SE	(%A)	Ø	(95% Limits)	F	p	p	M ± SE	A ± SE	Ø	(95% Limits)
All Subjects																
Pain	21	2.1	0.066	0.174	59.6 ± 3.0	1.2 ± 0.6	(1.9)	08:56h		1.2	0.290	0.258	100 ± 0.2	1.9 ± 1.1	08:42h	
Stiffness	21	1.5	0.198	0.200	59.3 ± 3.0	1.3 ± 0.7	(2.2)	06:15h		1.0	0.447	0.301	100 ± 0.2	2.2 ± 1.4	05:58h	
Fatigue	21	4.1	0.001	< 0.001	62.5 ± 3.0	4.1 ± 0.5	(6.5)	02:44h	(01:36, 03:56h)	8.3	< 0.001	< 0.001	100 ± 0.2	7.2 ± 1.0	02:31h	(01:16, 03:48h)
Subjects with Dolorimetry Score < 2.25																
Pain	12	3.3	0.006	0.010	64.0 ± 2.9	2.0 ± 0.5	(3.2)	09:38h	(07:48, 12:32h)	3.0	0.012	0.016	100 ± 0.2	3.2 ± 1.0	09:32h	(07:44, 12:40h)
Stiffness	12	2.7	0.019	0.040	64.0 ± 3.0	2.5 ± 0.8	(3.9)	06:52h	(04:00, 09:40h)	2.8	0.050	0.005	100 ± 0.2	4.3 ± 1.4	06:37h	(04:06, 09:08h)
Fatigue	12	2.8	0.016	0.002	67.5 ± 3.0	4.0 ± 0.8	(5.9)	03:50h	(02:32, 05:20h)	4.5	< 0.001	0.003	100 ± 0.2	6.5 ± 1.4	03:44h	(02:20, 05:16h)
Subject with Dolorimetry Score > 2.25																
Pain	9	0.1	0.971	0.820	53.7 ± 5.2	0.5 ± 0.8	(1.0)	03:33h		0.2	0.919	0.878	100 ± 0.3	0.9 ± 1.8	04:08h	
Stiffness	9	0.4	0.813	0.854	53.0 ± 5.1	0.6 ± 1.0	(1.1)	23:01h		0.5	0.721	0.874	100 ± 0.3	1.1 ± 2.0	22:27h	
Fatigue	9	5.5	< 0.001	0.001	55.9 ± 5.0	4.6 ± 0.7	(8.3)	01:29h	(00:00, 03:24h)	7.9	< 0.001	< 0.001	100 ± 0.3	8.9 ± 1.3	01:22h	(23:36, 03.28h)

For rhythm characteristics: p value from zero-amplitude test; M = mesor (middle value of fitted cosine); A = amplitude (distance from M to peak or trough of cosine); %A = percentage amplitude (A as percentage of M); Ø = acrophase (highest point of fitted cosine, referenced from 00:00 h). ANOVA: analysis of variance across six 4-hourly intervals.

the low and high dolorimetry score group is consistent with observations reported by Moldofsky[35]. Without a control group, the attribution of fatigue to the presence of FM is debatable, particularly given the observation of Klerman, *et al* that women with FM and control women had similar diurnal rhythms in self-reported alertness[36]. Our observation of a diurnal rhythm in pain may explain the controversy regarding the existence of diurnal variation in pain[35,36]. It appears that diurnal variation in pain may exist in a subset of the FM population with a lower pain threshold as defined by the mean dolorimetry score (< 2.25 kg). For similar reasons, the failure to detect diurnal variation in stiffness[36] may be due to heterogeneity in the FM population, such variation occurring predominantly in those with lower dolorimetry scores. It has been noted that FM symptoms are correlated with pain threshold in the general population, although the association is weaker for dolorimetry scores than tender point counts[42]. Together with the observed relationship in this study between dolorimetry scores and the clinical variables, this suggests that diurnal rhythmicity is more likely to be observed in those with more severe disease, where patients are more likely to be aware of and note larger changes in their pain and stiffness throughout the day.

