# Disease Status Predicts Fatigue in Systemic Lupus Erythematosus

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***ABSTRACT.*** ***Objective.*** To investigate the relative contributions of disease status, helplessness, and depression to fatigue in patients with systemic lupus erythematosus (SLE) in a path-analytic framework.

***Methods.*** The disease status of 81 patients with SLE was evaluated by a clinical rheumatologist using the Systemic Lupus Activity Measure. Patients completed self-report measures of psychosocial data, depression, helplessness, and fatigue at 2 assessment periods, 3 months apart. SLE diagnoses were confirmed with patients' physicians.

***Results.*** The model proposed that SLE disease status would predict fatigue directly, and indirectly, through helplessness and depression. At Time 1, disease status, helplessness, and depression were significantly correlated with each other and with fatigue, with helplessness and depression partially mediating the relationship between disease status and fatigue. Longitudinal analyses showed that disease status at Time 1 predicted fatigue, regardless of helplessness and depression operating as mediators at either Time 1 or Time 2.

***Conclusion.*** The cross sectional findings revealed direct and indirect relationships between disease status and fatigue, with helplessness and depression as mediating variables. However, disease status was the only predictor of fatigue over time. Disease status also predicted Time 2 helplessness, which, in turn, was associated with Time 2 depression. Fatigue amelioration may be an important result of successful management of the underlying SLE process. (J Rheumatol 2001;28:1999–2007)

*Key Indexing Terms:*
DISEASE STATUS HELPLESSNESS FATIGUE SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic autoimmune and rheumatic disorder characterized by troublesome and frequently unpredictable symptoms in addition to medical complications such as facial "butterfly rash," joint pain and swelling, kidney and liver malfunctioning, hypertension, and blocked cerebral blood flow. However, fatigue is commonly the chief presenting complaint of patients and one of the most debilitating symptoms of SLE. Over half of patients with SLE have reported chronic difficulties with fatigue and lethargy[1-3].

Despite its high prevalence and adverse effect on quality of life, SLE related fatigue is neither well understood nor adequately researched. Contrasting theories about the etiology of fatigue in SLE have been proposed[3,4]. A predominant view has been that fatigue is pathophysiologically mediated, i.e., a result of the disease process itself. This would account for the observation that fatigue increases during illness flares. A contrasting theory is that fatigue is the result of depression and/or the adverse psychosocial effects of the illness, with the high rate of mood disturbance in SLE making this position credible among SLE researchers[5]. A third perspective suggests that, while physiological mechanisms may give rise to fatigue, depression and other psychosocial factors may exacerbate or maintain fatigue over time[3,5,6]. Thus, physiological and psychological factors may jointly contribute to fatigue during the course of the illness.

*Psychosocial research on SLE fatigue*. Previous SLE research has analyzed associations between disease activity, psychological adjustment, and fatigue, employing cross sectional methodology.

The first study to address the relationship among psychosocial factors, disease processes, and fatigue in SLE was conducted by Krupp, *et al*[3]. Using the Fatigue Severity Scale (FSS)[7] as a measure of fatigue with 59 patients with SLE, these authors reported a moderate correlation between depression, measured by the Center for Epidemiological Studies Depression Scale (CES-D)[8], and fatigue. No significant relationships were found between fatigue and clinical or laboratory measures of disease activity, or between fatigue and medication use. Wang, *et al*[9], in a study with 100 patients with SLE, also found no relationship between disease activity, assessed by the SLE Disease Activity Index

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(SLEDAI)[10], and the FSS. Instead, fatigue was positively correlated with depression and the effect of the illness, measured by the SF-20[11]. However, since no regression analysis was reported, the unique contribution of depression and SF-20 scores to fatigue could not be determined. In a more recent study of 81 patients, Bruce, *et al*[12] reported similar findings. These investigators found that neither the SLEDAI nor the Systemic Lupus Activity Measure (SLAM)[13] was related to FSS scores. They concluded that fatigue reflected the effect of SLE, as measured by health status, rather than disease processes.

