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Depression and the Long-Term Risk of Pain, Fatigue, and Disability in Patients with Rheumatoid Arthritis

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Abstract

Objective. To determine whether a previous episode of major depression leaves a "scar" that places previously depressed patients with rheumatoid arthritis (RA) at risk for experiencing high levels of pain, fatigue, and disability.

Methods. A cohort of 203 patients with RA was randomly selected from a national panel and interviewed by phone about pain, fatigue, depressive symptoms, disability, and history of major depression.

Results. Excluding patients who met the criteria for current major depression, patients with both a history of depression and many depressive symptoms at the time of the interview (dysphoria) reported more pain than those without current dysphoria, irrespective of whether they had a history of depression. Dysphoria alone was not reliably related to pain reports.

Conclusion. An episode of major depression, even if it occurs prior to the onset of RA, leaves patients at risk for higher levels of pain when depressive symptoms persist, even years after the depressive episode.

Depressive symptoms in patients with rheumatoid arthritis (RA) frequently coincide with reports of greater pain (1-3) and functional disability (4-6). Although the link between depression and RA symptoms has been widely explored, our understanding remains limited due to the kinds of data available and the research questions that are typically asked. Most studies have examined symptoms of depression using depression questionnaires rather than structured diagnostic interviews, and have focused exclusively on the patient's current psychological status.

The study described herein departs from most others by focusing on the diagnosis of major depression, and by considering how both previous and current depression are related to reports of pain, fatigue, and disability. The clinical significance of our findings lies primarily in the practice implications. Until recently, rheumatologists and other physicians have paid scant attention to depression and its relationship to RA symptoms. Although there is now greater awareness of depression and its treatment, the focus of this awareness has been on current depression. Yet, even the most careful assessment of current depression will not reveal a history of depression, which has a reported prevalence of 20% in community studies (7).

The relationship between RA symptoms and emotional distress has attracted the attention of both clinicians and researchers. Published studies have taken a variety of perspectives on this relationship, including investigation of whether pain is a predictor of depression (1-3) or whether depression influences pain (8), and identification of factors mediating the pain-depression relationship (9-11). Although the number of studies linking depression and RA symptoms is growing, investigations have been limited primarily to cross-sectional studies that use depression questionnaires and examine concurrent associations. Compared with the large number of studies that have utilized questionnaires such as the Center for Epidemiological Studies Depression Scale (CES-D) (12) or the Beck Depression Inventory (13), very few published studies have examined the link with the *diagnosis* of major depression (2). Questionnaire indicators of depression have shown only modest concordance with the diagnosis of major depression (14, 15) and have a limited ability to discriminate between depression and anxiety (16). Unlike the diagnosis of major depression, which requires both necessary and sufficient symptoms, depression questionnaires reflect the presence of psychological distress or dysphoria, and not necessarily a depressive disorder (17). Thus, our knowl-

edge of the relationship between depressive disorder and the common symptoms of RA, such as pain, fatigue, and functional disability, derives from only a handful of studies (2).

Whereas questionnaire-based investigations of depression and RA have focused on global distress, and the few interview-based studies have examined current depression, a growing body of evidence has converged on the notion that major depression may leave a psychological "scar," as first suggested by Lewinsohn and colleagues (18), or may precipitate residual dysfunction even after the formerly depressed individual no longer meets the criteria for a depressive disorder. This "scar" makes the formally depressed person vulnerable to recurrent depression and to interpersonal, occupational, and health deficits between depressive episodes. At this point, it is not clear whether these deficits are residua of the prior depression, a constellation of traits that remain stable between and within episodes, or a risk factor for recurrence (19). Moreover, it is not clear whether such a "scar" remains latent until triggered, or "primed," by a particular emotional state. There is some evidence that dysphoric mood may be the priming condition (20-22). Despite growing evidence from the general population (18) and from a recent study of fibromyalgia patients (23) that major depression may leave a "scar," this idea has not been investigated in an RA patient population.

This study examined the hypothesis that an episode of major depression leaves a "scar," such that formerly depressed patients with RA, even years after the occurrence of depression, are at increased risk for experiencing high levels of pain, fatigue, and disability. We also tested the priming hypothesis (20-21), i.e., that the "scar" associated with a history of depression will only be evident in the presence of a current dysphoric mood. Thus, RA patients with a history of depression will report higher levels of pain, fatigue, and disability compared with patients with no such history, but only when experiencing a dysphoric mood.

