# Characterization and Consequences of Pain Variability in Individuals With Fibromyalgia

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*Objective.* A growing body of evidence suggests that real-time electronic assessments of pain are preferable to traditional paper-and-pencil measures. We used electronic assessment data derived from a study of patients with fibromyalgia (FM) to examine variability of pain over time and to investigate the implications of pain fluctuation in the context of a clinical trial.

*Methods.* The study group comprised 125 patients with FM who were enrolled in a randomized, placebo-controlled trial of milnacipran. Pain intensity levels were captured in real time by participants using electronic diaries. Variability in pain was assessed as the standard deviation of pain entries over time (pain variability index [PVI]).

*Results.* Substantial between-subject differences in pain variability were observed (mean ± SD PVI 1.61 ± 0.656 [range 0.27–4.05]). The fluctuation in pain report was constant over time within individuals ($r = 0.664$, $P < 0.001$). Individuals with greater variability were more likely to be classified as responders in a drug trial (odds ratio 6.14, $P = 0.006$); however, this association was primarily attributable to a greater change in pain scores in individuals receiving placebo ($r = 0.460$, $P = 0.02$) rather than active drug ($r = 0.09$, $P > 0.10$).

*Conclusion.* Among individuals with FM, there were large between-subject differences in real-time pain reports. Pain variability was relatively constant over time within individuals. Perhaps the most important finding is that individuals with larger pain fluctuations were more likely to respond to placebo. It is not clear whether these findings are applicable only to patients with FM or whether they may also be seen in patients with other chronic pain conditions.

Clinical practice as well as research data indicate that the intensity of chronic pain typically is not constant (1–3). This phenomenon may be particularly true in patients with fibromyalgia (FM) (4,5). FM is defined by the presence of widespread pain and tenderness (6) and affects 2–4% of the population (7). Within a single day, an individual with FM may note that his or her level of pain varies greatly; it is not uncommon for pain scores on a 10-cm visual analog scale (VAS) to range from 2 to 10 (5). This variability in pain magnitude reflects a volatility of pain in some individuals, yet relatively few studies have examined this characteristic.

Variation in the intensity of chronic pain has been thought to arise from the following 2 sources: systematic trends in pain levels that may be attributable to the pathogenesis of the condition (1–3), or fluctuations about a mean pain level that lack any underlying trend (1). Although some investigators have suggested that individuals with less predictable pain (i.e., no trend) have more depressive symptoms (2), this has not been confirmed by others (3).

The lack of studies focusing on pain variability within individuals over time may be due, in part, to the limits of previous data-recording methods, such as pencil-and-paper diaries (8). These problems have been largely overcome by the use of electronic diaries that capture symptoms in real time, using high sampling densities (9). We examined the within-subject pain variability across time in individuals with FM who were

enrolled in a clinical trial in which electronic diary methods were used.

The main questions of interest were as follows: What is the within- and between-subject variability of FM pain over time? How does pain variability differ across subjects? Finally, is there any information about an individual's pain variability that may be helpful in designing clinical trials in FM?

## PATIENTS AND METHODS

**Phase II drug trial of milnacipran in FM.** The study group comprised 125 patients with FM who were enrolled in a multicenter drug trial of milnacipran (a dual serotonin/norepinephrine reuptake inhibitor) versus placebo (10). Briefly, participants were randomized to receive either milnacipran or placebo after a 2-week baseline (observational) period and were followed up longitudinally for 12 weeks.

Patients with FM who were 18–75 years of age and met the American College of Rheumatology 1990 criteria for FM (11) were included in the study. Key exclusion criteria included severe psychiatric illness (although individuals with major depression or generalized anxiety disorder were not excluded); risk of suicide according to the investigator's judgment; alcohol or drug abuse; history of significant cardiovascular, respiratory, endocrine, genitourinary, liver, or kidney disease; systemic infection; cancer or current chemotherapy; significant sleep apnea; life expectancy of <1 year; and active peptic ulcer or inflammatory bowel disease. All participants gave informed consent, and the protocol was approved by the relevant institutional review boards.