In contrast, other studies indicate that severity of lupus fatigue is related to underlying disease activity. Dividing a sample of 83 patients into fatigued and nonfatigued groups based on a nonvalidated measure of fatigue, Wysenbeek, *et al*[4] found that fatigued patients had higher ratings for numerous clinical features such as hair loss, joint pain and ulcers, greater inflammation, evidenced by elevated erythrocyte sedimentation rate (ESR) scores, and a lower lymphocyte count. In Great Britain, Taylor, *et al*[14] found positive relationships between several indices of disease activity and the presence of fatigue in a sample of 216 patients; however, they did not assess psychosocial constructs or include a validated fatigue measure. Zonana-Nacach, *et al*[15] found that SLAM scores and numerous psychosocial variables, including abnormal illness related behaviors, helplessness, and pain, predicted higher fatigue, thus confirming the import of a multifactorial model. The large sample size (n = 223) and the use of regression analysis enhanced the credibility of these data.

A study by McKinley, *et al*[16] postulated that psychological variables may serve as intervening links between disease activity and fatigue. Using path-analytic procedures in a small sample of SLE patients (n = 48), they found that depression and sleep anxiety mediated the effects of disease activity on fatigue. SLAM scores had no direct relationship with fatigue. These findings suggest that the psychological sequelae to disease activity, rather than disease activity itself, may have the most proximal influence on SLE fatigue.

*Overview of research*. The conflicting data from these studies could be attributed to methodological differences (e.g., subject selection, different measurement of psychological constructs, disease activity), the lack of a theoretical model integrating disease related and psychosocial factors, nonvalidated fatigue measures, or cross sectional methodology, which is limited to identifying static relationships among constructs. In response to these concerns, this research evaluated a model in which disease status, helplessness[17], and depression were hypothesized to predict fatigue conjointly and over time. This study adopted validated measures of fatigue and a longitudinal design. In the proposed framework (Figure 1) disease status was hypothesized to lead to fatigue directly, and indirectly, through helplessness and depression. Helplessness has been associated with depression in previous SLE research[18], and has mediated the relationship between disease activity and depression in arthritis[19] and fibromyalgia[20]. The proposed framework allowed examination of the following relationships: (1) the direct relationship between disease status and fatigue, independently of helplessness and depression (a to d); (2) the separate mediational roles of helplessness and depression in explaining the disease-fatigue relationship, i.e., disease status leads to helplessness, which leads to fatigue (a to b to d), and disease status leads to depression, which leads to fatigue (a to c to d); and (3) the mediational role of helplessness in explaining the relationship between disease status and depression, which, in turn, contributes to fatigue (a to b to c to d). These relationships were tested cross sectionally and longitudinally.

## MATERIALS AND METHODS

*Subjects*. SLE patients were recruited via verbal and written announcements through the American Lupus Society (now the Lupus Foundation of America) and by letters sent to rheumatologists at university based clinics and in private practice in Southern California. Once recruited and prescreened over the telephone, patients gave informed consent to have their physicians contacted to confirm their SLE diagnosis according to the American College of Rheumatology SLE diagnostic criteria[21]. The recruitment process identified 99 patients who reported having SLE. However, since 18 patients were eliminated, because either their diagnosis could not be confirmed or they were unable to participate in both phases of data collection, a final sample of 81 patients was obtained.

The final sample consisted of 74 women and 7 men with an average age of 42.94 (SD 14.98) years, and a mean illness duration of 12.14 (SD 11.08) years. Most subjects were married (54%), were Caucasian (68%), and had at least some college, trade or technical school education (89%). The most commonly used medications were corticosteroids (54%), analgesics (41%), nonsteroidal antiiflammatory drugs (NSAID) (37%), and antimalarial agents (37%). Less frequent use of antidepressants (16%) and anxiolytics (12%) was reported. Only 3 subjects at Time 1 and 4 subjects at Time 2 reported no medication use.

*Data collection*. Patients were evaluated in research laboratories at the Clinical Trials Center of the University of California, San Diego, and at the California School of Professional Psychology, San Diego. A doctoral level psychology student collected demographic information and administered a mental status examination as well as a battery of paper-and-pencil questionnaires assessing fatigue and psychosocial variables. In addition, a clinical rheumatologist evaluated the disease status of each patient using the SLAM[13]. The rheumatologist was blinded to the psychosocial evaluation, and the doctoral student was blinded to the physical examination. Psychosocial and disease status assessments were repeated following the same procedures 3 months later.

