Symptoms of Depression Predict the Trajectory of Pain Among Patients with Early Inflammatory Arthritis: A Path Analysis Approach to Assessing Change

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ABSTRACT

OBJECTIVE: Symptoms of depression and chronic pain are closely related. The objective of this study was to assess the longitudinal relationships, including directionality, between pain, symptoms of depression and disease activity in patients with early inflammatory arthritis (EIA).

METHODS: 180 patients with EIA completed a physical examination, including swollen joint count, and were administered the Center for Epidemiological Studies Depression Scale (CES-D) and the McGill Pain Questionnaire (MPQ) at two time points 6-months apart. Cross-lagged panel path analysis was used to assess concurrent and longitudinal relationships between pain, symptoms of depression and number of swollen joints.

RESULTS: Pain, symptoms of depression and number of swollen joints decreased over time ($p < 0.001$) and were prospectively linked to pain, symptoms of depression and number of swollen joints, respectively, at 6 months. Symptoms of depression and pain were correlated with each other at baseline (0.47) and 6-month follow-up assessments (0.28). Baseline symptoms of depression significantly predicted pain symptoms at 6 months (standardized regression coefficient = 0.28, $p = 0.001$), whereas pain and disease activity did not predict the course of any other variable after controlling for baseline values.

CONCLUSION: Symptoms of depression predicted the trajectory of pain from baseline to 6 months. In addition, there were reciprocal/bidirectional associations between pain and symptoms

of depression over time. More research is needed to better understand the relationship between pain and depressive symptoms and how to best manage patients with EIA who have high levels of both.

Key Indexing Terms: Rheumatoid Arthritis, Pain, Depression, Outcomes Assessment, Longitudinal Studies.

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Running Footline: Depression and Pain

Between 8% and 50% of chronic pain patients have comorbid major depression(1). Among patients with rheumatoid arthritis (RA), 13-20% also have major depression as assessed by a structured clinical interview(2-4), and 23-46% have symptoms of depression above cutoff thresholds based on self-report measures(5). Rates are similarly high among patients with early onset inflammatory arthritis(6-8). Depression and chronic pain are each individually associated with poorer overall health status. Compared to either condition alone, patients with comorbid pain and depression experience greater health care costs, more disability, and higher morbidity and mortality(9-13). The temporal and causal directions between symptoms of depression and pain and the degree to which successfully treating one is affected by the presence of the other, however, are not well-understood(14, 15).

A systematic review of the relationship between symptoms of depression and chronic pain identified studies that supported three different hypotheses: (1) that depressive symptoms precede and increase the risk of developing pain symptoms (the antecedent hypothesis); (2) that chronic pain develops first and increases the risk of depressive symptoms (consequence hypothesis); and (3) that there are common mutual causal or bidirectional pathways between pain and symptoms of depression (the stress-diathesis hypothesis)(16).

These hypotheses are not specific to RA, but several studies have examined directional relationships between pain and depressive symptoms among RA patients. Although a number of cross-sectional studies of RA patients have explored the relationship between pain and depressive symptoms(17-27), their cross-sectional designs do not allow for conclusions about directionality. Similarly, longitudinal studies have arbitrarily designated either pain or depressive symptoms as the outcome variable(28, 29) in order to test a given directionality hypothesis, but have not considered alternative hypotheses. One longitudinal study with two time points 24 months apart

examined predictors of both pain and depressive symptoms within the same study of RA patients(30) and reported significant autoregressive effects for pain and symptoms of depression at T2 after controlling for T1 demographic variables, disease variables, functional impairment and sleep problems. In addition, T1 pain and an interaction term consisting of T1 pain and T1 sleep problems independently predicted T2 depressive symptoms. This study, however, used a series of multiple regression models rather than simultaneous analysis of the relationship between pain and depressive symptom variables over time.