Given the relatively short duration of this study (10 days), our observations suggesting the possible existence of weekly variation are tentative. Nevertheless, we have observed weekly rhythms in pain, stiffness, and fatigue. The relevance of this observation, with higher ratings occurring on Sunday and Monday, is speculative. Whether this tentative observation has a psychosocial explanation, for example relating to anticipation of increasing social and emotional demands associated with the beginning of the "working week," or relates to schedule differences between weekday versus weekend activities, or has a biologic basis, cannot be addressed by this study. It is notable that in our previous studies in OA, a weekly rhythm with higher ratings on Sunday was observed for knee pain[3]. Further evaluation of this rhythm will require a longer and more complex longitudinal study.

Potential limitations of this study include the absence of information on confounding variables such as analgesic consumption and biometeorological conditions, and the absence of relevant biochemical data. Analgesic counts, while recorded by the patients, were unavailable for analysis; neither were Environment Canada statistics on temperature and humidity obtained. We recognize that the modulating effects of these variables on diurnal and/or weekly variation cannot be fully dissected without such information[43,44]. However, in a study of diurnal and weekly rhythms in pain perception in knee OA we were unable to show any significant relation between fluctuations in pain scores and either analgesic consumption or the aforementioned biometeorological factors[3]. Since no differences have been observed between women with FM and control women in diurnal amplitude or phase of rhythms for cortisol or melatonin, we do not consider the absence of biochemical data to be of critical importance[35].

