The Reciprocal Effects of Pain Intensity and Activity Limitations

Implications for Outcomes Assessment in Clinical Trials

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Objectives: To examine the reciprocal effects of pain intensity and limitations in physical functioning over time.

Methods: This study presents findings from a reanalysis of a 7-center trial conducted in Ontario, Canada, included 209 adults with chronic knee pain secondary to osteoarthritis. Patients were randomized to receive 28 days of therapy with an active solution (1.5% w/w diclofenac sodium in dimethyl sulfoxide) or 1 of 2 control solutions containing no diclofenac. The key outcome measures used in the current analyses were administered throughout the study period and assessed pain intensity, perceived activity limitations, and a composite score measuring both domains. A structural cross-lagged regression approach was used to determine the reciprocal effects of pain and activity limitations over time.

Results: In both study groups, participants (N = 209) experienced significant reductions in mean pain intensity and activity limitations from baseline to weeks 1, 2, 3, and 4 ($P < 0.001$ for both variables). Similarly, there were significant reductions in the activity limitations outcome at weeks 1 and 4 for the active versus control group ($P < 0.05$ for both). Higher levels of perceived activity limitations predicted more future pain at all time points. Cross-lagged associations in which pain predicted subsequent perceived activity limitations were not significant at any time point. All 3 outcome measures evidenced similar responsiveness to the treatment.

Conclusion: These analyses showed that a decrease in activity limitations results in a decrease in pain intensity. However, changes in pain intensity had no effect on subsequent activity limitations in the study sample. None of the 3 outcome variables emerged as being more responsive to treatment than the others.

Key Words: pain, pain intensity, WOMAC

(*Clin J Pain* 2014;30:9–16)

Received for publication July 12, 2012; revised January 7, 2013; accepted January 12, 2013.

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Funding for this support was provided independently by the authors. The current analyses were funded by Covidien, Mansfield, MA. Mark P. Jensen has received consulting fees or research support from RTI Health Solutions, Research Triangle Park, NC, Covidien, Mansfield, MA, Bristol-Myers Squibb, New York, NW, Schwarz Biosciences, Raleigh, NC, Analgesic Research, Needham, MA, Depomed, Newark, CA, Eli Lilly, Indianapolis, CA, Pfizer, New York, NY, Merck, Whitehouse Station, NJ, Medtronic, Minneapolis, MN, and Smith & Nephew, Andover, MA within the past 36 months. Ivan R. Molton received consulting fees from Jensen Consulting for performing the analyses for this study.

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Chronic pain is a significant problem throughout the world. According to a 2008 study by the World Health Organization, an estimated 37% of adults in 10 developed countries experience chronic pain.[1] In the United States, approximately 116 million people experience chronic pain.[2] Unfortunately, many patients experience inadequate pain relief with currently available treatments. To identify and evaluate more effective pain treatments, researchers need valid and reliable outcome measures that are sensitive to treatment effects. However, there remain significant questions regarding the sensitivity of currently available measures.[3]

One potentially confounding factor in assay sensitivity for pain treatment studies is the potential mutual effects of pain intensity and disease-related activity limitations. *Pain intensity* reflects the magnitude of perceived pain, whereas disease-related *activity limitations* reflects the extent to which the symptoms of a disease (including pain, and in the context of osteoarthritis, stiffness) interferes with routine activities, such as walking and performing daily tasks.[4,5] Although often measured separately, these domains may influence one another.

In clinical trials that assess only pain intensity, the potential associations between intensity and activity limitations could limit or bias the ability to detect treatment effects. For example, it is possible that a decrease in pain intensity could lead to a decrease in the extent to which that pain interferes with activity,[6–8] resulting in an increase in activity and, possibly, a consequent increase in pain intensity.[9–11] To the extent that this process occurs, evaluating the effects of pain treatments using separate measures of pain intensity and activity limitations could potentially underestimate the direct effects of a pain treatment on pain intensity. In this situation, a composite score that takes into account a treatment's effects on *both* parameters—such as the pain intensity and functional limitations subscales of the Western Ontario and McMasters Universities (WOMAC) Osteoarthritis Index[12]—could be more indicative of the measure of a treatment's effect than either domain individually.[13]

In other pain populations, increased activity (as reflected by a decrease in activity limitations) could potentially contribute to a decrease in pain (eg, some samples of individuals with osteoarthritis (OA)[14] or fibromyalgia[15]). In such populations, when a treatment-related decrease in pain intensity contributes to decreases in activity limitations, the true direct effects of the analgesic on pain intensity could be overestimated. In this case, a composite score of measures of pain intensity and activity limitations would be unlikely to be more responsive to treatment than the measure of pain intensity alone.

