

# The Longitudinal Examination of Arthritis Pain (LEAP) Study: Relationships Between Weekly Fluctuations in Patient-Rated Joint Pain and Other Health Outcomes

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**ABSTRACT. Objective.** To examine relationships between weekly fluctuations in self-rated joint pain and other health outcomes among adults with osteoarthritis (OA).

**Methods.** In this observational study, 287 adults (aged  $\geq 50$  yrs) with hip or knee OA were recruited from 16 medical practices across the United States. Patients were telephoned weekly for 12 weeks to assess pain/stiffness, daily activities/function, productivity, emotional well-being, quality of life, and healthcare utilization. Associations between changes in joint pain levels and other health outcomes were evaluated using a generalized estimating equation model.

**Results.** The mean (SD) pain score at Week 1 was 4.2 (2.1) on the Western Ontario and McMaster Universities OA index (WOMAC) pain subscale (0 = no pain, 10 = extreme pain); during the study, 49% of patients reported a between-week fluctuation of  $\geq 2$  points. A 2-point decrease in WOMAC pain subscale score was associated with a 22% decrease in number of days of limited activity/week ( $\beta = -0.107$ ; 95% confidence interval  $-0.163, -0.051$ ); a 48% decrease in number of days of missed work/week ( $\beta = -0.217$ ; 95% CI  $-0.395, -0.039$ ); a 14% decrease in number of nights with pain-related sleep interference/week ( $\beta = -0.068$ ; 95% CI  $-0.109, -0.027$ ). Patients were 1.6 times more likely to contact a healthcare provider when their pain changed from “acceptable” to “unacceptable.”

**Conclusion.** Weekly fluctuations in pain levels and other health outcomes were identified among adults with OA. Decreases in patient-reported pain were associated with improvements in daily activities/functioning and decreases in work absenteeism, sleep interference, and healthcare resource use. (First Release Oct 15 2007; J Rheumatol 2007;34:2291–300)

#### Key Indexing Terms:

LONGITUDINAL STUDIES      ARTHRITIS      PAIN      QUALITY OF LIFE  
ACTIVITIES OF DAILY LIVING      OUTCOME ASSESSMENT      HEALTHCARE

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Osteoarthritis (OA) is one of the leading causes of pain and disability in the elderly<sup>1,2</sup>. When OA becomes symptomatic in the knee, as it does in around 13% of adults over 55 years of age<sup>3</sup>, the effect is often debilitating<sup>1</sup>. Pain in the knee is a key factor in the decision to seek medical care and an established antecedent to disability<sup>4</sup>. Pain management is, therefore, a major goal of OA treatment<sup>5-7</sup>.

Chronic OA joint pain influences patients' functional and social activities, relationships, socioeconomic status, and emotional well-being<sup>8-10</sup>. Chronic pain and functional limitations also contribute to absenteeism and to work related disability<sup>11,12</sup>, and patients with OA have elevated healthcare resource use and related costs<sup>13</sup>, as high pain levels are associated with increased odds of physician visits and analgesic and antiinflammatory medication use<sup>14</sup>.

The effects of chronic pain depend on the patient's perception of pain severity and their coping and management skills<sup>15,16</sup>. Radiographic and magnetic resonance imaging features of OA, such as joint space narrowing and cartilage defects, are moderately associated with pain levels experienced by patients<sup>17-19</sup>, while psychological well-being is

strongly correlated with reported knee pain<sup>20,21</sup>. The perception of joint pain is often the result of complex relationships between local peripheral mechanisms<sup>22</sup>, central sensitization<sup>23</sup>, and psychosocial factors<sup>24,25</sup>. For example, alleviation of pain can positively affect sleep, coping strategies, and mood, which then engender further improvements in pain levels and functional outcomes<sup>26,27</sup>. The relationships are complicated further, considering that perceived pain levels vary across sex and racial groups<sup>28-30</sup>, and can fluctuate on a daily<sup>31,32</sup> and monthly<sup>33</sup> basis.

To date, findings from a few longitudinal studies have indicated that longterm fluctuations in OA pain levels relate to quality of life<sup>33-35</sup> and healthcare resource utilization<sup>14,36</sup>; however, direct associations between changes in OA pain levels and a full range of other health outcomes have rarely been studied at intervals of less than 1 month. Greater knowledge of the effect of longitudinal OA pain fluctuations on other health outcomes could lead to reductions in the burden of OA pain for patients, their families, and healthcare services. Therefore the Longitudinal Examination of Arthritis Pain (LEAP) study was conducted to gain a more precise understanding of these relationships. The LEAP study is the first to examine the variability of self-rated OA joint pain and its associations with other health outcomes on a weekly basis, among adults diagnosed with OA.

## MATERIALS AND METHODS

**Study design.** The LEAP study was a longitudinal, observational study conducted in the US between May 1 and December 5, 2005. All patients who met the study eligibility requirements and completed the informed consent process underwent an initial physician interview. Patient-reported pain levels and other health outcomes were then collected using weekly telephone interviews over 12 weeks. The LEAP study was conducted in accordance with US Good Clinical Practice guidelines.