Traditional multiple regression approaches assume that there is a single clearly defined outcome variable and that predictor variables are stable over time and are associated with change in the outcome variable after controlling for its baseline value (e.g., pain as the outcome variable regressed on baseline symptoms of depression, which are assumed to be stable, controlling for baseline pain). These models are less adequate for testing hypotheses related to two variables, such as pain and depression, whose relationship likely evolves over time and where either variable may potentially function as a predictor variable and contribute to change in the trajectory of the other variable(31, 32). As shown in Figure 1, a prospective relationship between Time 1 depressive symptoms and Time 2 pain could potentially occur because (1) depression at Time 1 affects the *trajectory* or change in pain between Time 1 and Time 2 (Pathway A), consistent with the antecedent hypothesis; or (2) there are reciprocal relations between depressive symptoms and pain at Time 1 (Pathway B) and Time 2 (Pathway D) that are maintained over time (Pathways C). A combination of these scenarios is also possible. Multiple regression models would attribute each of these scenarios to depression influencing the trajectory of pain (Pathway A), even if the alternative hypothesis of a reciprocal or concurrent relationship that is stable over time (Pathways C to D) was more accurate(33). The same critique could be applied to an analysis of a possible prospective link

from pain to depressive symptoms (consequence hypothesis).

Cross-lagged panel path analysis models present an attractive alternative for examining the inter-relationships between two or more variables over time(31-34). These models allow for the assessment of multiple independent and dependent variables over time in a single model and, compared to multiple regression models with a single dependent variable, a stronger test of whether one variable may influence the trajectory of the other by allowing the researcher to test competing hypotheses simultaneously. Thus, in terms of Figure 1, the cross-lagged panel path analysis model is specified to have two independent variables (e.g., pain and depression) and two dependent variables (e.g., pain and depression) with simultaneous tests of all possible pathways within and between variables (Pathways A, B, C, and D).

The various forms of path analysis models were first developed for use in the social sciences and are now used more frequently in the health sciences as well. Several studies have used path analysis models to assess longitudinal relationships among variables over time or in mediation models among patients with musculoskeletal diseases(27, 35-37)..Covic et al.(38), for instance, used path analysis to test a series of cross-sectional models of the relationship between pain and symptoms of depression, but did not model this over time in any single model. Only one study(39) has used cross-lagged panel path analysis to address the issue of directionality between pain and depressive symptoms in RA. Brown et al.(39) found that among patients diagnosed with RA up to 7 years (mean 3.3 years) prior to enrollment in the study neither baseline symptoms of depression nor baseline pain predicted the other 12 months later. Pain at 2 years did significantly predict the trajectory of depressive symptoms between 2- and 3-year assessments, although the effect was relatively weak, providing partial support for the consequence hypothesis. Findings from patients with established RA and relatively stable symptoms, however, may not generalize

well to patients in the early stages of arthritic disease.

Early Inflammatory Arthritis (EIA) centers have been developed in recognition that early treatment of RA patients with disease modifying anti-rheumatic drugs (DMARDs) interferes with the disease process, slowing or preventing irreversible joint damage and disability(40-42). Indeed, the greatest improvements in pain, disability and health related quality of life (HRQoL) occur in patients treated within one year of symptom onset(43-46). Relatively few studies have investigated the relationship between pain and symptoms of depression among EIA patients. Most of these studies have been cross-sectional(7, 8, 47) or longitudinal studies that arbitrarily identified pain or symptoms of depression as a single outcome variable(48-52). Two longitudinal studies examined pain and depression outcomes in patients defined as having EIA, but each modeled pain and depression outcomes separately(53, 54) Smedstad et al.(53) studied 216 patients with disease duration up to 4 years and reported significant autoregressive effects of pain and depression at 1 and 2 years follow-up and significant concurrent relationships between pain and depression at baseline, 1 and 2 years. They did not, however, find any evidence for prospective effects of pain on depression or vice versa. Odegard et al.(54) also studied EIA patients with disease duration up to 4 years (N = 238) using repeated measures models with follow-ups at 1,2, 5, and 10 years, but did not find evidence for prospective relationships between pain and depression. The regression-based models used in each of these studies, however, were limited to assessing the trajectories of pain and depression over time in separate models. In addition, the mean disease duration in both studies was 2.2 years, whereas the goal of early inflammatory arthritis centers is to treat patients as early as possible, ideally in the first months after symptom onset(45, 46).