### Predictors

*Disease status*. The SLAM[13] was used to measure SLE disease status. The SLAM is an objective, physician scored measure of 25 SLE symptoms occurring over the past month. Based on interviewing and examining the patient, the rheumatologist scored each clinical feature as being active or inactive, and evaluated its severity using the following scale: 0 = symptom absent, 1 = mildly severe, 2 = moderately severe, and 3 = severely incapacitating. Total SLAM scores for each patient were derived by summing severity ratings across symptoms. The 8 laboratory measures that may be incorporated with symptom ratings were not adopted in this study. In support of this decision are data showing that the SLAM without laboratory

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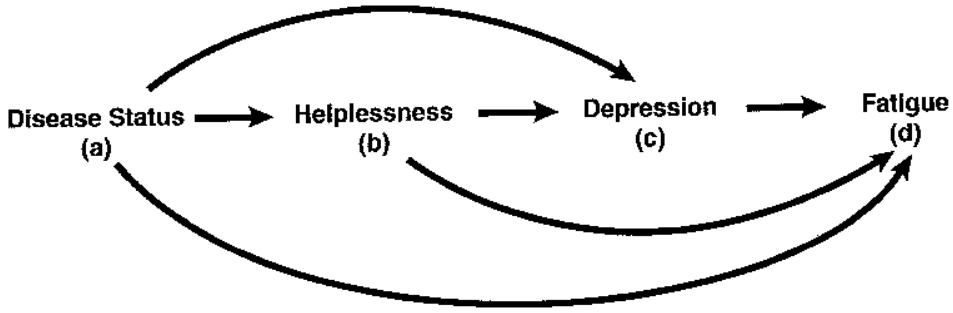


*Figure 1*. Hypothesized model depicting relationships among model variables.

data correlates as highly as 0.87 with the full SLAM[22]. Thus, laboratory data add relatively little variability to the total disease status score. In addition, other investigators have demonstrated that global assessments of health status in SLE are more sensitive to clinical change than expensive laboratory tests involving ESR, anti-dsDNA, and circulating immune complexes[23]. The item assessing fatigue in the SLAM was omitted to prevent confounding with fatigue as the outcome variable in the model. The internal consistency of the SLAM, based on Cronbach's alpha, was 0.72 at Time 1 and 0.65 at Time 2.

*Helplessness*. Helplessness was measured by the 5 item Helplessness Subscale of the Rheumatology Attitudes Index[24,25], which was derived from the Arthritis Helplessness Index[26]. Chosen for its brevity and comparable psychometric properties to the 15 item scale[27], the Helplessness Subscale measures the extent to which patients feel helpless in controlling the disease course (e.g., "My condition is controlling my life") and predominant symptoms (e.g., "No matter what I do or how hard I try, I can't get relief from my pain") of arthritic conditions and has been used in previous research with SLE[28]. Items are arranged in a Likert-type format with 5 response alternatives ranging from 1 = strongly disagree to 5 = strongly agree, with 3 = neither agree nor disagree. A total helplessness score is achieved by summing across items after making appropriate scoring reversals. Possible scores range from 5 to 25. The internal consistency of the Helplessness Subscale in this sample was 0.59 at Time 1 and 0.60 at Time 2. These reliabilities are equivalent to 0.81 and 0.82, respectively, when the 5 item measure is projected to a scale of 15 items, using the Spearman Brown prophecy formula.

*Depression*. Depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CES-D)[8] developed for use in community samples. The CES-D consists of 20 items reflecting cognitive, affective, and vegetative symptoms of depression. Patients indicated how frequently they experienced each symptom over the previous week on a Likert-type scale consisting of 4 response options, 0 = rarely or never, 1 = some of the time, 2 = occasionally, and 3 = most or all of the time. The CES-D has been effectively adopted in SLE research[28] and with other rheumatic populations[20,29]. The cutoff score for detecting clinical depression in community samples is 16, whereas a score of 19 has been suggested for populations in which chronic pain is a major symptom[30]. Due to their overlap with fatigue, two CES-D items, "My sleep was restless" and "I could not get going," were omitted from the scale for data analyses. With the deletion of these items, the revised 18 item scale retained a high degree of internal consistency at both measurement periods (alpha = 0.92 and 0.89, respectively).