Given these considerations, both clinical practice and the design of clinical trials in pain could benefit from an

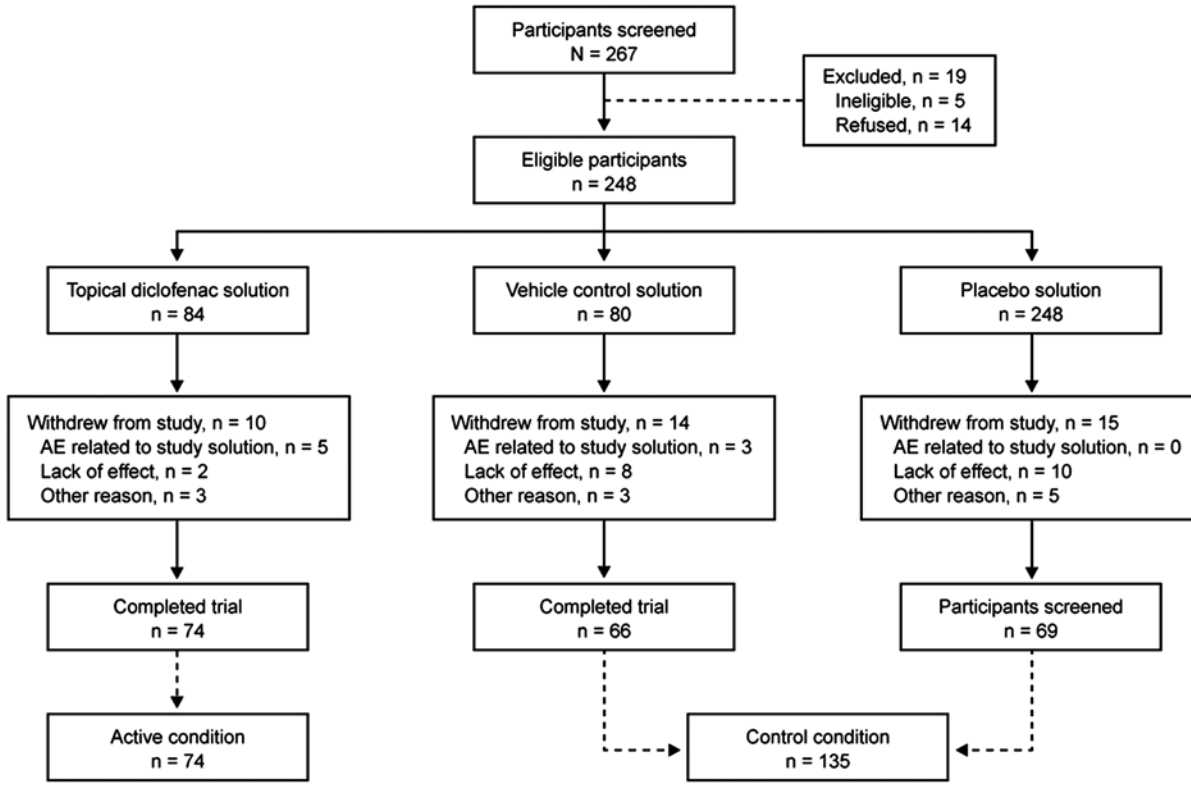

FIGURE 1. Participant flow. AE indicates adverse event.

increased understanding of the relationship between changes in pain intensity and changes in activity limitations (and vice versa) in the context of clinical trials. Additional research regarding the relative responsiveness of outcome measures assessing pain intensity and activity limitations alone, versus composite scores assessing both domains, is also important for developing a comprehensive understanding of how to assess outcomes in clinical trials and clinical practice.

To address these issues, we conducted a reanalysis of data from a recently completed clinical trial to clarify the impact of changes in pain intensity on activity limitations and the impact of changes in activity limitations on pain intensity. Furthermore, we examined the relative sensitivity of measures of pain intensity, activity limitations, and a composite measure of both domains for detecting treatment effects. To understand the potential reciprocal impacts of pain intensity and activity limitations, we used a cross-lagged panel design using the longitudinal data from a published clinical trial of topical diclofenac solution on pain intensity in a sample of patients with knee OA, and that assessed both pain intensity and activity limitations on multiple occasions throughout the trial.[16] We also examined the relative responsiveness to treatment of measures of (1) pain intensity, (2) activity limitations, and (3) a composite score made up of measures of both domains.

We hypothesized that a decrease in pain intensity would likely result in a decrease in activity limitations in the sample. Given that activity is associated with subsequent decreases in pain intensity in patients with OA,[14] we also hypothesized that a decrease in activity limitations would be followed by a decrease in pain in our sample. Finally, if these patterns of influence were supported, we hypothesized that the measure of pain intensity would be more responsive to treatment than either a measure of activity limitations or a composite score made up of measures of pain intensity and activity limitations.