**Outcomes.** Each participant carried a Palm-based electronic diary (invivodata, Pittsburgh, PA) and was prompted at random intervals (a mean of 3.4 times per day) to enter his or her pain level, using an anchored logarithmic scale (the Gracely Box Scale [GBS]; range 0–132) (12). These values were scaled down by a factor of 6.6 to facilitate comparison with the original GBS (range 0–20).

**Statistical analysis.** *Calculation of the pain variability index (PVI).* For each participant, the standard deviation of sequential entries within 2-week time blocks was used as the primary measure of the variability or spread in the data (PVI). This outcome was chosen because of its ability to capture both systematic and nonsystematic fluctuations in pain. In addition, this approach makes fewer assumptions about the structure of the data, such as averaging pain levels across or within days. The PVI was calculated separately for each individual and was then used to create a histogram representing all study participants. Mean pain levels were also calculated as the average of all entries over 2-week time blocks.

*Distribution properties of the PVI.* To test for ceiling or floor effects, the population was divided into quartiles based on individual PVI scores obtained during the first 2 (baseline) weeks. Histograms of the mean pain scores for the upper (highly variable) and lower (less variable) PVI quartiles were compared for skewness.

*Stability of the PVI over time.* To examine the stability of the measure, individual PVI scores during the 2 baseline weeks and the final 2 weeks of the trial (12 weeks later) were compared using a bivariate Pearson's correlation.

*Relationship of the PVI to treatment responsiveness.* To determine the relationship between pain variability and responsiveness to treatment (milnacipran or placebo), 3 analyses were performed: logistic regression, linear regression, and univariate correlations. For the logistic regression analysis, the binary response criterion (4-unit change in GBS from baseline to the end of treatment, which represents an ~50% improvement in pain [13]) measured with the electronic diary was used as the dependent variable. This criterion was chosen because it is within the range to designate clinical pain responders (13) and is used here to designate treatment responders. Treatment assignment (milnacipran or placebo) and ln(PVI) were entered as predictors. Age, duration of FM, and race (white = 1, nonwhite = 0) were also added as additional covariates. Goodness of fit was assessed with the Hosmer–Lemeshow test. For the linear regression analysis, the above covariates, in addition to the mean level of pain at baseline, were used to predict change in the mean level of pain (baseline − end).

For the univariate analysis, correlations were made between ln(PVI) and the change in the mean electronic diary pain scores (baseline − end) for individuals receiving placebo or milnacipran. PVI data were transformed to the log of PVI to better approximate the normal distribution needed to meet the assumption of the statistical methods being used. Graphs of random prompt entries of pain versus time were made for all milnacipran responders, to examine the time course of drug application on real-time pain assessment. A *t*-test was performed to detect differences in baseline PVI scores between individuals in whom either an exponential or a linear trend in pain was observed.

Analyses were performed using SPSS version 12.0.1 (SPSS, Chicago, IL) and SAS version 8.02 (SAS Institute, Cary, NC) software.

## RESULTS

**Demographics.** The study population (n = 125) comprised predominantly middle-age (mean ± SD age 47.05 ± 11.15 years) women (n = 122), which is consistent with the epidemiology of FM (14,15). Most of the subjects (n = 105) were white (12 were Hispanic, 5 were African American, 1 was Asian, and 2 were of other ethnicity), and most reported high levels of pain (mean ± SD pain score 6.90 ± 1.78) (on a 10-cm VAS) at baseline. The mean ± SD duration of FM was 4.06 ± 4.16 years.