Patients and Methods

Study design. The National Rheumatoid Arthritis Study is a prospective panel study that completed its tenth and final year in 1997. The data for the present analysis were obtained in the sixth year of the study, during an annual telephone interview.

Patient recruitment. Patients were recruited using a 2-stage sampling strategy. First, a random sample of board-certified rheumatologists was selected from the membership database of the American College of Rheumatology (ACR). In 1987, 2,400 members of the ACR were listed as fellows, which is an indication of board certification. To obtain a representative sample of 55-60 physicians, 116 physician names were selected using computer-generated random numbers. After mail and telephone contact, 56 physicians agreed to participate (a 48% response rate).

In the second stage, patients with a diagnosis of classic or definite RA according to the ACR (formerly, the American Rheumatism Association) 1958 criteria (24) were offered the opportunity to learn more about the study through participating physicians' practices. One thousand forty-nine patients completed a response card at the physician's practice setting, and the office staff returned the cards to the coordinators of the study at the University of Connecticut. The number of patients from each practice ranged from 3 to 43, with a mean of 20 patients from each practice.

Patients who returned cards were contacted by phone and asked if they would be willing to be interviewed and have their physicians submit to the investigators medical information from their charts. In 1987-1988, 988 (94%) of those initially expressing interest agreed to be interviewed, of whom 921 (93%) returned the written consent form by mail, qualifying them to participate in telephone interviews. Thus, the response rate was 88% (921 of 1,049). In the sixth year of the study (1993), 605 participants (66%) remained in the study. In an attempt to assess whether people with high levels of depressive symptoms were more likely to drop out of the study, thus biasing the sample toward less depression, we examined CES-D scores over the 6 years of the study. We found that while people scoring higher than the cutoff value of 16 (denoting possible clinical depression on the CES-D) were significantly more likely to drop out than those scoring below 16 in 3 of the 6 years, in every year, the majority of participants with high CES-D scores remained in the sample (between 78% and 91 % across the 6 years). In each of the 6 years, nearly the same percentage of study participants (30-36%) scored above 16 on the CES-D.

Among the 605 patients eligible to be interviewed in 1993, 227 (45 men, 182 women) were chosen at random to be questioned using the depression section of the Diagnostic Interview Survey III-A (DIS III-A) (25). This DIS subgroup was not significantly different in terms of any demographic, disease, or illness variable, including pain, fatigue, functional ability, and depressive symptoms, compared with the 378 patients who remained in the total sample by the sixth year of study. Among the 227 patients selected, 203 completed the DIS interview.

Patient assessment. The telephone interview consisted of >100 questions related to demographics, self-reported illness symptoms, functional ability, and depressive symptoms. In addition, the DIS III-A (25) interview included structured questions that identified both current and lifetime diagnoses of major depression.

Telephone interview. Demographic variables obtained included age, sex, education, family income, marital status, and working status. RA illness symptoms were measured by self- reported pain and fatigue. Pain was measured by asking patients, "On a scale of 0 to 100, with 0 being no pain and 100 being the most pain possible, how much arthritis pain did you feel in the past week?" Fatigue over the past week was measured on the same scale. Comparable scales have been applied successfully in other studies of RA (26).

Functional ability was measured using the Stanford Health Assessment Questionnaire (HAQ) (27). The HAQ has 20 items that measure functional ability in 8 domains: dressing, grooming, arising, eating, walking, hygiene, reach, and activities (α = 0.93). Scores on the HAQ range from 0 to 3. This scale has been shown to have good reliability and validity in RA studies (27).

To assess dysphoric mood, the CES-D (12) was used. The CES-D is a 20-item questionnaire that reflects various aspects of depression, including depressed mood, feelings of guilt and worthlessness, loss of appetite, and sleep disturbance (α = 0.70). It yields a single summary score that ranges from 0 to 60. Good reliability and validity have been reported (12).