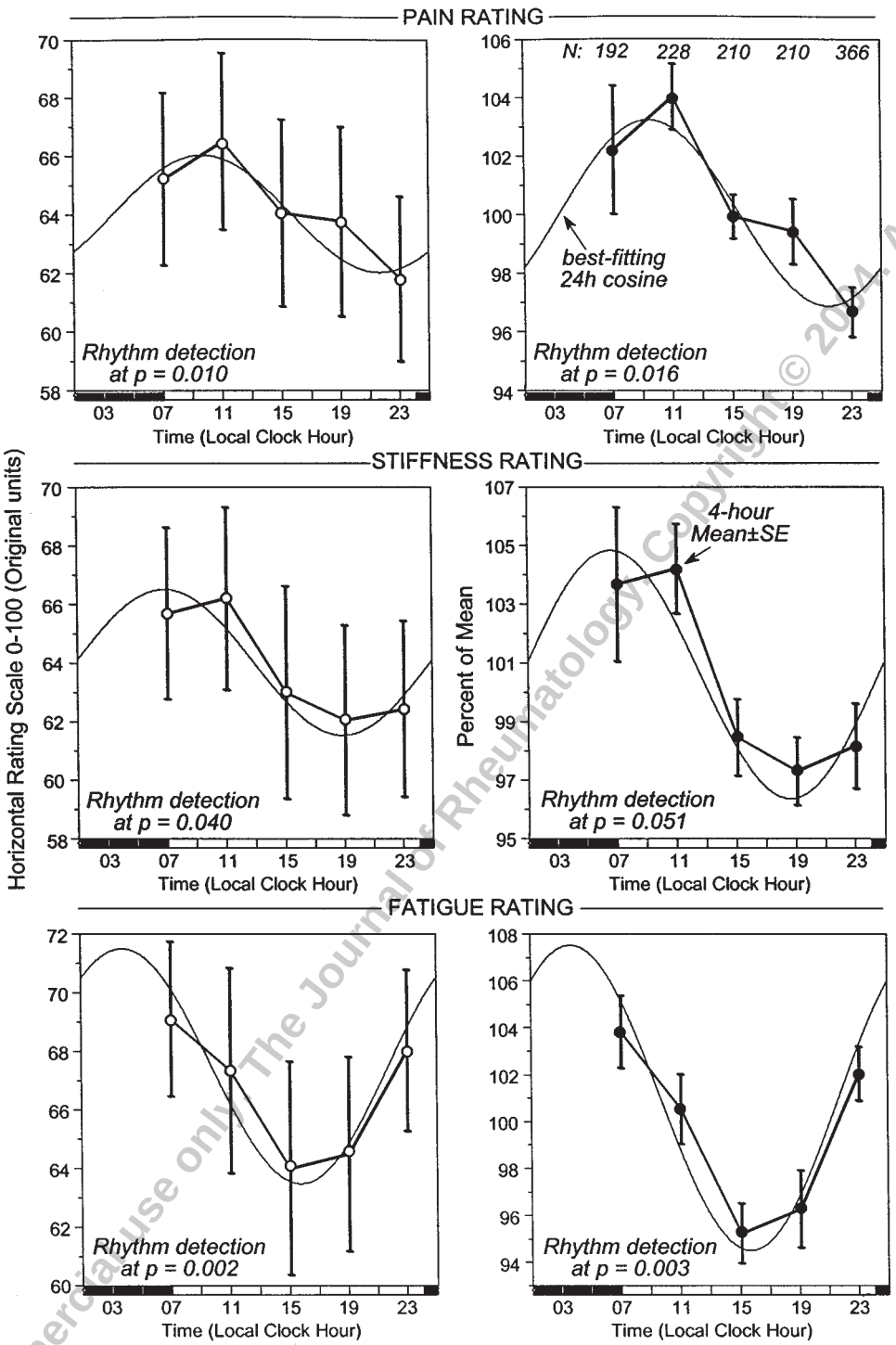

Figure 3. Diurnal patterns in self-ratings for 10 days by 12 women with FM with dolorimetery score < 2.25 kg. Women self-rated pain, stiffness, and fatigue 6 times daily for 10 days. Each time series was analyzed for rhythm by the least-squares fit of a 24 h cosine and group rhythm characteristics summarized by population mean cosinor. Rhythm detection significant if p = 0.05 from zero-amplitude test. Data analyzed using original units (left column) and after conversion to percentage of individual mean (right column). N: number of ratings/interval. Black bar on time scale: rest and/or sleep.

We conclude that ratings of pain, stiffness, and fatigue in FM are correlated, definitely show diurnal rhythmicity, and possibly show weekly rhythmicity. These observations on diurnal variation in pain and stiffness are generalizable to a subset of FM population having lower mean dolorimetry scores and possibly being more pain-sensitive. For these