**Patients.** English-speaking adults aged at least 50 years with physician-diagnosed hip and/or knee OA were eligible for enrollment in LEAP. Patients were recruited across 4 census regions of the US by 12 primary care and 4 rheumatology practices (4 sites in the Northeast, 8 in the South, 1 in the Midwest, and 3 in the West). Sites were selected using specific institutional criteria, to ensure high-quality study conduct and the ability to enroll sufficient numbers of patients with hip and/or knee OA. Participating practices received posters (displayed at the discretion of the site coordinator) to advertise the study and recruit potential participants. Practices received a one-time compensation of \$2000 for the cost of contracting, recruiting, and screening activities plus \$200 per patient enrolled.

All patients were required to have identified signal-joint pain in a hip or knee on at least 15 out of the 30 days prior to enrollment, and to hear well enough to participate in a telephone interview. Patients received \$25 compensation for each weekly questionnaire they completed, up to a total of \$325 for the maximum of 13 completed questionnaires. Potential participants were excluded if they had other pain sites or conditions that would interfere with their ability to assess pain in the signal joint, had a prosthesis in the signal joint, had received an intraarticular injection in the signal joint within the 3 months preceding enrollment, were currently participating in a clinical trial, or had taken glucosamine for less than 3 months prior to the enrollment date.

### Assessments

**Baseline data collection.** Baseline data for each patient were obtained during an initial visit to the physician's office, with input from the patient and a cli-

nician familiar with the patient's medical history. Sociodemographic characteristics, clinical characteristics, current therapy, and healthcare resource utilization data were recorded.

**Daily rating sheet.** Patients were provided with a diary and encouraged to complete structured daily rating sheets to rate their daily pain at its highest, at its lowest, and on average using a scale of 0 (no pain) to 10 (extreme pain). Daily rating sheets also included a question asking whether more or less pain medication than usual was taken on that day. The purpose of the daily rating sheets was to help patients complete their weekly telephone interviews, and thus patients were not instructed how or at what time each day to complete the sheets. The daily rating sheets were not formally collected.

**Weekly telephone interview.** Weekly telephone interviews were carried out over 12 weeks by 10 trained survey administrators; patients did not have a copy of the interview questions. Interviews took an average of 20 minutes. Patients completed their first interview within about 1 week of study enrollment. Subsequent interviews took place at prearranged times and dates and, if possible, the same interviewer conducted all interviews for a given patient. Patients could miss interviews and remain in the study. Any patient who missed a scheduled interview was contacted twice within 1 day (to complete the missed interview) and 3 times within a week (to schedule the next interview). Patients who missed 2 consecutive interviews received a reminder postcard. These patients, along with any who provided verbal indication that they no longer wished to continue, were no longer contacted by interviewers. However, patients could reinstate study involvement at any time during the 12-week period by calling a toll-free number.

Each interview was scripted and used an identical questionnaire that covered 6 areas of interest: pain/stiffness, daily activities and function, productivity, emotional well-being, quality of life, and healthcare resource use. The questionnaire was composed of 61 questions: 8 from the 8-item Medical Outcome Study Short-Form health survey (SF-8)<sup>37</sup>, 5 from the 5-item Mental Health Inventory (MHI-5)<sup>38</sup>, 24 adapted from the Western Ontario and McMaster Universities OA index (WOMAC)<sup>39</sup>, and an additional 24 free-standing questions developed specifically to assess pain severity, daily activities, productivity loss, sleep impairment, and use of healthcare services. Use of telephone interviews for the WOMAC and SF-8 are valid methods of obtaining outcome measurements<sup>40,41</sup> and, although use of MHI-5 by telephone has not been validated, respondents generally completed the questions with little or no intervention from an interviewer.

**Analytical methods.** Baseline data were summarized descriptively for the study population.

**Longitudinal pain fluctuations.** The patient-rated lowest, highest, and average pain scores provided during each interview were used to calculate weekly pain fluctuations for each patient who completed an interview during a given week. Within-week pain fluctuations were calculated by subtracting the lowest pain score for the given week from the highest pain score for the given week. Between-week fluctuations in WOMAC pain subscale score were also examined.

**Multivariable regression analyses.** The relationships of pain and pain fluctuations to other health outcomes were examined using multivariable regression analyses. The WOMAC pain subscale score, patient-rated highest weekly pain score, patient-rated average weekly pain score, patient-rated lowest weekly pain score, and the number of days per week when the patient deemed their pain to be manageable, were all individually tested as independent variables in separate models. The patient-rated dichotomous measure ("acceptable"/"unacceptable" pain) was also examined as a predictor of outcome. The WOMAC pain subscale and the "acceptable"/"unacceptable" pain rating proved to be the 2 most consistent predictors of outcome across all domains, and therefore outcome data based on these 2 measures of pain are presented. A 2-point change was considered to be a minimum clinically important difference on the WOMAC pain subscale (an 11-point scale)<sup>42,43</sup>. The other health outcome variables evaluated were daily activities and function, productivity (among workers and nonworkers), emotional well-being (mood, sleep interference), quality of life, and healthcare resource use.