Diagnosis of major depression. The DIS III-A (25) was used to confirm diagnoses of both current and lifetime depression according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (7). The DIS III-A represents a minor modification of the DIS III (25). The validity of the DIS III has been demonstrated previously (28), and Wells and colleagues (29) have found that phone and face-to-face administrations produce comparable results. One interviewer, trained by an experienced DIS editor, conducted all 203 interviews. All interviews were edited by one of the authors (JF), and difficult cases were reviewed by a clinical psychologist (HT). The interviewer decision as to whether a symptom was a plausible psychiatric symptom was reversed by the clinical psychologist in 5 of the interviews that were reviewed. None of the reversals resulted in a change in diagnosis different from that arrived at by the interviewer. Twenty-eight interviews were audited for accuracy by the study director (JF) and found to have better than 99% agreement, with a range of 95% to 100%.

The DSM-III-R (7) criteria that were required for participants to qualify for a diagnosis of lifetime major depression included the presence of depressed mood, or loss of interest and pleasure in things that the individual usually cared about or enjoyed, lasting every day or nearly every day for 22 weeks at sometime in the past, while at the same time, experiencing at least 4 of 8 symptoms, specifically problems with appetite, sleep, fatigue, energy, interest, self-worth, cognition, or suicidal ideas. In addition, the depressive episode could not be due to injury, illness, medication, or alcohol. Diagnosis of current major depression required the presence of all of the above-described criteria within 3 weeks of the interview. Those who met all the criteria were classified as having definite major depression (lifetime and/or current). Those who met all the criteria but reported symptoms lasting <2 weeks were classified as having subthreshold depression. Those who attributed ≥1 symptom to an illness, injury, or drug or alcohol use were classified as having either definite or subthreshold major depression with medical attribution.

Because we used a short window of only the past 2 weeks as the time frame for current depression, we created the category of subthreshold to capture those cases in which all criteria were met, but which lasted short of 2 weeks. Using the DIS III-A, no symptom was counted toward a depression diagnosis if it was attributed, by either the respondent or a clinician, to a physical illness, injury, medication, or alcohol.

We followed these strict exclusion criteria (30); however, instead of discarding the cases, we created the special categories of definite or subthreshold major depression with medical attribution. Doing so allowed us to determine the number of respondents with RA who appeared to have had definite or subthreshold depression, but who attributed some or all of their symptoms to something else (usually their RA).

Current therapy. Current use of medications was determined by self-report. Patients were read a list of frequently prescribed arthritis medications and were asked whether these particular medications were part of their current treatment regimen.

Statistical analysis. After examining the univariate distribution of the data, we assessed the relationship among lifetime depression diagnoses, current RA symptom reports, and dysphoric mood, using one-way analysis of variance (ANOVA) and logistic regression. This was done to explore whether a lifetime diagnosis carried a future risk for higher levels of symptoms, irrespective of a priming condition. We then used ANOVA to assess the relationship between lifetime diagnoses combined with current levels of dysphoria and current reports of fatigue and disability, to test the hypothesis that a priming condition is necessary to reveal the risk associated with a lifetime diagnosis. In the statistical analyses, we combined all definite cases of major depression with definite cases of depression with medical attribution, and we combined all subthreshold cases with all subthreshold cases with medical attribution. A consulting liaison psychiatrist, using an etiologic approach (31), reviewed a subsample of cases of major depression with medical attribution and deemed the majority of them to be actual cases of major depression, thus justifying the combining of cases.

Results

Description of the sample. Participants were primarily married (67%), middle-aged (mean ± SD 55.5 ± 10 years) women (78%) who were relatively well-educated (mean ± SD 13.6 ± 3 years of education completed) and from homes with middle-class incomes (median $35,000). Forty-six percent of the patients were working outside the home for pay. This profile is not unlike that in other large studies of RA patients.

The group had an average duration of RA of 17 years (SD 8). The mean score on the CES-D depressive-symptom scale was 11 (SD 10), which is above the general population mean of 9.25 but below the score of 16 that is often thought to indicate possible clinical depression (12). Participants reported moderate levels of fatigue (mean ± SD score 50 ± 27), pain (44 ± 29), and functional disability (0.69 ± 0.55), which has been seen in other studies as well. Correlations among these 4 health status indicators ranged from 0.48 (between functional ability and depressive symptoms) to 0.73 (between pain and fatigue).