**Characteristics of the PVI.** *Within- and between-subject variation in the PVI.* To examine the degree of variability in pain across all participants, a between-subject histogram of PVI values was created for data collected during the 2-week baseline period (Figure 1A). This distribution had a single mode and was skewed toward higher values (mean ± SD PVI 1.61 ± 0.656; $P$ = 0.002). A logarithmic transformation provided a good
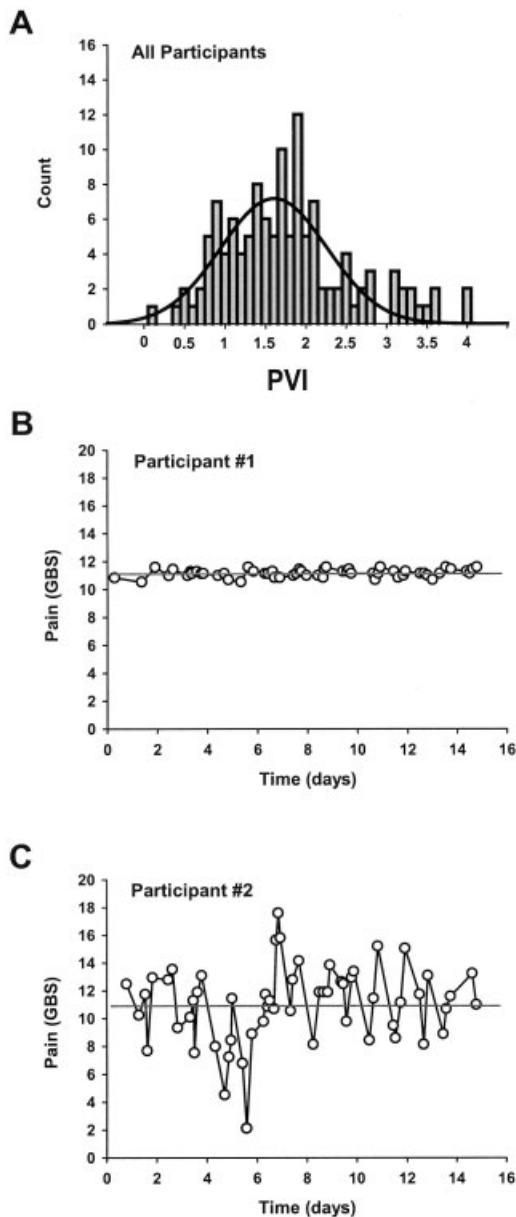
**Figure 1.** Pain variability in patients with fibromyalgia. **A,** Histogram of pain variability index (PVI) scores for all individuals, showing a single peak with a relatively large spread. **B** and **C,** Consecutive entries of pain levels for participant 1 and participant 2, respectively. Participant 1 displayed relatively consistent levels of pain over time, whereas participant 2 displayed greater variability. Horizontal lines show the mean. GBS = Gracely Box Scale.

fit to a normal distribution for PVI ($P = 0.20$). A large spread in the PVI was observed between subjects (PVI range 0.27–4.05), indicating significant variation in real-time measurements of pain across participants.

Figures 1B and C depict the raw pain scores for 2 different participants tracked longitudinally over 14 baseline days. Although these 2 individuals had similar mean pain scores (11.14 for participant 1 and 11.03 for participant 2), their pain score variability was noticeably different (for participant 1, PVI = 0.27; for participant 2, PVI = 2.78).

*Ceiling or floor effects*. To test for ceiling or floor effects, mean pain score distributions for the upper (more variable) and lower (less variable) PVI quartiles were investigated for asymmetries. Similar pain scores would be predicted if ceiling or floor effects were absent. The skewness and range in pain scores were relatively similar between quartiles (skewness [SEM] for the lower quartile 0.26 [0.42], for the upper quartile 0.30 [0.42]; range for the lower quartile 9.25–17.49, for the upper quartile 5.33–16.57), suggesting that ceiling and/or floor effects were not largely responsible for the between-subject variability in the PVI.

*Trait variability*. To assess whether symptom variability may represent a trait, we examined the correlation of the PVI observed at 2 different time periods (baseline versus 12 weeks later). The PVI within individuals was highly correlated over time (r = 0.664, $P < 0.001$), suggesting that this is a relatively stable construct.