The effect of pain assessed at baseline examination (Week 1) and changes

in pain status over time on each outcome variable were examined using generalized estimating equation models<sup>44</sup>, using a binomial link for 0–1 dependent variables, a Poisson link for count data, and a Gaussian link for continuous variables. This approach provides a coefficient for within-subject differences over time (i.e., the average change in an outcome measure of interest associated with a specific change in pain level). In all multivariable regression models, adjustments were made for age, sex, race/ethnicity, marital status, body mass index, comorbidity, education status, medication use, number of years since onset of OA symptoms, WOMAC physical functioning score, and WOMAC stiffness subscale score. The MHI-5 score was considered a potential confounding variable and was controlled in all analyses except mood. Medical insurance coverage was controlled when analyzing the effect of pain status on healthcare resource use<sup>45</sup>.

## RESULTS

**Patient disposition.** Of 303 adults screened for possible participation in the LEAP study, 287 were enrolled. The geographic distribution of enrolled patients in the US was 44% South, 28% Northeast, 20% West, and 9% Midwest. Patient retention was high: only 33 patients (11%) did not complete the study and 21 of these withdrew prior to their fourth weekly interview. The most common reasons for patient discontinuation (based on anecdotal evidence from interviewers) were unspecified personal reasons, finding the daily diary and weekly interviews cumbersome, or going on vacation. Among the 279 patients (97%) who completed at least 1 interview, the mean  $\pm$  SD number of completed interviews was  $10.7 \pm 2.5$ ; 234 patients (82%) completed 10 or more interviews. The most common reasons for missed interviews were vacation, hospitalization, or forgetting the appointment.

**Baseline characteristics.** Sociodemographic and clinical characteristics of the enrolled patients are summarized in Table 1 and Table 2, respectively. The healthcare providers most frequently consulted by patients for their OA were orthopedic surgeons (38%), physical therapists (17%), and rheumatologists (10%). At study entry, 91% of patients were taking at least 1 prescription or over-the-counter OA medication. Nonselective nonsteroidal antiinflammatory drugs (NSAID) were most commonly taken (66%). The mean  $\pm$  SD number of OA medications taken by each patient was  $3.7 \pm 0.7$ . The baseline mean  $\pm$  SD pain intensity rating was  $4.4 \pm 2.4$ , indicating moderate pain.

**Population characteristics at Week 1.** Of 287 enrolled patients, 275 completed interviews at Week 1. Sample mean responses are detailed in Tables 3 and 4. The mean WOMAC pain subscale score at Week 1 was 4.2 (indicating moderate pain). The differences between the mean “average” weekly pain rating (4.5) and the mean lowest (2.7) and mean highest (6.9) weekly pain ratings indicated a within-week pain fluctuation of roughly  $\pm 2$  points (on the 11-point daily rating scale). Nonworkers were more likely than workers to report missed work/normal activity: 62% of nonworkers and 33% of workers missed all or part of a day of work/normal activity during Week 1.

**Association between pain levels and other health outcomes at Week 1.** Cross-sectional associations between pain levels

Table 1. Sociodemographic characteristics of LEAP study patients.

| Characteristic                                | All Patients*, n = 287 |
|-----------------------------------------------|------------------------|
| Age, mean $\pm$ SD yrs                        | 65.0 $\pm$ 8.7         |
| Age group, %, yrs                             |                        |
| 50–59                                         | 28                     |
| 60–69                                         | 40                     |
| 70–79                                         | 24                     |
| $\geq 80$                                     | 6                      |
| Women, %                                      | 70                     |
| Race/ethnicity, %                             |                        |
| Non-Hispanic Caucasian                        | 89                     |
| Non-Hispanic Black/African American           | 6                      |
| Hispanic                                      | 4                      |
| Marital status, %                             |                        |
| Married/domestic partner                      | 60                     |
| Separated/divorced/widowed/never married      | 39                     |
| Living situation (all residential setting), % |                        |
| Alone                                         | 27                     |
| Spouse/partner                                | 61                     |
| Relative/friend                               | 11                     |
| Education level, %                            |                        |
| No high school diploma or GED equivalent      | 10                     |
| Completed high school or GED                  | 34                     |
| Some college or higher                        | 53                     |
| Employment status, %                          |                        |
| Work or volunteer, fulltime                   | 24                     |
| Work or volunteer, part-time                  | 23                     |
| Retired                                       | 41                     |
| Disabled                                      | 8                      |
| Other                                         | 3                      |
| Health insurance coverage, %                  |                        |
| Private                                       | 68                     |
| Medicare and no other insurance               | 45                     |
| Other insurance                               | 13                     |
| None                                          | 3                      |

\* Patients are included only in those categories for which they have known values. GED: General Educational Development

(WOMAC pain subscale score and “acceptable”/“unacceptable” pain) and other health outcomes at Week 1 are described in Tables 5 and 6. Lower WOMAC pain subscale scores were associated with lower levels of limited activity, lower levels of missed activity (nonworkers only), less sleep interference, and better quality of life. WOMAC pain subscale scores at Week 1 were not associated with levels of missed work (workers only), mood, or healthcare provider contact (Table 5). A rating of “acceptable” pain was associated with lower levels of limited activity, lower levels of missed activity (nonworkers only), less sleep interference, better quality of life, better mood, and less healthcare provider contact. A rating of “acceptable” pain at Week 1 was not associated with levels of missed work (workers only; Table 6).