Table 1. Distribution of diagnoses of current and lifetime major depression*

Diagnosis	Frequency	Percent
Current		
MD definite	7	3.4
MD definite/medical	4	2.0
MD subthreshold	2	1.0
MD subthreshold/medical	3	1.5
No current diagnosis	187	92.0
Lifetime		
MD definite	57	28.1
MD definite/medical	28	13.8
MD subthreshold	11	5.4
MD subthreshold/medical	15	7.4
No lifetime diagnosis	92	45.3

* Total of 203 patients evaluated. MD = major depression.

Table 1 shows that only 3.4% of the subset of 203 participants met the full DSM-III-R (7) criteria for current definite major depression, with another 4.5% meeting the criteria for definite major depression with medical attribution, subthreshold major depression, or subthreshold major depression with medical attribution. These proportions were very similar to those found in community studies (7). Many more participants met the criteria for a lifetime diagnosis. Twenty-eight percent met the full criteria for lifetime depression, and another 26.6% met the criteria for definite depression with medical attribution, subthreshold depression, and subthreshold depression with medical attribution. The proportions meeting the full criteria were very similar to the high end of the range for women meeting the full criteria in community studies (7). Overall, more than half of the participants had an episode of definite depression, subthreshold depression, or depression with medical attribution at some time in their life. There were no significant differences between the groups in terms of age, income, education, or sex.

The frequency of current major depression was not equally distributed across the various categories of lifetime depression. Individuals with a history of depression who met the criteria for definite major depression were more likely to meet the criteria for current definite or subthreshold depression ($\chi^2 = 38.58$, $P < 0.001$). Of the 56 patients with a past episode of major depression, 15 (27%) qualified for a current depression diagnosis, whereas among those without a history of depression, only 1 met the criteria for current depression. There were no current cases of major depression among patients who reported a lifetime diagnosis of definite depression with medical attribution, subthreshold depression, or subthreshold depression with medical attribution.

To explore whether patients with a lifetime diagnosis were at risk for elevated levels of distress even years later (mean ± SD years since episode of depression 14.4 ± 10.3), we compared the difference in dysphoric mood, measured with the CES-D, across diagnostic categories with and without the inclusion of current definite cases of depression. It is noteworthy that 55% of those reporting a past episode of depression reported experiencing the depression prior to the onset of their RA. When current definite cases were included, we found a significant difference in CES-D scores ($F[2,203] = 6.6$, $P < 0.002$). Those with a lifetime definite diagnosis of depression obtained a mean CES-D score of 13.60 (SD 10.2) compared with 8.4 (SD 9.4) for those with no history of depression and 8.6 (SD 9.7) for those with a subthreshold depression. When cases of current depression were removed from the analysis, no significant differences in dysphoria emerged across the lifetime depression categories ($F[2,184] = 1.59$, $P > 0.20$). Thus, there was no significant difference in the intensity of depressive symptoms for those with and those without a history of definite major depression or subthreshold depression. Logistic regression revealed that neither patients with a history of subthreshold depression (B = –0.12, $P = 0.83$) nor those with a history of definite depression (B = 0.58, $P = 0.13$) were more likely to report current dysphoric symptoms above a CES-D score of 16, which is the cutoff value that, according to Radloff (12), may indicate a case of depression.

We hypothesized that the levels of pain, fatigue, and functional ability would differ across categories of lifetime depression. Table 2 summarizes the ANOVA results, which revealed that pain and fatigue did not vary across lifetime diagnostic categories. However, functional disability did vary across diagnoses ($F[2,184] = 3.6$, $P < 0.03$). Although no 2 groups were significantly different at the 0.05 level, those with a definite lifetime diagnosis reported more functional disability (mean 0.80) compared with those with a subthreshold lifetime diagnosis (mean 0.51) and those with no lifetime diagnosis (mean 0.61).

Table 2. Pain, fatigue, and functional ability by lifetime diagnoses, excluding currently diagnosed cases.

Lifetime diagnosis	Mean pain score	Mean fatigue score	Mean disability score	*N*
Definite MD*	41.96	51.7	0.80	67
Subthreshold MD	39.4	46.7	0.51	26
No lifetime diagnosis	41.7	44.1	0.61	91
Total	41.5	47.3	0.66	184
P	0.922	0.211	0.03	-

* MD = major depression.