MATERIALS AND METHODS

Participants

Participants in the present study were 209 individuals with chronic knee pain secondary to OA, assessed as part of a 7-center trial testing the efficacy of a topical diclofenac solution in southern Ontario, Canada. A full description of study recruitment and participant characteristics for this randomized, controlled trial is provided in Bookman et al.[16] Briefly, these participants were men and women, selected on the basis of radiologically verified osteoarthritis in at least 1 knee, with at least moderate pain during the 2 weeks before random assignment.[16] Exclusion criteria included acute trauma, history of drug or alcohol abuse, corticosteroid use, ochronosis, or metabolic bone disease.[16]

A total of 267 individuals were screened for the study. Nineteen were excluded (5 were ineligible and 14 declined to participate). Of the remaining 248, 209 completed all assessments and were included in the present analysis. The flow chart for study completion is presented in Figure 1.[16]

Procedures

All procedures were approved by the Committee for Research on Human Subjects at Toronto Hospital, and by similar committees at all other participating sites. All

participants provided written informed consent to participate in the study.

As a part of the original research trial, participants were randomly assigned to receive either an active solution (1.5% w/w diclofenac sodium in dimethyl sulfoxide [DMSO]) or 1 of 2 controls: (1) a vehicle control (DMSO 45.5%, with no diclofenac) or (2) a placebo solution consisting of a modified carrier with a small amount of DMSO (4.55% w/w) but no diclofenac.[16] Participants were instructed to apply about 40 drops of solution around the affected knee or knees 4 times daily for 28 days. Patients completed assessments of pain and activity limitations at baseline (after a 1-week "washout" period of abstinence from other analgesics) and during each trial day through a standardized diary. Compliance regarding use of the solution was assessed by measurement of residual weights.[16]

The current analyses were designed to determine the pattern of reciprocal causality among outcome variables over time, and to test intervention effects at several time points. Therefore, data collected during the original trial were reanalyzed for cross-lagged effects using path analysis (see the Statistical Approach section).

Measures

The key outcome measures for these analyses were 2 subscales of the WOMAC LK3.0 Osteoarthritis Index. The WOMAC index is a 24-question, multidimensional pain and functioning questionnaire that assesses pain, perceived limitations in physical function due to pain, and stiffness on a series of 5-point Likert scale (ranging from 0 to 4; 0 representing "None" and 4 representing "Extreme"). This instrument has been well validated and demonstrates adequate psychometric characteristics, including good reliability, construct, and content validity.[12,17] The subscales used in the present analysis were: (1) pain intensity, measured by 5 questions about pain intensity during activities (such as walking on a flat surface, going up or down stairs, and standing upright) and (2) perceived activity limitations, measured by 17 questions about difficulties due to arthritis (such as difficulty shopping, rising from bed, sitting, getting on/off the toilet, and doing light domestic duties).

Creation of Outcome Variables

We used 3 outcome variables in the current study: pain intensity, activity limitations, and a composite score measuring both intensity and limitations (computed as a mean of the WOMAC pain intensity and activity limitations scales). Reports were collected for both knees at baseline and for each trial day thereafter. For longitudinal analyses, we created outcomes for pain intensity and activity limitations at each of 5 time points: (1) baseline (this score was either post-washout [for those who were using other analgesics] or prewashout [for those who were not using analgesics])[16]; (2) week 1 (mean score of daily diary reports from trial days 1 to 7); (3) week 2 (mean score of daily diary reports from trial days 8 to 15); (4) week 3 (mean score of daily diary reports from trial days 16 to 22); and (5) week 4 (mean score of daily diary reports from trial days 22 to 28).

For individuals who only reported pain in 1 knee, the average includes only pain reports for that knee. For the significant number of individuals (46%) who reported pain in both knees, the study knee was defined as the more painful knee at baseline, based on the WOMAC pain dimension baseline assessment. If the 2 knees had the same scores, the left knee was designated as the study knee.

Statistical Approach

All analyses were conducted using the SPSS version 16.0 (IBM, http://www-01.ibm.com/software/analytics/spss/) and Mplus version 6.12 (Muthén & Muthén, http://www.statmodel.com/) software packages.

Normality Assumptions

Before analysis, all outcome and predictor variables were assessed for normality. Significant skew or kurtosis (ie, >2.0) would result in attempts to normalize through log or other transformation.

Cross-lagged Effects

To determine the reciprocal effects of pain and limitations in physical functioning over time, we used a structural cross-lagged regression approach.[18] Cross-lagged analyses are useful in that they allow for simultaneous evaluation of 3 different kinds of information: (1) autoregressive paths, allowing for the estimation of the effect of pain intensity at time *t*, on pain intensity at time $t + 1$, and for the effect of activity limitations at time *t* on physical limitations at time $t + 1$; (2) cross-lagged paths, allowing for the estimation of the effect of pain at time *t* on activity limitations at time $t + 1$ and vice versa, and (3) concurrent residual correlations, allowing for estimation of the pathways between pain and perceived activity limitations at each time point. Placing all of these pathways in the same model has the advantage of allowing one to estimate the mutual effects over time of each variable on the other, while simultaneously controlling for autoregressive and concurrent associations. This means, in application, that one can determine whether changes in pain coincide with or predict changes in activity limitations, and vice versa. This approach has been widely used in longitudinal research of complex psychosocial variables,[19] including pain.[20] The theoretical model for the present analyses is presented in Figure 2.