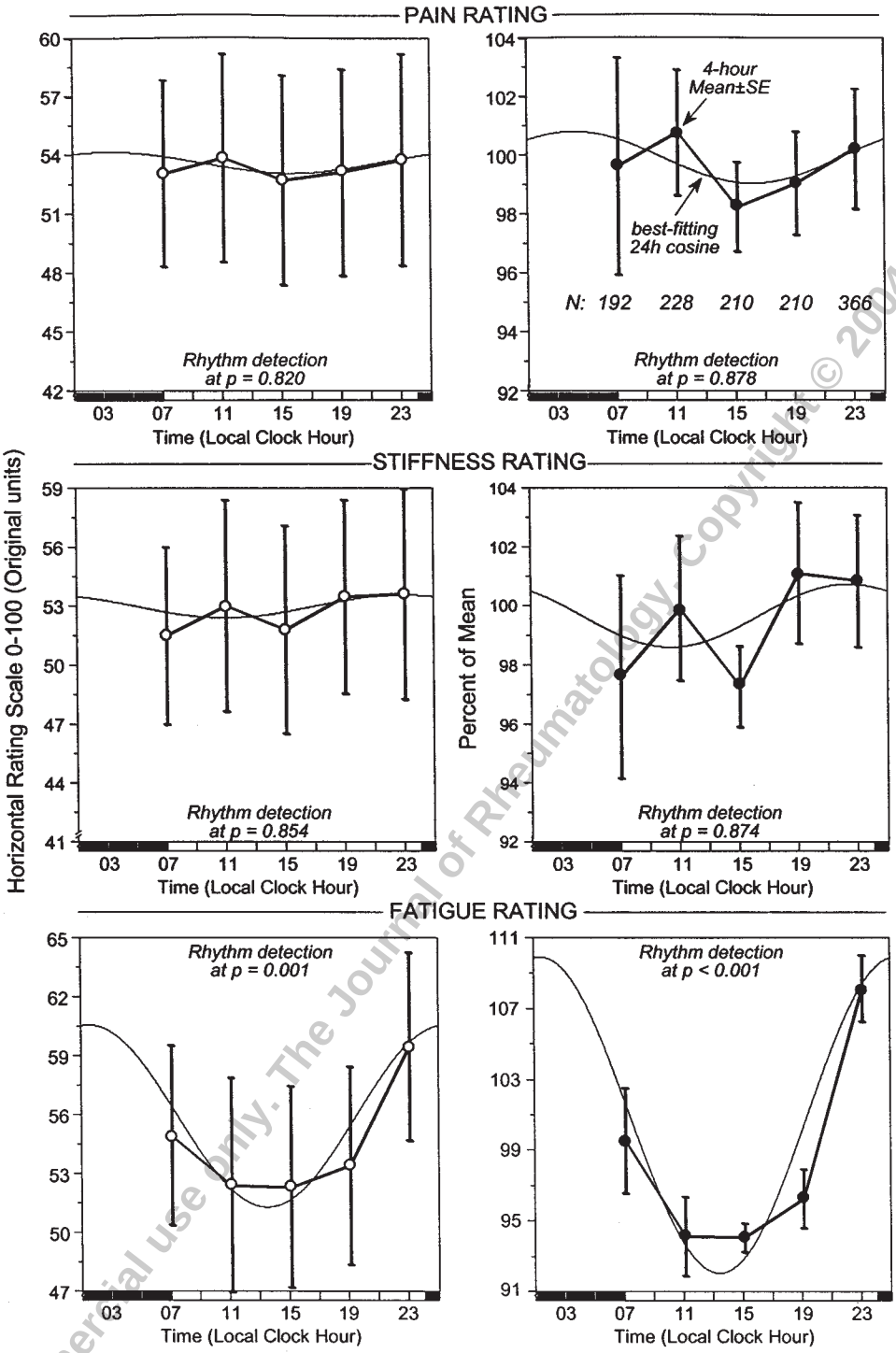

Figure 4. Diurnal patterns in self-ratings for 10 days by 9 women with FM with dolorimetery score > 2.25 kg (see Figure 3 legend for details).

patients, the results of this study may have important implications for scheduling activities of daily living, for measurement in clinical trials, and possibly for timing the administration of medication. As well, these observations may have important implications for future studies of the pathogenesis of FM, since the clinical expression of FM appears to differ between the high and low pain threshold subgroups. Further evaluation of the diurnal rhythm in fatigue and the purported weekly rhythm in pain, stiffness, and fatigue in FM is recommended.