Criterion Variable

*Fatigue*. Two measures of fatigue were used in this study, the Fatigue Severity Scale (FSS)[7] and the Vanderbilt Fatigue Scale (VFS), an adaptation of the Multidimensional Assessment of Fatigue (MAF)[31]. Both measures were used because they assessed different components of the construct of fatigue.

The FSS is a self-report scale consisting of 9 items that address the effect of fatigue on daily functioning. The scale also assesses how easily one feels fatigued and the effect of fatigue on motivation. Patients rated each item on a Likert-type scale ranging from 1 to 7, and an average fatigue score was obtained by dividing the sum of the ratings by the number of items for each subject. The FSS is a well established, valid measure of fatigue that has been previously used in SLE[9]. The internal consistency of the FSS was 0.91 at both Time 1 and Time 2.

In contrast to the FSS, the VFS measures the frequency and severity of fatigue. Patients answered the following questions from the MAF on a 1 to 10 Likert scale: (1) To what degree have you experienced fatigue? (2) How severe is the fatigue you've been experiencing? (3) To what degree has fatigue interfered with your ability to do what you want to do?, and (4) To what degree has fatigue caused you distress? In addition, patients were asked to indicate how many days over the past week they experienced fatigue. An overall fatigue score was obtained by multiplying the frequency item by the average of the 4 severity items, yielding a measure that takes into account the combination of frequency and severity ratings. The internal consistency of the VFS, based on the 4 Likert items, was 0.93 at both Time 1 and Time 2. Research on the MAF with rheumatoid arthritis (RA) patients[32] has reported an alpha reliability of 0.93 and construct validity through correlations with other fatigue and mood measures. Schuman[33] found an average alpha of 0.90 in repeated administrations of the VFS in patients with fibromyalgia, and moderate to strong correlations with measures of pain, depression, and helplessness.

## RESULTS

Descriptive data (presented for all study variables at Time 1 and Time 2 in Table 1) reflect a wide range of severity on all indices. The mean level of helplessness (Time 1 M = 14.42; Time 2 M = 14.10) is similar to that found in other arthritis samples[27], while CES-D scores (Time 1 M = 15.90; Time 2 M = 15.00) indicate a high level of mood disturbance given that a score of 16 is the recommended cutoff for depression in community research[8]. Scores on all variables declined slightly from Time 1 to Time 2, but these trends did not reflect statistically significant changes.

Correlations between study variables within Time 1 and Time 2 were highly consistent (Table 2). Disease status, helplessness, and depression were significantly correlated with each other, and with fatigue. The bivariate relationships with fatigue were highly similar at both time periods (ranging from r = 0.53 to r = 0.59). Longitudinal correlations (Table 3) reflect the same general pattern. Time 1 disease status, helplessness, and depression were all associated with

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*Table 1*. Descriptive statistics for variables in the model.

| | Time 1 | | | Time 2 | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | Range | Alpha | Mean (SD) | Range | Alpha |
| Disease status | 6.06 (4.17) | 0–19 | 0.72 | 5.51 (3.47) | 0–17 | 0.65 |
| Helplessness | 14.42 (4.89) | 5–24 | 0.59 | 14.10 (4.94) | 5–25 | 0.60 |
| Depression | 15.90 (12.09) | 0–46 | 0.92 | 15.00 (10.64) | 0–39 | 0.89 |
| Fatigue Severity Scale | 4.81 (1.50) | 1–7 | 0.91 | 4.73 (1.50) | 1–7 | 0.91 |
| Vanderbilt Fatigue Scale | 18.56 (10.94) | 0–38 | 0.93 | 17.90 (11.32) | 0–38 | 0.93 |

*Table 2*. Cross sectional correlations between variables in the model at Time 1 and Time 2.

| | Time 1 | | | | Time 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | DS | H | D | F | DS | H | D | F |
| Disease status (DS) | — | | | | | | | |
| Helplessness (H) | 0.39* | — | | | 0.52* | — | | |
| Depression (D) | 0.49* | 0.52* | — | | 0.44* | 0.62* | — | |
| Fatigue (F) | 0.53* | 0.54* | 0.59* | — | 0.59* | 0.54* | 0.56* | — |

* $p < 0.01$.