Treatment Effects

Treatment effects from baseline to posttreatment have been reported[16] and were not a focus of these analyses. However, for purposes of interpretation, we sought to confirm efficacy results by testing them over 4 time points and by reporting effect sizes. Carrier control and placebo groups were combined into 1 "control" condition (n = 135) and compared with individuals receiving the active treatment (n = 74). Simple between-group and within-group *t* tests were performed at each time point, and the effect size for each significant difference was estimated using Cohen *d* and ϵ^2.

Assay Sensitivity of Outcome Measures

To determine whether a composite variable containing measures of both pain intensity and activity limitations would be better able to capture treatment effects than measures of either outcome domain alone, we used a 1-way multivariate analysis of variance (MANOVA) approach to compare the sensitivity of the different measures for detecting differences due to the treatment conditions at each time point. Before performing the MANOVAs, we examined the outcomes to ensure that they met criteria for MANOVA testing. Type III sum of squares was used to

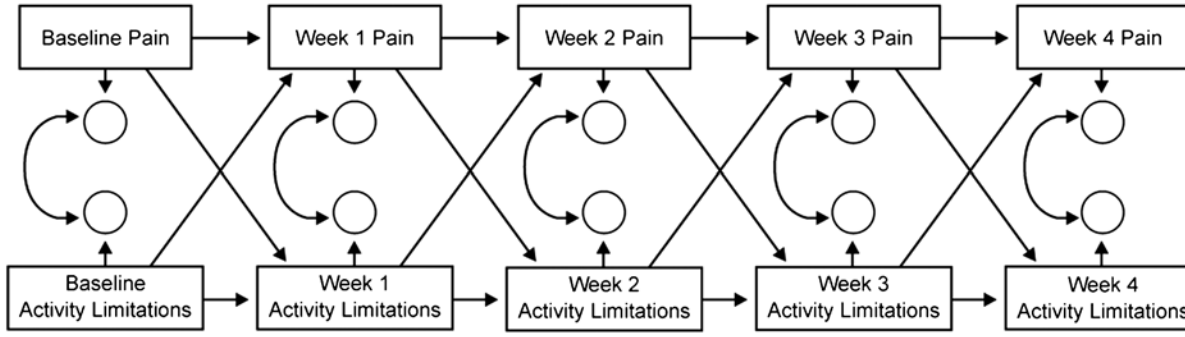

FIGURE 2. Theoretical cross-lagged panel model. Activity limitations = WOMAC limitations in physical activity subscale. Pain = WOMAC pain subscale. WOMAC indicates Western Ontario and McMasters Universities.

manage the effects of differences in sample size between treatment groups.

RESULTS

Participants

Demographic and medical data for these participants (N = 209) are reported in Bookman et al.[16] Briefly, the participants were predominantly middle-aged or older (*M* age = 61.7 y) women (63.3%) with radiologically confirmed OA of the knee. Almost half (46%) reported bilateral knee pain, with the rest (54%) reporting pain in just 1 knee. Participants did not differ by demographic or medical variables between active and control conditions.

Assumptions Testing

All study outcome variables met normality assumptions (all skew and kurtosis values <1.0), and visual inspection of standardized residuals did not suggest heteroscedasticity. The data were therefore considered adequate for multiple regression and used in non-transformed form.

Treatment Effects

At baseline, participants did not vary in pain intensity score by treatment condition ($p = 0.79$). In both study groups, participants experienced a significant drop in pain and limitations in physical functioning from baseline to weeks 1, 2, 3, and 4 ($P < 0.001$ for all variables; Fig. 3). However, mean WOMAC pain intensity scores at week 1 were lower for those in the active treatment group compared with controls ($t = 2.09$, $P < 0.05$), and there was a trend for a significant difference in pain at week 4 ($t = 1.70$, $P = 0.09$). Similarly, there were significant differences between the active and control conditions at weeks 1 and 4 on the WOMAC activity limitations outcome ($t = 2.27$ and 2.19, respectively; $P < 0.05$ for both time points). For both pain and activity limitations, the effect size for differences between the active and control solutions was modest, ranging from Cohen $d = 0.25$ to 0.34.

Cross-lagged Model Testing

Model Fit

The final cross-lagged panel model was an adequate fit to the data ($\chi^2/df = 1.80$; comparative fit index = 0.99; root mean square error of approximation = 0.06; standardized root mean square residual = 0.018). This model is presented in Figure 4. For ease of interpretation, paths not reaching $P < 0.10$ have been removed from the figure.

Concurrent Associations

Concurrent residual correlations were positive and significant during baseline ($B = 0.71$, $P < 0.001$), week 1 ($B = 0.84$, $P < 0.001$), week 2 ($B = 0.87$, $P < 0.001$), week 3 ($B = 0.86$, $P < 0.001$), and week 4 ($B = 0.20$, $P < 0.01$). These findings suggest that pain and activity limitations due to pain were related across time, although the association dropped considerably during the final week of the trial.