**Longitudinal fluctuations.** Based on all responses given during the study, average pain levels reported by patients over 12 weeks were similar to those described at Week 1. The overall mean scores  $\pm$  SE were:  $3.8 \pm 0.04$  on the WOMAC pain subscale (2967 responses);  $4.3 \pm 0.04$  on the “average” weekly

Table 2. Clinical characteristics of LEAP study patients.

| Characteristic                                              | All Patients*,<br>n = 287 |
|-------------------------------------------------------------|---------------------------|
| Body mass index, mean ± SD                                  |                           |
| Male                                                        | 31.4 ± 6.4                |
| Female                                                      | 31.6 ± 7.7                |
| Time since onset of OA symptoms, mean yrs ± SD              | 10.9 ± 9.2                |
| Signal joint, %                                             |                           |
| Right knee                                                  | 44                        |
| Left knee                                                   | 38                        |
| Right hip                                                   | 10                        |
| Left hip                                                    | 8                         |
| OA in signal joint confirmed by radiograph, %               | 80                        |
| Length of time since confirmation, %, mo                    |                           |
| 1–6                                                         | 30                        |
| 7–24                                                        | 38                        |
| > 24                                                        | 31                        |
| Other sites with OA, mean ± SD                              | 1.9 ± 1.2                 |
| Other sites with OA, %                                      |                           |
| Knee                                                        | 68                        |
| Hip                                                         | 36                        |
| None                                                        | 9                         |
| Care received from OA specialist, %                         | 66                        |
| Dietary supplements ever used to treat OA symptoms, %       | 41                        |
| Comorbid conditions, mean ± SD                              | 1.4 ± 1.3                 |
| Most common comorbid conditions, %                          |                           |
| Cardiovascular condition (e.g., hypertension, heart attack) | 63                        |
| Diabetes                                                    | 15                        |
| Respiratory condition (e.g., asthma)                        | 15                        |

\* Patients are included only in those categories for which they have known values.

pain rating (2962 responses);  $2.6 \pm 0.04$  on the lowest weekly pain rating (2967 responses); and  $6.5 \pm 0.04$  on the highest weekly pain rating (2968 responses). The mean values and variability of other continuous outcomes reported throughout the study (data not shown) were also consistent with the data reported for Week 1. During the study, patients exhibited a mean  $\pm$  SD within-week pain fluctuation (the difference between their lowest and highest pain score during the past week) of  $3.9 \pm 1.9$  points. Forty-nine percent of patients reported at least one between-week difference in WOMAC pain subscale score of 2 or more points.

*Association between changes in pain levels and other health outcomes.* Effects of weekly pain change (as measured by the WOMAC pain subscale score and “acceptable”/“unacceptable” pain ratings over time) on other health outcomes are described in Tables 5 and 6.

*Association between changes in WOMAC pain subscale score and other health outcomes.* Weekly changes in the WOMAC pain subscale score were associated with changes in the number of days of limited activity each week, number of days with limited productivity (nonworkers and workers) each week, number of nights with sleep interference each week, mood, and quality of life (Table 5). Changes in WOMAC pain subscale score were not associated with changes in healthcare provider contact.

Change in WOMAC pain subscale score was strongly associated with productivity. A 2-point decrease in pain score was associated with a 32% improvement in the number of days of missed activity (nonworkers only) and a 48% improvement in the number of days of missed work (workers only) each week (Figure 1A). No such effect, however, was observed for mood or quality of life.

*Association between changes in “acceptable”/“unacceptable” pain and other health outcomes.* Changes between ratings of “acceptable” and “unacceptable” pain were associated with differences in the number of days of limited activity each week, the number of days with limited productivity (nonworkers and workers) each week, the number of nights with sleep interference each week, mood, quality of life, and healthcare provider contact (Table 6).

Productivity was again particularly strongly associated with these pain ratings — when pain status changed from “unacceptable” to “acceptable,” the number of days of missed work/activity improved by 64% (Figure 1B). Consistent with the observations with the WOMAC pain subscale score, change to a rating of “acceptable” pain had a relatively modest effect on quality of life and mood (degree of change < 5%; Figure 1B).

Healthcare resource use was significantly reduced when pain status changed from “unacceptable” to “acceptable.” Patients were 1.6 times more likely to contact a healthcare provider when their pain became “unacceptable.” Health insurance status did not significantly affect healthcare resource use.

## DISCUSSION

LEAP is the first observational study involving adults with OA to describe longitudinal relationships between frequent (weekly) changes in patient-rated pain levels and other health outcomes. Weekly fluctuations in signal-joint pain scores and other health outcomes were identified over 3 months; these observed reductions in pain intensity were directly associated with increased functionality, decreased sleep interference, increased productivity, improved quality of life, and decreased healthcare resource use. The LEAP study shows that a longitudinal study with weekly contact can be successfully carried out in a US population of adults with hip and/or knee OA. The results broaden the current evidence that changes in chronic pain levels affect other health outcomes, and demonstrate that small changes in OA pain have a significant and contemporaneous impact on personal and socioeconomic outcomes.