**Effects of PVI in a drug trial.** *Association of PVI with response to placebo*. We next investigated the extent that pain variability (PVI) influenced binary responder classification as assessed by electronic diary methods in a drug trial. A logistic regression on responder status was performed using age, race, duration of FM, treatment (milnacipran versus placebo), and ln(PVI) as predictors (Table 1). Treatment, ln(PVI), race, and duration of FM significantly predicted response. Interestingly, individuals with increased pain variability were more likely to be responders. This finding was replicated in a linear regression analysis using the change in pain (mean at

**Table 1.** Results of logistic regression analysis of clinical pain responder status*

| Predictor | Estimate | SEM | OR | P |
|---|---|---|---|---|
| ln(PVI) | 1.815 | 0.660 | 6.143 | 0.006 |
| Duration of FM, years | 0.145 | 0.062 | 1.156 | 0.020 |
| Race (white vs. nonwhite) | −1.462 | 0.643 | 0.232 | 0.023 |
| Treatment (milnacipran or placebo) | 1.706 | 0.759 | 5.507 | 0.025 |
| Age | 0.019 | 0.023 | 1.019 | 0.405 |

* Each independent variable was force-entered into the following regression model: logit(responder: 0,1) = ln(pain variability index [PVI]) + duration + race + treatment + age. OR = odds ratio; FM = fibromyalgia.
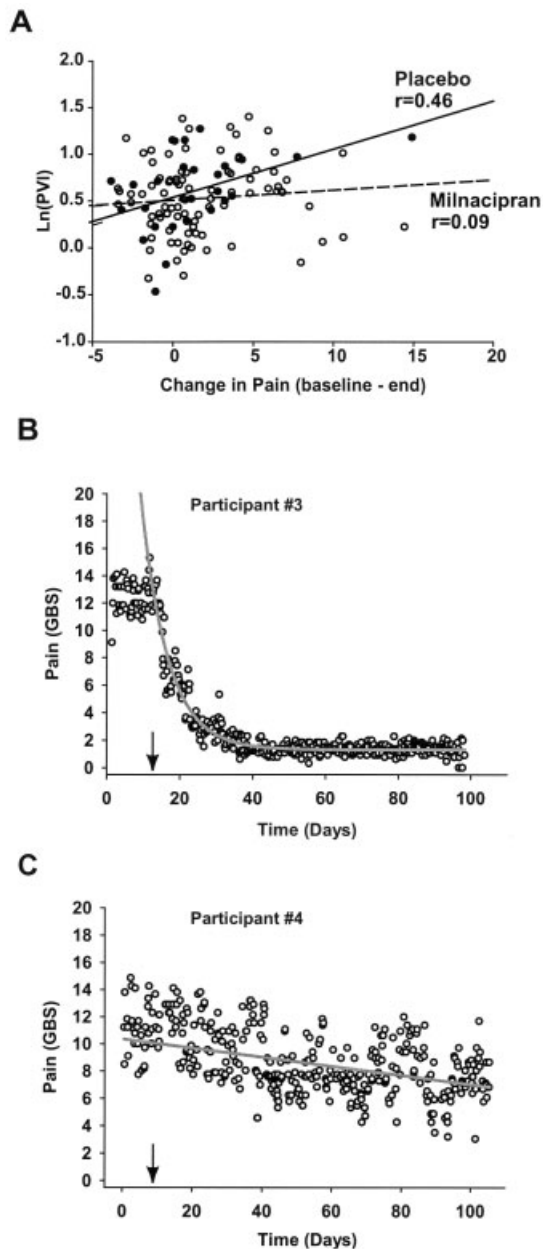
**Figure 2.** Relationship between the pain variability index (PVI) and the response to placebo. **A,** Scatterplot showing the change in mean pain scores (baseline − end) versus ln(PVI) for individuals receiving placebo or milnacipran. A significant correlation was observed for those receiving placebo (r = 0.460, P = 0.02) but not for individuals assigned to milnacipran (r = 0.09, P > 0.10). **B** and **C,** Consecutive diary entries for 2 typical individuals. The plots for participant 3 (**B**) and participant 4 (**C**) showed differing courses following administration of milnacipran (arrows). Participant 3 displayed an exponential decline in pain ($\tau = 7.30$ days), whereas participant 4 displayed a linear trend (slope = −0.034/day). Note that participant 4 had increased variability in pain reporting over the course of the trial, as compared with participant 3.

baseline − mean at end) as the dependent variable. A significant effect of ln(PVI) on change in pain ($\beta = 1.624$, $P = 0.028$) was observed after adjusting for age, duration of FM, race, and baseline pain levels, again with greater PVI predicting larger improvements in pain. This association was primarily attributable to greater changes in pain scores in individuals receiving placebo. Figure 2A depicts the association between ln(PVI) and the change in mean pain scores within the 2 study arms. Variability was significantly correlated with a change in pain for those randomized to placebo (r = 0.460, P = 0.02) but not for patients receiving milnacipran (r = 0.09, P > 0.10).