Autoregressive Pathways

An evaluation of the autoregressive pathways for outcomes showed that previous pain predicted subsequent pain at all time points, and that this was most consistent after baseline (ie, once the trial had started and the treatment [placebo or active] was stable). Autoregressive pain coefficients were as follows: baseline to week 1 ($B = 0.22$, $P < 0.001$); week 1 to week 2 ($B = 0.60$, $P < 0.001$); week 2 to week 3 ($B = 0.68$, $P < 0.001$); week 3 to week 4 ($B = 0.77$, $P < 0.001$). Similar autoregressive results were established for activity limitations due to OA, for which previous limitation predicted future limitations for the first 3 time points: baseline to week 1 ($B = 0.73$, $P < 0.001$); week 1 to week 2 ($B = 0.95$, $P < 0.001$); week 2 to week 3 ($B = 0.89$, $P < 0.001$). However, activity limitations during week 3 were not significantly predictive of physical limitations during week 4 ($B = 0.31$, $P = 0.17$).

Cross-lagged Pathways

Physical Limitations

Cross-lagged associations suggested that higher levels of perceived activity limitations due to OA predicted more future pain from baseline to week 1 ($B = 0.59$, $P < 0.001$), from week 1 to week 2 ($B = 0.29$, $P < 0.01$), and from week 2 to week 3 ($B = 0.25$, $P < 0.01$). The path from activity limitations due to pain at week 3 to pain during week 4 trended toward significance ($B = 0.15$, $P = 0.09$). The path model is presented in Figure 4.

Pain

Cross-lagged associations in which pain predicted subsequent perceived activity limitations due to OA were not significant at any time point: from baseline to week 1

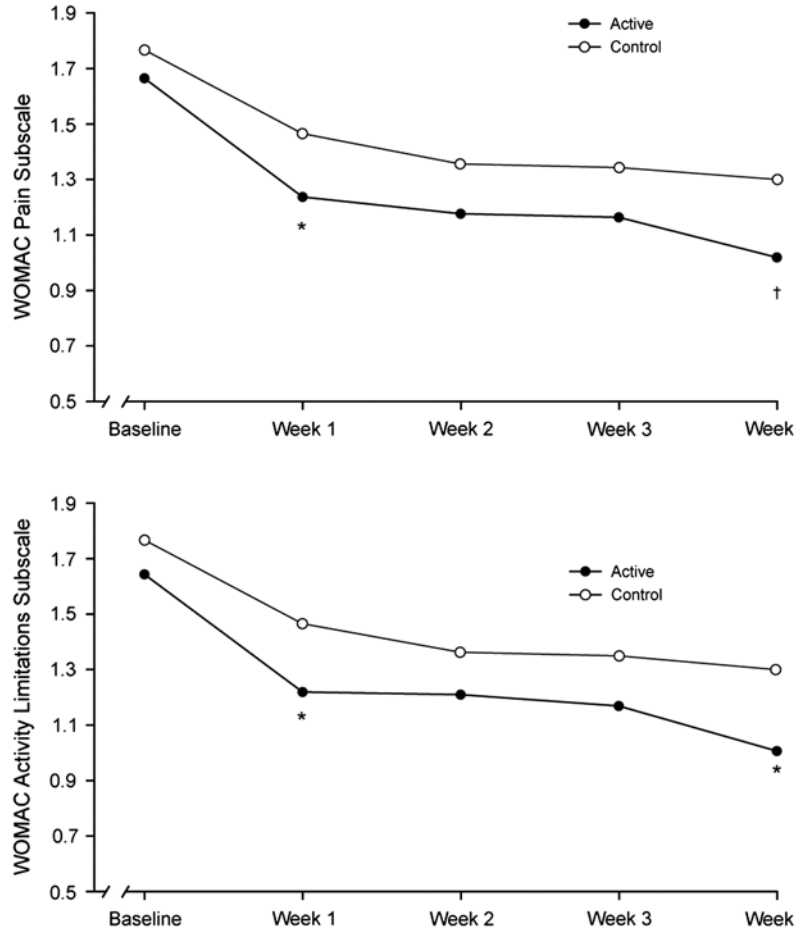

FIGURE 3. Key study outcomes by time and experimental condition. *$P<0.05$; †$P<0.10$. WOMAC indicates Western Ontario and McMasters Universities.

($B = 0.08$, $P = 0.20$), from week 1 to week 2 ($B = -0.05$, $P = 0.52$), from week 2 to week 3 ($B = 0.05$, $P = 0.45$), or from week 3 to week 4 ($B = -0.34$, $P = 0.14$; Fig. 4).