Table 3. Analysis of variance results of pain, fatigue, and disability by lifetime diagnoses and current dysphoria (high/low)

Lifetime diagnosis	Mean pain score	Mean fatigue score	Mean disability score	No.
1. Definite MD*, low dysphoria	34.51	45.6	0.66	49
2. Subthreshold MD, low dysphoria	38.64	43.6	0.44	22
3. No diagnosis, low dysphoria	39.64	39.9	0.52	76
4. Definite MD, high dysphoria	62.22	68.3	1.18	18
5. No diagnosis, high dysphoria	51.63	65.6	1.08	15
P	0.003	0.000	0.000	–
Scheffe groups†	4 vs. 1 and 3	4 vs. 1 and 3; 5 vs. 3	4 vs. 1 and 3; 5 vs. 3	180

* MD = major depression.
† Comparisons show a significant difference between the means of each group at the 0.05 level.

According to the priming hypothesis, RA patients with a history of depression will report higher levels of pain, fatigue, and disability than patients without a depression history only in the presence of a currently dysphoric mood. To test this priming hypothesis. ANOVA was used to compare the mean levels of pain and fatigue across categories based on lifetime diagnoses and current high levels (CES-D score ≥16) or low levels (CES-D score <16) of dysphoria. The 4 cases of subthreshold depression with high dysphoria were excluded from the analysis. Table 3 shows that patients with a lifetime history of definite major depression who were currently experiencing high levels of dysphoria reported the highest levels of pain, fatigue, and disability. Those with no lifetime diagnosis, but who reported high levels of current dysphoria, reported the next highest levels of all 3 health status indicators. Most critical to the priming hypothesis, those who had an episode of definite major depression at some time in their life and who reported high levels of current dysphoria, but did not currently qualify for even a subthreshold DSM-III-R diagnosis, reported significantly more pain than those who had a similar past episode of depression but reported low levels of current dysphoria. Although patients with high levels of current dysphoria in the absence of a prior depression also reported high levels of pain, the intensity of their pain was not significantly different from any other group. Thus, in relation to self-reported pain, the group that stands out as different had both a history of depression and high current dysphoria.

In contrast to the relationship with pain, both groups with high levels of current dysphoria irrespective of a history of major depression reported more fatigue and functional disability than did their low-dysphoric counterparts. Interestingly, those with a history of definite depression but low current dysphoria reported levels of all 3 health status indicators in the same range as those with no depression history of any kind and low levels of current dysphoria.

Finally, because pain, fatigue, and functional disability are all interrelated, and because arthritis medications may explain differences in pain reports across groups, we examined pain reports across the same lifetime categories in Table 3, controlling for fatigue, functional disability, current methotrexate therapy, and current prednisone therapy. Pain reports differed significantly across the 5 lifetime diagnostic categories ($F[4,180] = 2.83$, $P < 0.02$) after controlling for fatigue and disability. Planned contrasts showed that patients with high dysphoria but without a history of depression did not report higher levels of pain than those with a history of depression but low levels of current dysphoria. Only patients with past definite major depression and high current dysphoria reported more pain than those with a history of definite depression, but low current dysphoria.

Discussion

The connection between depression and the illness experience of patients with RA has attracted considerable attention from researchers and clinicians. However, scant attention has been paid to the history of affective disorder and the possibility that the past could shape the future illness experience. The present study departs from the nearly exclusive focus on the connection between current emotional distress and current illness, to suggest that a patient's affective history may influence his or her future illness experience. Thus, this study is unique in the arthritis depression literature, since it includes depressive diagnoses, both past and current,

from a large national sample of RA patients. We found the clearest evidence of a "scar" in the association between past episodes of major depression and current reports of pain, However, we also found that, at least with respect to pain, the "scar" is only evident under current mood-priming conditions (20-21).