*Table 3*. Longitudinal correlations (Time 1 to Time 2) between variables in the model.

| | Time 2 | | | |
|---|---|---|---|---|
| | DS | H | D | F |
| Time 1 | | | | |
| Disease status (DS) | 0.72* | 0.52* | 0.48* | 0.53* |
| Helplessness (H) | 0.33* | 0.67* | 0.38* | 0.40* |
| Depression (D) | 0.40* | 0.45* | 0.65* | 0.42* |
| Fatigue (F) | 0.43* | 0.43* | 0.38* | 0.71* |

* $p < 0.01$.

higher fatigue at Time 2 (r = 0.53, 0.40, and 0.42, respectively). Autocorrelations, referring to the correlation of each variable with itself across time (r = 0.72 for disease status, 0.67 for helplessness, 0.65 for depression, and 0.71 for fatigue), reflected considerable stability in these criteria.

*Tests of the model*. According to Figure 1, it was hypothesized that disease status would be associated with greater fatigue directly, and indirectly, by contributing to higher helplessness and depression. A series of hierarchical multiple regression analyses was conducted to evaluate this path-analytic framework. In each regression, significant covariates involving demographic variables and medication use were entered on the first step before testing model variables. Medication variables were dummy coded according to 1 = did not use, 2 = did use. The first regression examined the contribution of disease status to helplessness; the second analysis examined the contribution of disease status and helplessness to depression; and the final analysis evaluated the contribution of disease status, helplessness, and depression to fatigue. Interpretation of mediational pathways followed guidelines recommended by Baron and Kenny[34].

*Cross sectional findings (Time 1)*. Collectively, on the first step of the analysis predicting helplessness, NSAID, steroids, and socioeconomic status contributed 17.1% of the variance in helplessness scores [$F(3, 77) = 5.30$, $p < 0.01$]. Lower socioeconomic status (ß = –0.25), NSAID use (ß = 0.25), and steroid use (ß = 0.22) were each associated with higher helplessness. Following these covariates, the contribution of disease status to helplessness was significant [$F(1, 76) = 7.33$, $p < 0.01$, ß = 0.30], accounting for an additional 7.3% of the variance in helplessness scores.

Since no covariates for depression were found, disease status and helplessness were entered on the first step of the analysis, and contributed significantly to the prediction of depression [$F(2, 78) = 22.77$, $p < 0.001$], accounting for 37% of the variance in depression scores. Higher disease status (ß = 0.33) and higher helplessness (ß = 0.40) were uniquely associated with greater depression scores.

The effects of steroids and antidepressants, which were both positively associated with fatigue, were entered on the first step of the analysis predicting to fatigue, and collectively accounted for 10.3% of the variance in fatigue scores [$F(2, 78) = 4.49$, $p < 0.05$]. However, only steroid use was uniquely associated with fatigue (ß = 0.23). When disease status, helplessness, and depression were entered on the next step, their contribution was highly significant [$F(3, 75) = 17.51$, $p < 0.001$]. Together, these variables accounted for 37% of the variance in fatigue scores (Table 4). The unique variance contributed by each model variable is depicted by $sr^2$. As hypothesized, disease status (ß = 0.27, $sr^2 = 0.037$), helplessness (ß = 0.26, $sr^2 = 0.048$), and depression (ß = 0.32, $sr^2 = 0.063$) were uniquely associated with greater concurrent fatigue. As indicated by the change in $sr^2$ at step 2 in Table 4, neither antidepressant nor steroid use made a

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*Table 4*. Cross sectional multiple regression analysis predicting fatigue.

| Step | Variable | df | $R^2$ | $R^2$ Change | F | ß[a] | ß[a] | $sr^{2\,a}$ | $sr^{2\,b}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Antidepressants | (2,78) | 0.103 | — | 4.49* | 0.21 | –0.01 | 0.050 | 0.000 |
| | Steroids | | | | | 0.23* | 0.02 | 0.044 | 0.000 |
| 2 | Disease status | (3,75) | 0.473 | 0.37 | 17.51** | — | 0.27* | — | 0.037 |
| | Helplessness | | | | | — | 0.26* | — | 0.048 |
| | Depression | | | | | — | 0.32* | — | 0.063 |

[a] At Step 1; [b] at Step 2. * $p < 0.05$; ** $p < 0.01$.

significant contribution to fatigue after model variables were entered.