The LEAP study population was comparable to populations enrolled in similar OA studies<sup>14,46-48</sup> and resembled US patients who have symptomatic hip OA in terms of sociodemographics and clinical features<sup>47-49</sup>. The population was characterized by high levels of pain medication use, moderate levels of pain, and detectable variations in pain levels. The pain fluctuations were broadly similar to those described

Table 3. Patient-reported health outcomes at Week 1 (baseline).

| Domains and Questions                                                                          | No. of Patients | Mean $\pm$ SD or % |
|------------------------------------------------------------------------------------------------|-----------------|--------------------|
| <b>Pain/stiffness</b>                                                                          |                 |                    |
| Stiffness, mean $\pm$ SD, WOMAC subscale score                                                 | 274             | 4.8 (2.3)          |
| Pain, mean $\pm$ SD, WOMAC subscale score                                                      | 275             | 4.2 (2.1)          |
| Weekly pain rating, mean $\pm$ SD of 0 (no pain) to 10 (extreme pain)                          |                 |                    |
| Highest                                                                                        | 275             | 6.9 (2.1)          |
| Average                                                                                        | 273             | 4.5 (2.1)          |
| Lowest                                                                                         | 274             | 2.7 (2.0)          |
| Pain “acceptable” during past week, %                                                          | 274             | 69                 |
| Pain “manageable” during past week, mean $\pm$ SD days/week                                    | 274             | 5.4 (1.9)          |
| <b>Daily activities and function</b>                                                           |                 |                    |
| Function, mean $\pm$ SD WOMAC subscale score                                                   | 275             | 3.9 (1.9)          |
| Daily activities limited, mean $\pm$ SD days/week                                              | 272             | 1.9 (2.1)          |
| Able to do planned activities due to pain, %                                                   | 275             |                    |
| None/little of the time                                                                        |                 | 9                  |
| Some of the time                                                                               |                 | 26                 |
| Most/all of the time                                                                           |                 | 65                 |
| Asked for help with activities due to pain, %                                                  | 275             |                    |
| Nearly every day/more than half of days                                                        |                 | 10                 |
| On several days                                                                                |                 | 26                 |
| Never                                                                                          |                 | 64                 |
| Unable to engage in enjoyable activities due to pain, %                                        | 274             |                    |
| Every day                                                                                      |                 | 8                  |
| 2–3 times a week                                                                               |                 | 32                 |
| Once/never                                                                                     |                 | 60                 |
| <b>Productivity</b>                                                                            |                 |                    |
| Entire day of work/normal activity missed due to pain, mean $\pm$ SD days/week                 | 274             | 0.5 (1.2)          |
| Part of a day of work/normal activity missed due to pain, mean $\pm$ SD days/week              | 274             | 1.1 (1.6)          |
| <b>Emotional well-being</b>                                                                    |                 |                    |
| Mood/emotion, mean $\pm$ SD MHI-5 score                                                        | 272             | 24.2 (3.9)         |
| Sleep interference due to pain, mean $\pm$ SD rating of 0 (slept well) to 10 (unable to sleep) | 275             | 3.4 (2.9)          |
| Woken by pain, mean $\pm$ SD nights/week                                                       | 273             | 2.4 (2.6)          |
| Woken by pain, mean $\pm$ SD times/night                                                       | 175             | 2.3 (1.5)          |
| Time to fall back asleep if woken, mean $\pm$ SD hours                                         | 46              | 1.7 (1.4)          |
| <b>Quality of life</b>                                                                         |                 |                    |
| Quality of life and general health, mean $\pm$ SD SF-8 score                                   | 274             | 44.9 (6.5)         |

WOMAC: Western Ontario and McMaster Universities OA index; MHI-5: 5-item Mental Health Inventory; SF-8: 8-item Short-Form health survey.

in a study evaluating the reliability of pain flare assessment<sup>50</sup>, and similar levels of pain and pain variation have been reported in clinical trials of patients with hip and/or knee OA<sup>31,51</sup>. Importantly, although most patients in our study rated their pain levels as “acceptable,” quality of life was lower than that of the general population, as reported previously for patients with symptomatic hip and/or knee OA<sup>14,35,52</sup>. Further, about one in 10 patients reported severe and disabling levels of pain during most days. When pain control was inadequate, patients adopted self-coping approaches to deal with their pain (e.g., limiting their daily activities). Only 10% of patients had consulted a rheumatologist regarding their OA. These results suggest that many patients with OA tolerate a considerable burden of pain through self-coping mechanisms, and that the clinical management of OA pain may be inadequate in a notable subgroup of patients.