No published longitudinal studies in EIA however have examined directional hypotheses between pain and depression while controlling for disease activity using cross-lagged panel path

analysis. Thus, the objective of this study was to examine the longitudinal relationship between pain and symptoms of depression, controlling for disease activity, using cross-lagged panel path analysis in patients with EIA treated by a rheumatologist within one year of symptom onset.

PATIENTS AND METHODS

Patient Sample. The study sample consisted of patients enrolled in the McGill Early Arthritis Registry (McEAR) between January 2004 and December 2007 who completed baseline and 6-month follow-up registry visits. Patients in the registry are referred by 21 rheumatologists from greater Montreal, Quebec, Canada and, to be included in the registry, must have one or more swollen joints for at least 6 weeks, but less than one year duration, be 16 years of age or older, and be fluent in French or English. Exclusion criteria include clinical evidence of remote joint damage suggestive of a previous RA episode, any rheumatic diagnosis other than RA or undifferentiated inflammatory arthritis (UIA), severe functional limitation from a disease other than arthritis, and any disorder that compromises the ability to give informed consent. Patients in the registry provide an extensive clinical history, undergo a physical examination, and complete a series of self-report questionnaires related to their psychosocial and clinical health status at baseline, every 6 months for the first two years of follow-up, and annually thereafter. In this study, data from the baseline and 6-month assessments were used. The smaller number of patients with longer follow-up data did not allow for longitudinal analysis of additional assessment points. All patients in the McEAR provide informed consent, and the research ethics boards of McGill University, the Sir Mortimer B. Davis – Jewish General Hospital, and all referring hospitals approved the data collection protocol.

Measures.

Pain. The Short-Form McGill Pain Questionnaire (MPQ)(55, 56) was used in this study. It contains 11 items related to the sensory dimension of pain and 4 related to the affective dimension. Each descriptor is ranked on a four-point intensity scale (0-3; *none* to *severe*), and total scores range from 0-45. The MPQ has been extensively used and has excellent psychometric

properties(57).

Symptoms of depression. The Center for Epidemiologic Studies Depression Scale (CESD)(58) is a 20-item self-report scale that asks patients to rate frequency of depressive symptoms in the past week from 0 (*rarely or none of the time*) to 3 (*most or all of the time*). The cut-off for depression used in psychiatric samples and in the general population is 16, although a higher cut-off of 19 has been recommended for patients with RA(59, 60). Cutoffs are referenced for illustrative purposes, but the CES-D total score was used in all multivariate analyses as an index of severity of self-reported symptoms of depression.

Disease activity. Disease activity was assessed using a swollen joint count based on the American College of Rheumatology joint count of 66 swollen joints, scored 0 if there is no swelling or 1 if swelling is present(61, 62). Joint counts were performed by one of two trained McEAR research nurses who traveled to the referring rheumatology office to perform the joint counts and obtain a blood sample on the same day of the rheumatologist assessment. The same joint examiner conducted baseline and follow-up assessments. Although other measures such as the DAS28(63) exist to assess disease activity in rheumatoid arthritis, these include subjective factors such as tender joint count and patient global assessment of disease activity which may be affected by the patient's concurrent perceptions of pain and/ or symptoms of depression. In addition, swollen joint counts have been shown to be just as sensitive to change and predictive of radiographic damage as commonly used acute phase reactants such as erythrocyte sedimentation rate or C-reactive protein(62). Therefore, for the purposes of this study, the number of swollen joints was used as an objective measure of disease activity.

Statistical Analyses.

Bivariate comparisons: Clinical variables were compared between baseline and follow-up

assessments using paired sample t-tests for continuous variables (pain, depressive symptom severity) and McNemar's chi-square tests for the proportion of patients above cutoff levels on the CES-D**.** The distribution of the swollen joint count was skewed, therefore differences in the number of swollen joints at baseline and 6-month follow-up were compared using the Wilcoxon signed ranks test. All comparative analyses were conducted using SPSS version 15.0 (Chicago, IL), and all statistical tests were 2-sided with a $p < 0.05$ significance level.