Figure 2, which illustrates the outcome of these analyses, provides evidence for the significance for all hypothesized relationships, namely, the direct relationship between disease status and fatigue (a to d), the separate mediational roles of helplessness (a to b to d) and depression (a to c to d) in explaining the indirect relationship between disease status and fatigue, and finally, the mediational role of helplessness in explaining the relationship between disease status and depression, which, in turn, was associated with fatigue (a to b to c to d).

*Longitudinal findings*. Two longitudinal analyses were conducted to analyze prospective relationships between predictor variables and fatigue over time. In the first analysis, all predictors were from Time 1, whereas in the second analysis, disease status was from Time 1 and the mediators were from Time 2. In both analyses, significant covariates from Time 1 and Time 2 were removed from Time 2 helplessness, depression, and fatigue scores.

In the first analysis predicting to Time 2 fatigue, Time 1 antidepressants and sedatives, and Time 2 steroids, antidepressants, benzodiazepines, NSAID, sedatives, and hormones were entered on the first step of the analysis, contributing 29.8% of the variance in fatigue scores [$F(8, 72) = 0.3.82$, $p < 0.01$]. Although no medication variable by itself uniquely predicted fatigue, Time 2 steroids, NSAID, and sedatives showed a trend toward significance (all $p <$

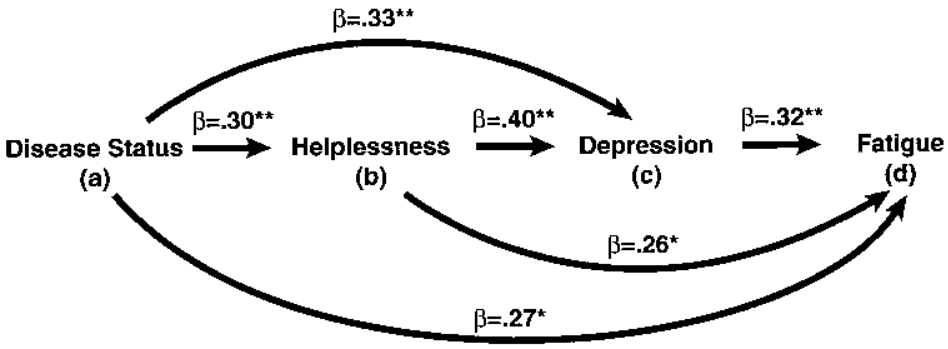


*Figure 2*. Cross sectional model at Time 1 illustrating empirical relationships among model variables. *$p < 0.05$, **$p < 0.01$.

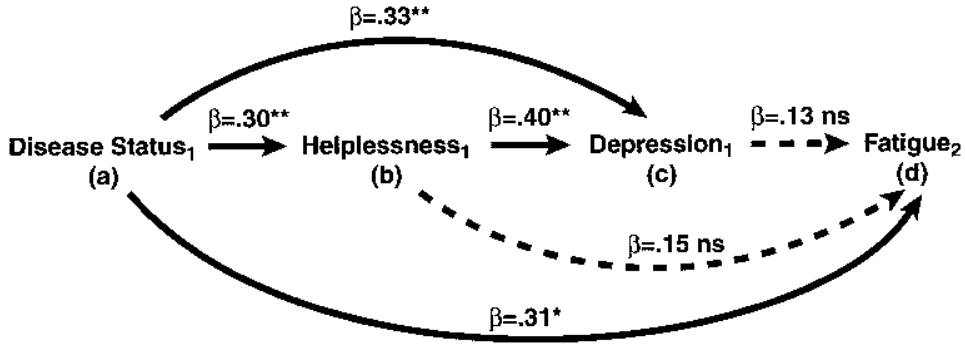


*Figure 3*. Longitudinal model with Time 1 disease status, helplessness, and depression, and Time 2 fatigue. * $p < 0.05$; ** $p < 0.01$.