Follow-Up Testing: Multivariate Comparisons

Based on cross-lagged regression results suggesting a complex interaction between pain and perceived activity

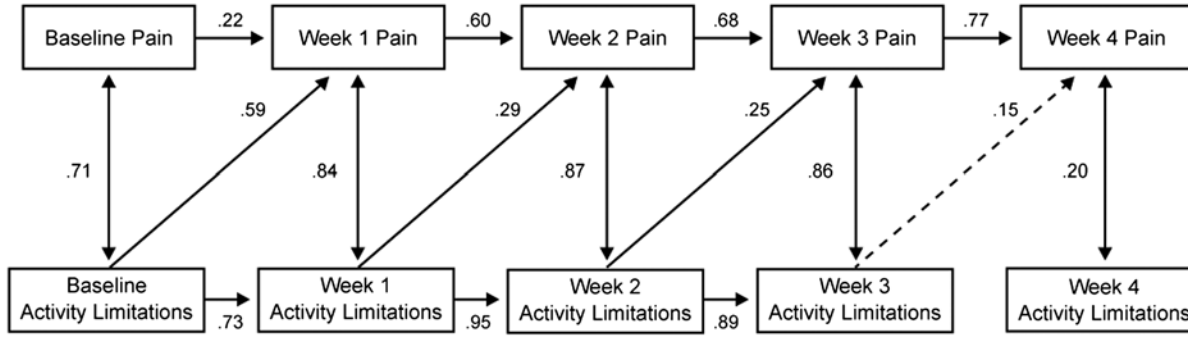

FIGURE 4. Cross-lagged panel model: pain and activity limitations over 4 weeks; N = 209. Fit indices: χ^2 (24) = 43.25; CFI = 0.99; RMSEA = 0.06; SRMR = 0.018. Solid lines indicate significance at $P<0.05$; dashed line indicates significance at $P<0.10$. Activity limitations = WOMAC limitations in physical activity subscale. Pain = WOMAC pain subscale. CFI indicates comparative fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; WOMAC, Western Ontario and McMasters Universities.

limitations in these data, we sought to determine whether a composite variable containing both outcomes would be better able to capture treatment effects than either outcome variable when treated separately. To this end, we used a 1-way MANOVA approach to compare treatment conditions at each time point. All data met criteria for MANOVA testing, including homogeneity of covariance (tested by Box test; $P > 0.01$ for all variables). Type III sum of squares was used to manage the effects of differences in sample size between treatment groups.

Results from MANOVA generally suggested that an outcome variable created by combining measures of both pain intensity and activity limitations did not outperform or underperform the measures of each individual outcome domain. There were very slight changes in the significance values of between-group comparisons as a result of use of the composite, with the difference at time 1 becoming a trend (Wilk $\lambda = 0.98$, $P = 0.08$ as a composite) and the difference at time 4 becoming significant (Wilk $\lambda = 0.97$, $P < 0.05$ as a composite). However, the effect sizes reflecting differences between treatment and control conditions were very similar whether one used the composite score or each individual variable alone (composite score vs. pain or limitations in physical function: time 1 (partial $\epsilon^2 = 0.024$ vs. 0.021 vs. 0.024); time 2 (partial $\epsilon^2 = 0.007$ vs. 0.005 vs. 0.007); time 3 (partial $\epsilon^2 = 0.011$ vs. 0.004 vs. 0.008); time 4 (partial $\epsilon^2 = 0.030$ vs. 0.014 vs. 0.023). The largest difference in effect size was at time 4, in which the composite measure outperformed the individual pain measure by a degree of partial $\epsilon^2 = 0.016$. This very small difference would not meet recommended minimum standards for significance in data analysis.[21]

DISCUSSION

The results of these analyses suggest a direct relationship between change in perceived activity limitations due to OA and pain intensity, with a decrease in perceived activity limitations resulting in a subsequent decrease in intensity. However, we did not identify any effect of changes in pain intensity on subsequent activity limitations. Moreover, none of the 3 outcome variables (pain intensity, activity limitations, and a composite score of both pain intensity and activity limitations) emerged as being more responsive to treatment than the others. These findings have important implications for understanding outcome measures in pain clinical trials.

Our finding that decreased activity limitations precedes decreased pain intensity in this sample (of patients with OA) is consistent with research showing a positive association between moderate activity levels and pain relief in this population.[14] To the extent that this pattern exists and to the extent that a decrease in pain contributes to a decrease in activity limitations, a measure of pain intensity could potentially overestimate the direct effects of treatment, because the change in pain could be due to both the direct effects of the treatment and the subsequent beneficial effects of decreased activity limitations (ie, increased activity) on pain intensity.

However, because an effect of decreased pain on subsequent activity limitations did not emerge in our analyses, this potential overestimate would not be expected in our sample, and in fact did not emerge in the analyses. If anything, the treatment had a slightly greater beneficial effect on the activity limitation measure than on the pain intensity measure. Given this, and the lack of effect of change in pain intensity on activity limitations, the measured effect of the treatment on pain intensity appears to be accurate in this sample.