Among patients with OA pain, reductions in pain levels of 20% or more (equivalent to a decrease of ~2 points on an 11-point scale) are associated with self-rated improvements in overall clinical status after 5–12 weeks<sup>53</sup>. Although there are presently no standard definitions of pain flare in OA, a 20% variation (equivalent to a 2-point difference on the WOMAC pain subscale or a 20 mm change on a 100 mm scale) seems to be consistent and clinically significant in terms of pain perception and functional impairment<sup>42,43</sup>. In our study, clinically relevant (2-point) reductions in weekly WOMAC pain subscale scores, along with a change in pain rating from “unacceptable” to “acceptable” pain, were consistently associated with substantial improvements in activity, productivity, and sleep — outcomes that are likely to influence indirect health-care costs<sup>9,13</sup>. Mood and quality of life also improved when pain levels decreased, although the magnitude of change was

Table 4. Healthcare resource use at Week 1 (baseline).

| Domains and Questions                                      | No. of Patients | Mean ± SD or % |
|------------------------------------------------------------|-----------------|----------------|
| Healthcare resource use                                    |                 |                |
| Prescription medication taken for pain during past week, % | 275             | 90             |
| Pain relief when medication taken, %                       | 243             |                |
| None/mild                                                  |                 | 30             |
| Moderate                                                   |                 | 58             |
| Complete                                                   |                 | 12             |
| Action taken if pain relief was “none” or “mild”, %        | 72              |                |
| Reduce activities                                          |                 | 71             |
| Try different medication                                   |                 | 31             |
| Increase dose                                              |                 | 25             |
| Use a cane                                                 |                 | 24             |
| Get assistance from others                                 |                 | 14             |
| Contact doctor                                             |                 | 8              |
| Pain medication used, mean ± SD days/week                  |                 |                |
| Any                                                        | 253             | 5.4 (2.3)      |
| Over-the-counter medication                                | 246             | 3.7 (2.8)      |
| Prescription OA medication                                 | 236             | 3.2 (3.2)      |
| Medications changed by doctor, %                           | 273             | 6              |
| Contacted healthcare professional during past week, %      | 275             | 12             |
| In-person visit                                            |                 | 7              |
| Scheduled a visit                                          |                 | 3              |
| Telephone discussion                                       |                 | 6              |

Table 5. Association between adjusted WOMAC pain subscale scores and other health outcomes. Outcomes were adjusted for the covariables age, sex, race/ethnicity, marital status, body mass index, comorbidity, WOMAC stiffness score, WOMAC physical functioning score, education status, medication use, number of years since the onset of OA symptoms, and insurance status.

| Domains                              | Week 1 Pain Level<br>β-coefficient<br>(95% CI) | p      | Decrease in Pain Level*<br>β-coefficient<br>(95% CI) | p        |
|--------------------------------------|------------------------------------------------|--------|------------------------------------------------------|----------|
| Daily activities and function        |                                                |        |                                                      |          |
| Days of limited activity             | 0.1192<br>(0.0223, 0.2161)                     | 0.0159 | -0.1070<br>(-0.1632, -0.0507)                        | 0.0002   |
| Productivity                         |                                                |        |                                                      |          |
| Days of missed work (workers)        | 0.0869<br>(-0.2246, 0.3984)                    | 0.5845 | -0.2170<br>(-0.3947, -0.0393)                        | 0.0167   |
| Days of missed activity (nonworkers) | 0.1706<br>(0.0135, 0.3277)                     | 0.0333 | -0.1441<br>(-0.2366, -0.0516)                        | 0.0023   |
| Emotional well-being                 |                                                |        |                                                      |          |
| MHI-5 score                          | 0.0074<br>(-0.0089, 0.0236)                    | 0.3760 | 0.0106<br>(0.0042, 0.0170)                           | 0.0012   |
| Nights with sleep interference       | 0.1644<br>(0.0537, 0.2752)                     | 0.0036 | -0.0680<br>(-0.1089, -0.0271)                        | 0.0011   |
| Quality of life                      |                                                |        |                                                      |          |
| SF-8 score                           | -0.0123<br>(-0.0209, -0.0038)                  | 0.0049 | 0.0126<br>(0.0079, 0.0174)                           | < 0.0001 |
| Healthcare resource use              |                                                |        |                                                      |          |
| Contact with healthcare provider     | 0.0870<br>(-0.1555, 0.3296)                    | 0.4818 | -0.1012<br>(-0.3180, 0.1155)                         | 0.3599   |

\*1-unit decrease (improvement) in WOMAC pain subscale score. WOMAC: Western Ontario and McMaster Universities OA index; MHI-5: 5-item Mental Health Inventory; SF-8: 8-item Short-Form health survey.

smaller than for productivity, activity, or sleep. The associations represent the direct effect of pain, as the models were adjusted for age, sex, race/ethnicity, marital status, body mass index, comorbidity, education status, medication use, number

of years since onset of OA symptoms, WOMAC physical functioning score, and WOMAC stiffness subscale score.