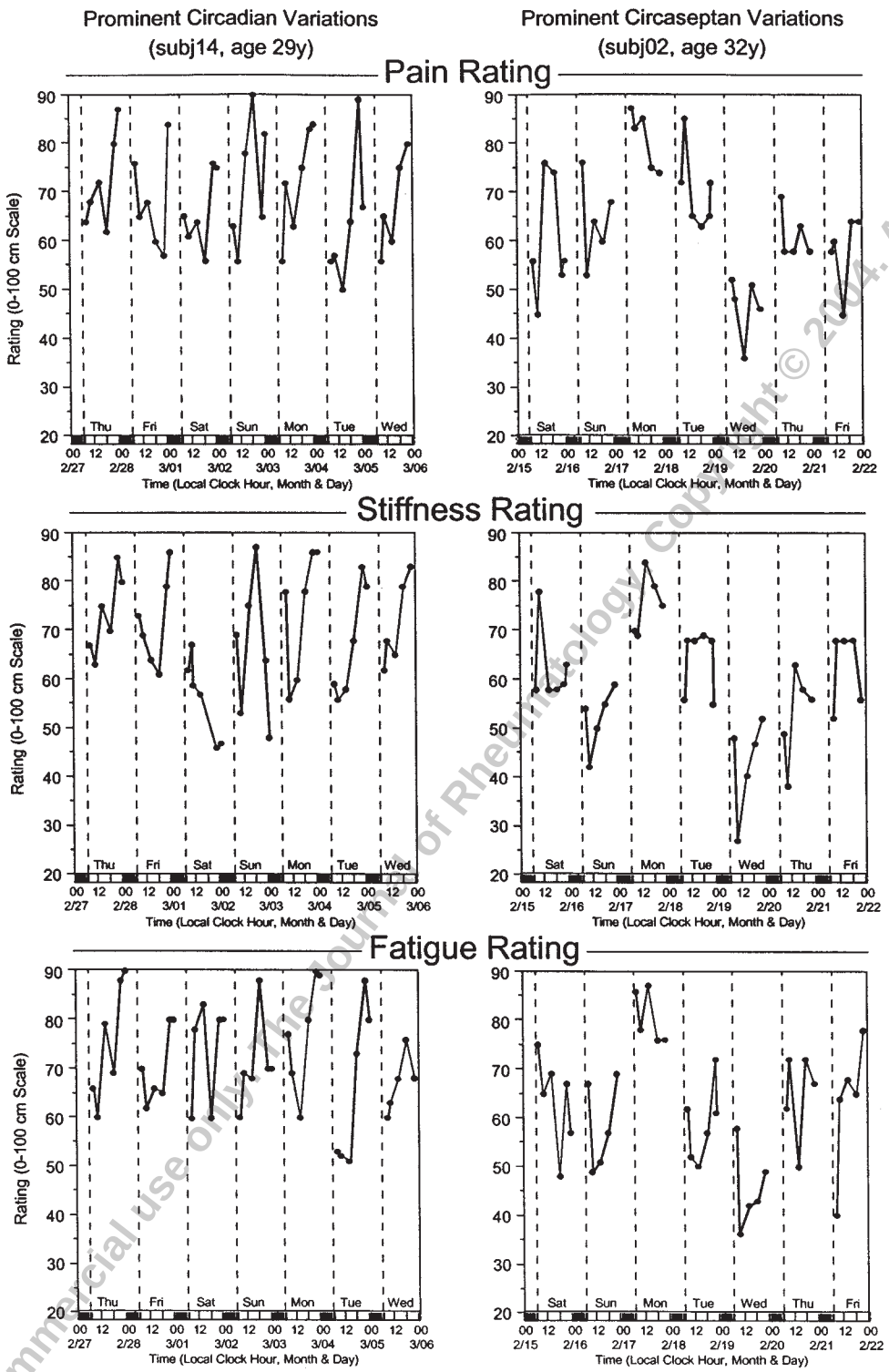

Figure 5. Examples of diurnal and weekly patterns in self-ratings over 7 days by 2 women with FM. Each subject self-rated pain, stiffness, and fatigue on a 100 mm VAS 5–6 times daily during waking-only. Black bars on time scale: sleep periods.

Table 4. Group circaseptan (weekly) rhythm characteristics for ratings of pain, stiffness, and fatigue by women with FM. Data obtained by self-measurement every 2–4 h during waking-only for 10 days. Data from Days 1–3 removed due to possible learning effect. All data from Days 4–10 analyzed by ANOVA for time-effect and circaseptan rhythm by the least-squares fit of a 168 h (7 day) cosine.