Evidence of a "scar" that must be primed was revealed when we compared the pain, fatigue, and disability reports of those with and those without a history of major depression. In the absence of current high levels of dysphoria, RA patients who met the criteria for definite major depression at some time in their life but did not currently meet the criteria for even a subthreshold episode, did not report greater pain, disability, or fatigue than those without a depression history. However, when we compared the same history of depression groups in the context of their current reports of dysphoria (the priming condition), we found that patients with a history of depression and high levels of current dysphoria but no current definite major depression reported the highest pain, fatigue, and disability of any patient group. Those with currently high levels of dysphoria, but without a history of depression, reported the next highest level on the 3 illness indicators.

Although both groups reported relatively high levels of symptoms, the pain reports of patients with a history of depression offered the clearest indication of how past major depression operates to influence the future illness experience. The "scar" group, i.e., patients with a history of major depression and high levels of current dysphoria, reported more pain than those with low levels of current dysphoria irrespective of depression history. Although patients without a depression history but with high levels of current dysphoria also reported high levels of pain, the intensity of their pain was not different from that of any other group. Thus, the combination of past depression and current dysphoria created a risk factor for RA pain reports that exceeded the risk associated with high dysphoria alone.

To our knowledge, this is the first study in a medical population to examine the "scar" hypothesis in relation to medical symptoms, and we can only speculate as to the possible mechanisms that operate with respect to major depression and future symptom reports in RA. Others have postulated that the "scar" is a residua of the prior depression, a constellation of traits that remain stable between and within episodes, or a risk factor for recurrence of depression (19). Our data suggest that in addition to being a risk factor for recurrence (27% of those with a past episode of depression reported a current episode as well), major depression leaves a residua, but that it operates primarily with respect to reports of pain. Our data also suggest that a history of depression alone is not sufficient to explain the high levels of pain reported in the "scar" group in this study. Thus, a history of depression is not a stable trait that operates consistently, since many patients with a history of depression did not report higher levels of pain. Rather, the "scar" associated with a history of depression appears to be episodic and conditional on current symptoms of dysphoria.

Most clinicians appreciate the relationship between current distress and their RA patients' pain reports. Our data suggest that it is important to inquire beyond the current distress to the patient's history of affective disorder. This assessment needs to include both the patient's current complaints of distress and his or her history of affective disorder. New directions in cognitive-behavioral therapy for primary care patients that focus on brief (one-to-three-session) interventions (31) and interventions designed for patients with a history of depression (32) should be considered for these high-risk patients with RA. Although the depression history itself cannot be influenced by such interventions, the priming factor (current dysphoria) should respond to the self- control strategies and cognitive-restructuring techniques offered in these approaches.

Although this study has revealed new and persuasive evidence of the long-term risk associated with a past episode of major depression, two rival explanations for our findings should be considered. First, it is possible that people with a past episode of depression simply experience higher levels of pain. This is unlikely, because our "scar" group reported levels of pain that were significantly higher than the group that shared their history of depression but not their high current dysphoria. Alternatively, it is possible that what we describe as a "scar" is actually an example of mood (state)-dependent recall (33), in which those with current dysphoria are more likely to overestimate their pain or more likely to recall past episodes of depression. It is unlikely that mood-dependent recall explains either possibility in this study, because the current dysphoria group without a history of depression did not report the same intensity of pain as our "scar" group. Similarly, our patients with current dysphoria were not more likely to recall a past episode of depression than were patients without current dysphoria. However, future studies should investigate these possibilities and should examine the "scar" and priming hypotheses using a prospective study design with multiple, perhaps daily, reports of pain and mood, to avoid retrospective bias in symptom reports.

Future studies should also take advantage of other diagnostic interviews that do not share the limitations of the DIS III-A. Our study was limited due to the problems inherent in obtaining unbiased reports of major depression using such instruments as the DIS III-A, which relies on the participant's attribution of organic versus nonorganic symptoms. Reliance on individual clinician judgment or on patient attribution increases the concept referred to by Spitzer et al. (34) as criterion variance, i.e., variations in formal inclusion and exclusion criteria used to reach diagnosis, which is a principal contributor to di-

agnostic unreliability. Although we attempted to correct for this bias by having a psychiatrist review the problem cases, future studies that limit criterion variance by including frequency and duration requirements, decision rules, and more specific probes on an item-by-item basis will bring us closer to understanding how an episode of depression might, years later, influence pain, fatigue, and functional limitations in patients with RA.

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