The links between changes in pain levels and quality of life observed in this study are consistent with the results of other

*Table 6.* Association between adjusted “acceptable”/“unacceptable” pain ratings and other health outcomes. Outcomes were adjusted for the covariables age, sex, race/ethnicity, marital status, body mass index, comorbidity, WOMAC stiffness score, WOMAC physical functioning, education status, medication use, number of years since the onset of OA symptoms, and insurance status.

| Domains                                  | Week 1 Pain Rating<br>“acceptable”<br>β-coefficient<br>(95% CI) | p        | Change in Pain Rating<br>to “acceptable”<br>β-coefficient<br>(95% CI) | p        |
|------------------------------------------|-----------------------------------------------------------------|----------|-----------------------------------------------------------------------|----------|
| Daily activities and function            |                                                                 |          |                                                                       |          |
| Days of limited activity                 | −0.5466<br>(−0.7943, −0.2990)                                   | < 0.0001 | −0.3012<br>(−0.4321, −0.1702)                                         | < 0.0001 |
| Productivity                             |                                                                 |          |                                                                       |          |
| Days with limited productivity (workers) | −0.4990<br>(−1.0722, 0.0742)                                    | 0.0880   | −0.5051<br>(−0.9460, 0.0643)                                          | 0.0247   |
| Days with limited activity (nonworkers)  | −0.5677<br>(−0.9016, −0.2337)                                   | 0.0009   | −0.4916<br>(−0.7122, −0.2709)                                         | < 0.0001 |
| Emotional well-being                     |                                                                 |          |                                                                       |          |
| MHI-5 score                              | 0.0615<br>(0.0194, 0.1037)                                      | 0.0043   | 0.0269<br>(0.0114, 0.0423)                                            | 0.0007   |
| Nights with sleep interference           | −0.2763<br>(−0.5408, −0.0117)                                   | 0.0407   | −0.1953<br>(−0.3017, −0.0889)                                         | 0.0003   |
| Quality of life                          |                                                                 |          |                                                                       |          |
| SF-8 score                               | 0.0541<br>(0.0349, 0.0733)                                      | < 0.0001 | 0.0341<br>(0.0198, 0.0484)                                            | < 0.0001 |
| Healthcare resource use                  |                                                                 |          |                                                                       |          |
| Contact with healthcare provider         | −0.8463<br>(−1.3653, −0.3272)                                   | 0.0014   | −0.4939<br>(−0.9328, −0.0550)                                         | 0.0274   |

\* Change from “unacceptable” to “acceptable” pain rating. WOMAC: Western Ontario and McMaster Universities OA index. MHI-5: 5-item Mental Health Inventory; SF-8: 8-item Short-Form health survey.

studies<sup>34,35,46</sup>, including those that have described associations between pain levels, quality of life, and healthcare resource use over periods of 6 months or more<sup>14,36,54</sup>. Thus, quality of life and mood appear to respond to changes in pain levels, albeit more gradually than other outcomes such as productivity. These data emphasize the importance of evaluating patients’ current level of OA pain and the frequency with which their pain fluctuates. Management strategies designed to cope with breakthrough pain, such as lifestyle interventions (self-awareness of physical limitations and pacing activities) and healthcare system interventions (cognitive-behavioral therapy and use of rapidly acting analgesia) may also be beneficial to patients with OA pain<sup>55</sup>.

Most of the health outcomes examined were dependent on absolute levels and on relative changes in pain, but productivity (workers only) was sensitive only to fluctuations in pain. It may be that workers are reluctant to let pain affect their paid employment, and only miss work when their pain becomes unmanageable<sup>11</sup>, whereas nonworkers have more freedom to limit their activities. In support of this, most patients who reported missed work/activity during Week 1 were nonworkers. Interestingly, healthcare provider contact was associated with the pain rating of “acceptable”/“unacceptable,” but not with the WOMAC pain subscale score. It is likely that patients cope with small variations in pain by limiting activities and increasing medication usage, and only go to their doctor when

their pain management strategies are exhausted and their pain becomes “unacceptable.” Overall, the “acceptable”/“unacceptable” pain measure was predictive of change across a range of assessments, highlighting its potential value as a patient-based definition of pain flare. However, since patients who rated their pain as “acceptable” also reported considerable limitations in their work and daily activities, this tool may best be used to complement other clinical pain measures.

Several observations regarding the LEAP study warrant further attention. The fluctuating nature of OA pain means that measurements taken at one point in time may under- or overestimate the overall pain burden of individual patients<sup>33</sup>. The LEAP study was specifically designed to enable within-patient changes in pain levels and other health outcomes to be identified and related over time. Most patients experienced weekly fluctuations in pain scores, which enabled the relationships between pain fluctuations and other health outcomes to be examined. Although relationships between weekly fluctuations in pain levels and other health outcomes were observed, the causality of these associations has not been fully defined. In LEAP, factors not identified in the weekly interviews (e.g., self-coping mechanisms, pain triggers, diurnal variation, subjective stress, and exercise)<sup>56</sup> may have contributed to the reported fluctuations in pain levels and other health outcomes. Repeated administration of identical questionnaires may have influenced patient responses, and the