*Association of PVI with nonspecific response to drug.* Because treatment response was associated with the PVI among placebo responders, we investigated placebo or nonspecific response patterns in the real-time pain entries for responders receiving milnacipran (n = 33), over the entire study period. Two major types of profiles were observed: an exponential decline in pain, or a linear trend toward reduced pain. Figure 2B shows the pattern for participant 3, who displayed an exponential decline in pain, and Figure 2C shows the pattern for participant 4, who displayed a linear trend. Of the 33 responders given milnacipran, 13 displayed an exponential pattern, 15 displayed a linear pattern, and 5 had other patterns of pain. Those displaying a linear decline in pain had significantly greater baseline pain variability than those displaying an exponential decline in pain (mean ± SD ln[PVI] 0.73 ± 0.31 linear, 0.47 ± 0.35 exponential; $P = 0.048$).

## DISCUSSION

In this study, we explored pain variability in patients with chronic FM who were participating in a drug trial. Our results confirm previous findings (5) that temporal fluctuations in FM pain span a continuum, with some individuals displaying a large variation in pain intensity while others have more constant levels.

Pain variability was moderately stable over time. Individuals in whom pain was classified as highly variable at one time point tended to be classified as having highly variable pain patterns later. In addition, variability in pain was not explained by data-collection artifacts such as ceiling or floor effects, because pain score distributions were similar in participants with a large versus a small PVI. One would expect these distributions to have differing skewness if floor or ceiling effects were present. Instead, pain variation was attributable primarily to fluctuations around a stable mean score.

One advantage of this investigation is that we were able to assess the consequences of pain variability in a drug trial. We observed that pain variability predicts drug responsiveness. Individuals with a greater PVI at baseline were more likely to be responders; this effect was seen almost exclusively in those randomized to placebo as compared with those receiving milnacipran, suggesting that high pain variability may be a predictor of a placebo response.

If this is correct, one would also predict that this effect would also be present to some extent within responders to milnacipran, because placebo mechanisms should also occur in those randomized to active drug. Interestingly, our real-time pain data demonstrated that some milnacipran responders displayed a nonspecific response to drug (i.e., a gradual linear decline in pain during milnacipran therapy). Individuals with such a nonspecific response also had greater baseline pain variability than those displaying a more immediate (i.e., exponential) response.

These results have direct implications for drug trials in FM and perhaps broader implications for other pain syndromes. Although we detected no difference in PVI scores between the 2 study arms in our trial ($P > 0.05$), investigations that randomize individuals with greater baseline PVI scores to placebo may be biased toward the null due to a greater placebo effect. To counteract or control for this effect, one could either stratify participants based on baseline PVI scores or even remove individuals with high pain variability prior to randomization. Examining the pattern of response to placebo interventions may also offer further insight into the mechanisms of placebo-induced analgesia.

This investigation has several limitations. First, our results may be limited to patients with FM. Second, participants were enrolled in a drug trial, and the stability of their pain may have been influenced by treatment. Third, most participants were women, and as such our results may not be applicable to a male population, especially because it is known that women display changes in pain intensity depending on the time of their menstrual cycle (16). Fourth, we did not make an attempt to differentiate systematic versus nonsystematic trends in the data when estimating variability. Finally, most of our participants were white, thus limiting the applicability of our conclusions to this population.

In some patients with FM, the variation in pain intensity over time is significant. This variability is relatively constant within individuals and may predict a nonspecific response to treatment (i.e., a placebo effect). Extrapolation of these results to other chronic pain states is warranted.

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