Multivariate Analysis: Cross-lagged panel path analysis models developed with EQS 6.1(64) were used to simultaneously assess the cross-sectional and prospective relationships between levels of pain, symptoms of depression and the number of swollen joints. These path models can be used to simultaneously estimate correlation coefficients between concurrently measured variables (e.g., pain and depressive symptoms at time 1) and standardized regression coefficients over time between variables (e.g., depressive symptoms at time 2 regressed on pain at time 1) and within variables (e.g., depressive symptoms at time 2 regressed on depressive symptoms at time 1).

An initial model (Model 1) was specified so that pain, symptoms of depression, and number of swollen joints were allowed to correlate with each other at both baseline and 6-month assessments. In addition, each outcome variable (pain, depressive symptoms, number of swollen joints at 6 months) was regressed on its baseline value. Subsequent to Model 1, a series of 3 models with different cross-lagged associations between the 3 variables of interest were tested. Model 2 specified cross-links from baseline symptoms of depression to both 6-month pain and swollen joints (testing the antecedent hypothesis). Model 3 specified cross-links from baseline pain to both 6-month symptoms of depression and swollen joints (testing the consequence hypothesis). Model 4 specified cross-links from baseline number of swollen joints to both 6-month pain and

symptoms of depression. In each model, the "crossing" paths represent a potential association between the baseline variable tested and the trajectory of the other variables from baseline to the 6-month follow-up.

To be plausible explanations of possible causal relationships, models must fit well. That is, they must explain the bulk of the variance between model variables. This was tested by applying a series of fit indices, including the comparative fit index (CFI) which indicates how much variance is explained when going from a null model where no variables are allowed to correlate with each other to the estimated model(65); the Tucker-Lewis Index (TLI)(66) which is similar to the CFI but is more resistant to sample size; and the root mean square error of approximation(RMSEA) which indicates how much variance is not accounted for when comparing a saturated model (where are all variables are specified to correlate with each other) to the estimated model per degree of freedom(67). Standard guidelines suggest that models with TLI and CFI between 0.80 and 0.90 fit moderately well, with > 0.90 indicating a well-fitting model(67, 68). RMSEA values < 0.05 are considered to be representative of good fitting models, and values between 0.05 and 0.08 of moderate fit(68). Chi-square tests of fit are also presented. However, since they are highly sensitive to sample size and can lead to the rejection of well-fitting models, practical fit indices (CFI, TLI, and RMSEA) were emphasized(69, 70).

In addition, improvement in model fit was assessed to determine if adding links between variables improved the overall model significantly (e.g., comparing Models 2, 3, or 4 to Model 1). If adding links between variables did not improve overall model fit, then these links were not retained. Assessment of model fit and change in fit between nested models were evaluated using the Satorra-Bentler robust chi-square (S-B χ^2) and the Scaled Difference Chi-Squares test (SDCS)(71) as a conservative approach given the non-normality of the data.

RESULTS

Sample Characteristics. A total of 320 McEAR patients completed baseline assessments; 52 (16.3%) completed baseline assessments less than 6 months previous and were not eligible for the study, and 77 (of the 268 eligible patients; 28.7%) did not complete their scheduled 6-month follow-up assessment (withdrew from study or missed visit). Of the 191 patients who completed their second visit, 11 (5.1%) patients had incomplete data and were not included in the present study. Thus, 180 (67.2%) patients with complete baseline and follow-up assessments were included in the present study. The 88 patients excluded from the present analysis were not significantly different from the patients included in the study with respect to demographic variables (age, gender and education) or study outcomes (pain, symptoms of depression and number of swollen joints).