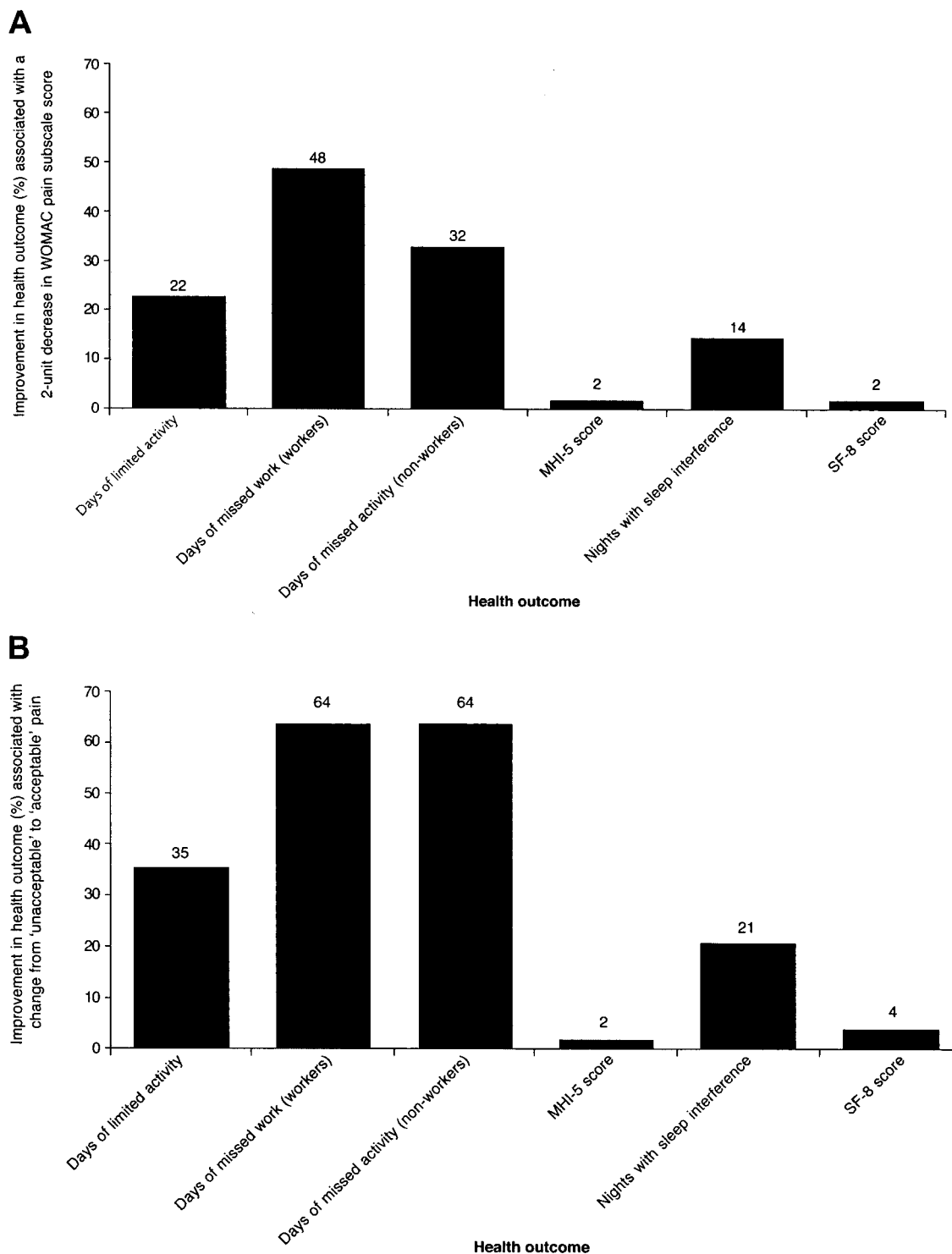


Figure 1. A. Improvements in other health outcomes associated with a 2-unit decrease in WOMAC pain subscale score. B. Improvements in other health outcomes associated with a change from “unacceptable” to “acceptable” pain rating. WOMAC: Western Ontario and McMaster Universities osteoarthritis index; MHI-5: 5-item Mental Health Inventory; SF-8: 8-item Short-Form health survey.

potential therapeutic effect of the telephone interviews themselves cannot be excluded<sup>57</sup>. Further, Black Americans may report higher levels of OA pain and poorer health outcomes than Caucasians<sup>29,58</sup>, but Black Americans and Hispanics

were underrepresented in the study population<sup>59</sup>. Finally, the 12-week LEAP study may have limited sensitivity to detect gradual changes. A similarly designed study that considers all of these factors, conducted across seasons (e.g., temporal



overlap of winter and spring) and in additional countries would be informative. Assessing the level of commitment to participate in such a study should be a consideration, since most withdrawals occurred during the early weeks of the study.

In summary, significant and direct associations between weekly fluctuations in patient-rated pain levels, functionality, quality of life, and healthcare resource use were identified among US adults with knee and/or hip OA. A reduction in pain equivalent to 2 points on the WOMAC pain subscale was associated with substantial benefits in productivity and healthcare resource use, and with additional improvements in activity, sleep, and quality of life. This in-depth examination of the relationships between joint pain and other health outcomes should help clinicians gain a better understanding of the daily experience and burden of OA pain.

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