An interesting pattern that emerged in the association between change in activity limitations and subsequent change in pain was a decrease in the strength of this association over time, from baseline through week 4. Given that the results of longitudinal analyses involving these variables have not previously been reported, we do not know if this pattern represents a reliable trend (ie, that would replicate in future studies of clinical trial data) or merely represents random variation in the strength of the association at different time points. If it is a reliable pattern, such a pattern might be due to there being greater change in the outcomes earlier in the trial versus later in the trial. In this case, the effects of one variable on the other, even if such effects are very real, might be more difficult to detect later in a clinical trial when outcomes begin to stablize.

The lack of an effect of change in pain intensity on subsequent activity limitations was not anticipated, given the strong and consistent associations found between these 2 outcome variables in individuals with OA.[22–24] There are a number of possible explanations for the lack of significant effects of pain intensity on activity limitations in the current sample. First, it is possible that larger changes in pain intensity than occurred in this study are needed for significant effects in activity limitations to emerge. The analyses we performed should be repeated in samples of patients who report more varied changes in pain intensity than those that occurred here to determine if (and how much) change in intensity is needed to produce a change in activity limitations. Also, activity limitation due to OA was not the primary endpoint of the treatment studied in the clinical trial from which the data for this study came. This may have resulted in a limited range of response in the activity limitation measure, which can attenuate associations found. It would be interesting to perform a similar analysis using data from a study evaluating a treatment that targets activity limitation as a primary outcome, for example,[14,15] to determine if the associations between changes in pain and changes in activity limitation differ from those found in the current analysis. Third, it is possible that the effects of pain intensity on activity limitation are very rapid (ie, occur within hours or just a few days), and that these effects might not have been detected because we examined the lagged effects of an average of each variable from 1 entire week on an average of the other variable over the course of the next week. It would be useful to examine these effects over shorter periods of time to test this possibility. Finally, the lack of effects of pain intensity on activity limitations in this study might be related to the possible heterogeneity of the sample. Subgroups of patients evidencing different associations between pain and activity level have been identified in persons with low back pain, for example,[25–27] including groups of individuals who have more or less fear of pain. Future research should determine if similar such subgroups can be identified in persons with osteoarthritis, and if group membership moderates the strength of the effects of pain on activity level.

Our analyses were also limited in that the measure of activity limitations used in the study was not a direct measure of activity. Past research has suggested that, despite rigorous validation, the WOMAC scales cannot provide a clear measure of change in physical function due

to the possibility that both pain and physical function can affect this domain.[28] Moreover, research shows that the associations between self-reported activity level and objectively assessed activity level are weak, at best.[29] In addition, like all self-report measures, the WOMAC scale scores may be affected by fatigue, other comorbid symptoms, and depression; it is therefore possible that the associations found may be explained, at least in part, by shared method variance.[24,30,31] Future researchers might consider examining the associations between pain intensity and activity using objective measures of activity, such as actigraphy.[32,33] On the other hand, it is also important to keep in mind that the domains of arthritis-related activity limitations (what an individual is not able to do because of arthritis symptoms such as pain) and activity level, while related, are not the same. Thus, reliable and "objective" measures of activity limitations do not (yet) exist.

In addition, these data were from patients with OA, a population that differs from other pain populations in regard to cause and effects of pain and the impact of physical function and activity on pain intensity. Thus, it is possible—even likely—that the current findings are not applicable to other chronic pain populations. It would be instructive to replicate them in other groups of patients to determine broader generalizability.

Despite the limitations of the current study, however, the findings provide important information that can inform the design and analysis of clinical trials in studies examining the efficacy of pain treatments in patients with OA. Importantly, the findings suggest that measures of pain intensity (specifically, the WOMAC Pain Intensity scale) likely provide accurate estimates of the direct effects of pain treatment on pain associated with knee OA, and support continued use of such measures as primary outcome domains in clinical trials. The findings also raise the intriguing possibility that activity level—or at least, in this case, measures of activity limitations—may have a larger effect on pain intensity than vice versa in persons with OA. If this finding is replicated in other pain populations, then concerns about the potential biasing impact of changes in pain intensity on activity, and subsequent impact of activity on pain intensity on estimates of treatment outcome, may not be warranted. More research is needed to determine the extent to which this intriguing finding replicates in other samples. Finally, although not a specific goal of this study, the findings suggest the possibility of a causal (and positive) impact of a decrease in activity limitations as producing a decrease in pain. If this finding is replicated in other samples of patients, including those with OA, it supports the idea of activity as a potential analgesic, consistent with behavioral interventions that target decreased activity limitations/increased activity as a way to improve not only overall quality of life, but to decrease pain intensity as well.[14,15]

ACKNOWLEDGMENTS

The authors would like to thank Julia Schroeder, of Synchrony Medical, LLC, West Chester, PA, for overseeing the creation of the figures in the paper (which were designed by the authors), helping identify articles to cite for some of the points made in the article, and providing editorial support by making suggestions for changes to earlier drafts written by the authors.