Approximately two-thirds (n = 125, 69.4%) of the sample was female; 126 patients (70.0%) were married or living as married; 107 (59.4%) had postsecondary education; and 91 (50.6%) were working. The mean age was 57.1 years (SD 14.2). Mean disease duration was 7.0 months (SD 3.5); 123 (68.3%) patients had already been treated with at least 1 DMARD (hydrochloriquine 78 [43.3%], methotrexate 69 [38.3%], sulfazaline 30 [16.7%], leflunomide 1 [0.6%]); 84 (46.7%) had been treated with prednisone; 42 patients (23.3%) met the full American College of Rheumatology criteria for RA; and slightly more than half (n = 95, 52.8%) of patients in the study were rheumatoid factor positive. The sample was similar to published data from other EIA samples of at least 100 patients in terms of age (range of mean age 49 years to 60 years)(47, 51, 53, 54, 72) and percent female (63% to 74%)(47, 51, 53, 54, 72). The sample in the current study appeared to have a higher level of education than the only other study of at least 100 patients that provided education data (60% less than 9 years), although data from that study may not be

representative(51)..

At baseline, the median number of swollen joints was 6.0 (inter-quartile range [IQR] 2.0 to 10.0), mean MPQ score was 8.0 (SD 8.6), and mean CES-D score was 13.5 (SD 9.3); 73 patients (40.6%) scored at least 16 on the CES-D, and 48 (26.7%) scored 19 or higher. At the 6-month follow-up, patients reported significantly lower scores on all 3 measures (median number swollen joints = 2.0, IQR 0.0 to 5.0, $p < 0.001$; mean MPQ = 5.5, SD = 6.7, p = < 0.001; mean CES-D = 11.0, SD = 9.0, $p < 0.001$). The number of patients scoring ≥ 16 on the CES-D was 51 (28.3%, p = 0.003), and the number of patients scoring 19 or above was 38 (21.1%, p = 0.164).

Cross-lagged panel path analysis models. The initial model, Model 1, in which baseline scores of pain, depressive symptoms, and number of swollen joints were specified to predict 6-month scores with no cross-predictions across variables, fit reasonably well (S-B $\chi^2_6 = 15.4$, p = 0.018, CFI = 0.95, TLI = 0.93, RMSEA = 0.09) (Figure 2). All prospective paths from baseline to 6-month scores were significant ($p < 0.001$). Bivariate correlations between pain, depressive symptoms and swollen joints ranged from 0.28 to 0.47 at baseline and from 0.17 to 0.28 at 6 months ($p < 0.05$). Model 2 added cross-links from baseline symptoms of depression to pain and swollen joints at 6 months (Figure 3). Baseline depressive symptoms significantly predicted pain at 6-months (standardized regression coefficient = 0.28, p = 0.002), but not swollen joints (standardized regression coefficient = 0.02, p = 0.823), so the model was re-specified after removing the link between baseline depressive symptoms and swollen joints at 6 months. Depressive symptoms at baseline continued to predict 6-month pain (standardized regression coefficient = 0.28, p = 0.001), and the model fit significantly better than Model 1 as determined by the scaled difference in chi-squares test (SDCS(1) = 11.02, $p < 0.001$). Model 3 included the prospective links of Model 1 plus cross-links from pain at baseline to depressive symptoms and

swollen joints at 6-months, but neither was significant (pain to depression, standardized regression coefficient = 0.09, p = 0.278; pain to swollen joints, standardized regression coefficient = 0.03, p = 0.652), and the model did not fit significantly better than the baseline Model 1. Model 4 added cross-links between swollen joints at baseline and the other two outcome variables at 6 months, but neither link was significant (swollen joints to depression, standardized regression coefficient = 0.09, p = 0.148; swollen joints to pain, standardized regression coefficient = 0.08, p = 0.399).

DISCUSSION

This is the first study to use cross-lagged panel path analyses methods to assess the relationship between pain and symptoms of depression over time in EIA patients who were treated by a rheumatologist within one year of symptom onset. The main findings of the study were (1) that pain, symptoms of depression and the number of swollen joints all improved significantly from the baseline visit to the 6-month follow-up; (2) that the most robust predictors of pain, symptoms of depression and swollen joints at 6 months were baseline values of these variables; and (3) that symptoms of depression predicted change in pain symptoms, but pain and swollen joints did not predict change in other variables, supporting the antecedent hypothesis. Since pain decreased between baseline and 6-month assessments, high levels of depressive symptoms were associated with less improvement in pain. There were also strong correlations between depression and pain at baseline and 6-month follow-up, which suggests important bidirectional causal processes that evolve over time.