	Units analyzed: Original									Percentage of Mean						
Time-effect:	ANOVA, Cosine Period = 24.0 h									ANOVA, Cosine Period = 24.0 h						
Variable	N	F	p	p	M ± SE	A ± SE	(%A)	Ø	(95% Limits)	F	p	p	M ± SE	A ± SE	Ø	(95% Limits)
Pain	21	4.0	< 0.001	< 0.001	58.0 ± 0.6	3.2 ± 0.8	(5.4)	Mon 19:36h	(Mon 05:24, Tue 09:52)	7.3	< 0.001	< 0.001	100 ± 0.8	5.8 ± 1.2	Mon 19:52h	(Mon 09:08, Tue 06:36)
Stiffness	21	3.8	<0.001	0.002	57.4 ± 0.6	3.1 ± 0.9	(5.5)	Mon 13:06h	(Sun 21:56, Tue 04:16)	6.1	< 0.001	< 0.001	100 ± 0.8	5.9 ± 1.3	Mon 12:24h	(Mon 01:12, Mon 22:36)
Fatigue	21	3.4	0.002	0.003	61.0 ± 0.6	3.0 ± 0.9	(4.9)	Mon 13:48h	(Mon 03:08, Tue 05:40)	5.0	< 0.001	< 0.001	100 ± 0.8	5.2 ± 1.2	Mon 13:20h	(Mon 01:12, Tue 01:28)

For rhythm characteristics: p value from zero-amplitude test; M = mesor (middle value of fitted cosine); A = amplitude (distance from M to peak or trough of cosine); %A = percentage amplitude (A as percentage of M); Ø = acrophase (highest point of fitted cosine, referenced from 00:00 h). ANOVA: analysis of variance across seven 24-hourly intervals.

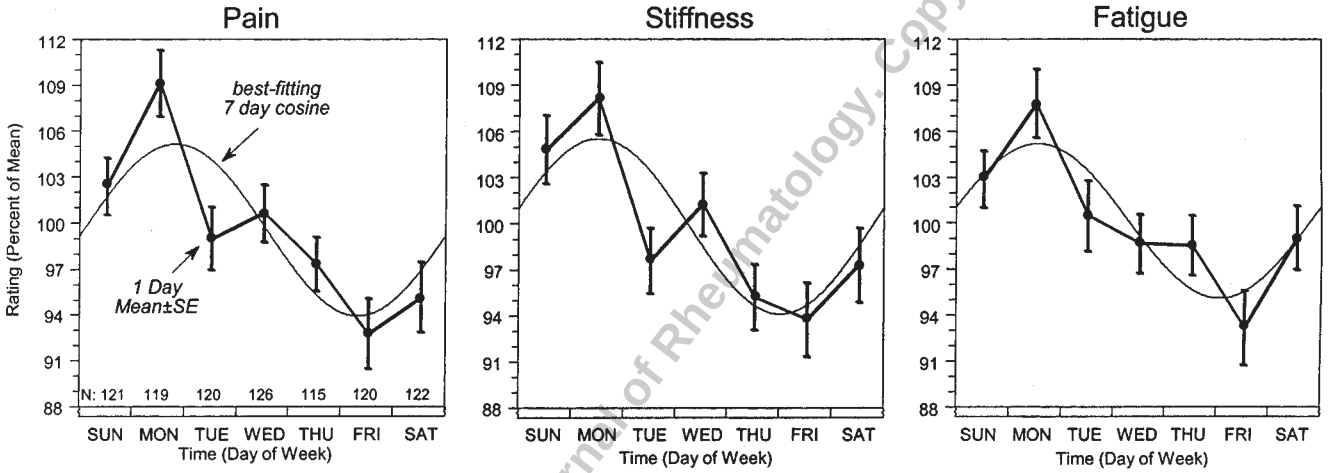

Figure 6. Weekly variations in self-ratings for 7 days by 21 women with FM. Women self-rated pain, stiffness, and fatigue 6 times daily for 10 days (Days 1–3 excluded for learning effect). Each time series converted to percentage of mean and grouped data analyzed for rhythm by the least-squares fit of a 168 h (7 day) cosine. P < 0.001 for rhythm detection from zero-amplitude test for each variable. N: number of total ratings/day.

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