REFERENCES

1. Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain*. 2008;9:883–891.
2. Institute of Medicine; Committee on Advancing Pain Research, Care, and Education; Board on Health Sciences Policy. *Relieving Pain in America: a Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
3. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.
4. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23:129–138.
5. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment*. 3rd ed. New York, NY: Guilford Press; 2011:19–44.
6. Jensen MP, Gould EM, Victor TW, et al. The relationship of changes in pain quality to pain interference and sleep quality. *J Pain*. 2010;11:782–788.
7. Buchser E, Paraschiv-Ionescu A, Durrer A, et al. Improved physical activity in patients treated for chronic pain by spinal cord stimulation. *Neuromodulation*. 2005;8:40–48.
8. Nieto R, Raichle KA, Jensen MP, et al. Changes in pain-related beliefs, coping, and catastrophizing predict changes in pain intensity, pain interference, and psychological functioning in individuals with myotonic muscular dystrophy and facioscapulohumeral dystrophy. *Clin J Pain*. 2012;28:47–54.
9. Huijnen IP, Verbunt JA, Peters ML, et al. Differences in activity-related behaviour among patients with chronic low back pain. *Eur J Pain*. 2011;15:748–755.
10. Hasenbring MI, Verbunt JA. Fear-avoidance and endurance-related responses to pain: new models of behavior and their consequences for clinical practice. *Clin J Pain*. 2010;26:747–753.
11. Lim JY, Tchai E, Jang SN. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. *PMR*. 2010;2:723–731.
12. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15:1833–1840.
13. Turk DC, Dworkin RH, Revicki D, et al. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain*. 2008;137:276–285.
14. Tak E, Staats P, Van Hespen A, et al. The effects of an exercise program for older adults with osteoarthritis of the hip. *J Rheumatol*. 2005;32:1106–1113.
15. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. *Arthritis Res Ther*. 2010;12:R55.
16. Bookman AA, Williams KS, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. *CMAJ*. 2004;171:333–338.
17. Bellamy N. Osteoarthritis clinical trials: candidate variables and clinimetric properties. *J Rheumatol*. 1997;24:768–778.
18. Ferrer E, McArdle JJ. Alternative structural models for multivariate longitudinal data analysis. *Struct Equ Modeling*. 2003;10:493–524.
19. Wood JJ, Lynne-Landsman SD, Langer DA, et al. School attendance problems and youth psychopathology: structural cross-lagged regression models in three longitudinal data sets. *Child Dev*. 2012;83:351–366.
20. Campbell CM, Quartana PJ, Buenaver LF, et al. Changes in situation-specific pain catastrophizing precede changes in pain report during capsaicin pain: a cross-lagged panel analysis among healthy, pain-free participants. *J Pain*. 2010;11:876–884.
21. Ferguson CM. An effect size primer: a guide for clinicians and researchers. *Prof Psychol Res Pr*. 2009;40:532–538.

22. Williams VS, Smith MY, Fehnel SE. The validity and utility of the BPI interference measures for evaluating the impact of osteoarthritic pain. *J Pain Symptom Manage*. 2006;31:48–57.
23. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Rheum*. 2001;45:453–461.
24. Kennedy D, Stratford PW, Pagura MC, et al. Exploring the factorial validity and clinical interpretability of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Physiother Can*. 2003;55:160–168.
25. Hasenbring MI, Plaas H, Fischbein B, et al. The relationship between activity and pain in patients 6 months after lumbar disc surgery: do pain-related coping modes act as moderator variables? *Eur J Pain*. 2006;10:701–709.
26. Huijnen IP, Kindermans HP, Seelen HA, et al. Effects of self-discrepancies on activity-related behaviour: explaining disability and quality of life in patients with chronic low back pain. *Pain*. 2011;152:2165–2172.
27. McCracken LM, Samuel VM. The role of avoidance, pacing, and other activity patterns in chronic pain. *Pain*. 2007;130:119–125.
28. Stratford PW, Kennedy DM. Does parallel item content on WOMAC's pain and function subscales limit its ability to detect change in functional status? *BMC Musculoskelet Disord*. 2004;9:5–17.
29. Lin CW, McAuley JH, Macedo L, et al. Relationship between physical activity and disability in low back pain: a systematic review and meta-analysis. *Pain*. 2011;152:607–613.
30. Wolfe F. Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. *Rheumatology (Oxford)*. 1999;38:355–361.
31. Terwee CB, van der Slikke RM, van Lummel RC, et al. Self-reported physical functioning was more influenced by pain than performance-based physical functioning in knee osteoarthritis patients. *J Clin Epidemiol*. 2006;59:724–731.
32. Cunningham JM, Blake C, Power CK, et al. The impact on sleep of a multidisciplinary cognitive behavioural pain management programme: a pilot study. *BMC Musculoskelet Disord*. 2011;12:5.
33. Lunde LH, Pallesen S, Krangnes L, et al. Characteristics of sleep in older persons with chronic pain: a study based on actigraphy and self-reporting. *Clin J Pain*. 2010;26:132–137.