The findings from this study are consistent with other studies in EIA that report significant improvements in clinical status (pain and swollen joints) in the first year after diagnosis in response to early detection and treatment(72, 73). In terms of change in depressive symptoms,

other studies of EIA patients have yielded conflicting results. Some studies(49, 50) have reported that depressive symptoms remain stable over time, whereas other studies(51, 74) have reported that depressive symptoms improved, which is consistent with results from the present study. Variability in results may be due to the use of different depressive symptom measures across studies as well as different follow-up assessment schedules. The general finding that high levels of depressive symptoms are common in a sample of EIA patients, however, is consistent with previous findings that rates of depression appear to be similar for patients newly diagnosed and patients with chronic RA(52, 75). Biologically, basic neuroscience research has established connections between inflammatory processes common to RA and *sickness behaviors*, such as fatigue, malaise, and depressed mood(76-78). Chronic inflammation enhances cytokine production, and several proinflammatory mediators, including the *acute response* cytokines IL-1β and TNF-α, as well as IL-6 and INFγ, have been linked to altered central nervous system activity and fatigue or symptoms of depression(76-78).

Results from this study are also consistent with other studies that have reported evidence for bidirectional causal pathways linking pain and symptoms of depression in both chronic RA and EIA(30, 53, 75). Pain is related to work disability and reduced social and recreational participation, all of which may contribute to the development of depressive symptoms(75). In addition, numerous studies have identified environmental and psychosocial influences, in addition to the role of nociceptive signals, in the pathogenesis of pain(79, 80). Depression has been hypothesized to act directly on pain by sensitizing pain pathways(81). Moreover, depression may indirectly contribute to pain by reducing positive coping behaviors, self-efficacy and perceived control, all of which are predictive of better health outcomes(8, 29, 82-85). RA patients with depression are three times as likely to be non-adherent to medical treatments as non-depressed patients(86). It is

possible that poorer health behaviors early in the course of disease among patients with depression could influence the pervasiveness of depression and pain symptoms common in patients with established RA who do not receive early intervention. More research is needed, however, to better delineate the bidirectional nature of processes linking pain and symptoms of depression.

Several limitations should be considered when interpreting findings from this study. First, this study examined baseline and 6-month follow-up data and should be replicated in a sample with a longer follow-up period in order to determine whether these relationships persist. Second, only approximately 20% of patients were strictly defined RA cases according to American College of Rheumatology criteria. However, this is likely an underestimate because, although dosages are not reported in the registry, most patients were treated with at least one DMARD prior to the first assessment point when patients are classified as RA or UIA. Third, although all patients undergo a tender joint count at the same time as the swollen joint count, fibromyalgia is not formally assessed and we cannot rule out that fibromyalgia and not active RA may be involved in some cases. Fourth, although patients in the present study were similar to other published EIA cohorts in terms of age and sex, sampling was not random, and it is possible that the sample may not be representative in terms of education, income, or other important sociodemographic variables. Finally, the present study used a self-report measure of depressive symptoms and did not formally assess major depression. Thus, while it is tempting to suggest that the implementation of depression treatment would improve EIA patient outcomes, this would be premature. As noted by Sheehy(75), key considerations, such as how to best facilitate early and effective screening of depression in EIA clinics warrants further attention.

In summary, the present study was the first longitudinal study to examine directional relationships between pain and depressive symptoms in EIA using cross-lagged panel path analysis

in patients diagnosed and treated by a rheumatologist within one year of symptom onset. Results from the present study demonstrated that depressive symptoms significantly contributed to the trajectory of pain symptoms from baseline assessment to 6-month follow-up. In addition, there were reciprocal/bidirectional associations between pain and depression that continued across assessment points. Pain and depression are intricately related and more research is necessary to better understand this relationship.

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