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0.10). The entry of Time 1 disease status, helplessness, and depression on the next step of the regression equation accounted for an additional 12% of the variance in fatigue scores [$F(3, 69) = 4.72$, $p < 0.01$] and significantly diminished the variability accounted for by medications (see $sr^2$ [b] in Table 5). However, only Time 1 disease status (ß = 0.31, $sr^2 = 0.043$) proved to be predictive of fatigue (Figure 3). Thus, in contrast to the cross sectional findings, helplessness and depression did not contribute to fatigue over time when they competed with disease status.

The second longitudinal analysis differed from the first in that Time 2 mediators were used, allowing examination of the pathways between Time 1 disease status and Time 2 helplessness and depression. Thus, the path from Time 1 disease status to Time 2 helplessness was evaluated first. Time 1 antidepressants and Time 2 steroids, antidepressants, benzodiazepines, NSAID, sedatives, and vitamins accounted for 34.3% of the variance in Time 2 helplessness [$F(7, 72) = 5.37$, $p < 0.001$], although only steroids (ß = 0.22), benzodiazepines (ß = 0.24), and vitamins (ß = 0.26) were uniquely related to greater helplessness. Time 1 disease status, entered on the next step, contributed significantly to helplessness [$F(1, 71) = 6.34$, $p < 0.05$, ß = 0.32], accounting for an additional 5.4% of the variance in helplessness scores.

In the prediction of Time 2 depression, the contribution of Time 1 antidepressants and sedatives and Time 2 steroids, antidepressants, benzodiazepines, NSAID, and sedatives accounted for 31% of the variance in Time 2 depression [$F(7, 73) = 4.68$, $p < 0.001$]. Time 2 steroids (ß = 0.23) and antidepressants (ß = 0.25) individually predicted greater depression. The contribution of Time 1 disease status and Time 2 helplessness on the next step was significant [$F(2, 71) = 10.26$, $p < 0.001$], explaining 15.6% of the variability in depression beyond the effects of medication use. However, only Time 2 helplessness was uniquely predictive of depression (ß = 0.44), as Time 1 disease status had no independent relationship with Time 2 depression scores when the effects of Time 2 helplessness were taken into account.

In the final analysis predicting to Time 2 fatigue, after the entry of medications on the first step (see the first longitudinal analysis), the aggregate contribution of Time 1 disease status, Time 2 helplessness, and Time 2 depression was highly significant [$F(3, 69) = 9.03$, $p < 0.001$], explaining an additional 19.8% of the variance in fatigue scores. Of these 3 variables, Time 1 disease status (ß = 0.27, $sr^2 = 0.033$) and Time 2 depression (ß = 0.31, $sr^2 = 0.049$) were predictive of fatigue, whereas helplessness did not reach significance. As in the preceding longitudinal analysis, medication use did not predict fatigue after model variables were entered into the regression equation (Table 6).

Thus, both longitudinal analyses supported the importance of prior disease status as a direct predictor of fatigue whether using Time 1 or Time 2 mediators. The contribution of disease status remained significant after controlling for medication use across time. Neither helplessness nor depression predicted subsequent fatigue. In addition, when Time 2 mediators were used, prior disease status predicted greater helplessness, which was associated with greater depression, which, in turn, was related to higher fatigue (Figure 4). Prior disease status was associated with Time 2 depression only through Time 2 helplessness, and Time 2 helplessness was associated with fatigue only through Time 2 depression.

## DISCUSSION

A major purpose of this research was to investigate the relative contributions of disease status and psychological variables to fatigue in patients with SLE. A significant feature of this study was the adoption of a theoretical paradigm that hypothesized direct and indirect pathways between disease status and fatigue. In addition, a longitudinal design was employed to determine whether disease status and psychological variables would predict fatigue over time.

This research also has illustrated the importance of examining the role of disease status and psychological variables in an integrative framework, and of using both cross sectional and longitudinal methodologies. This biopsychosocial framework has been proposed by other SLE

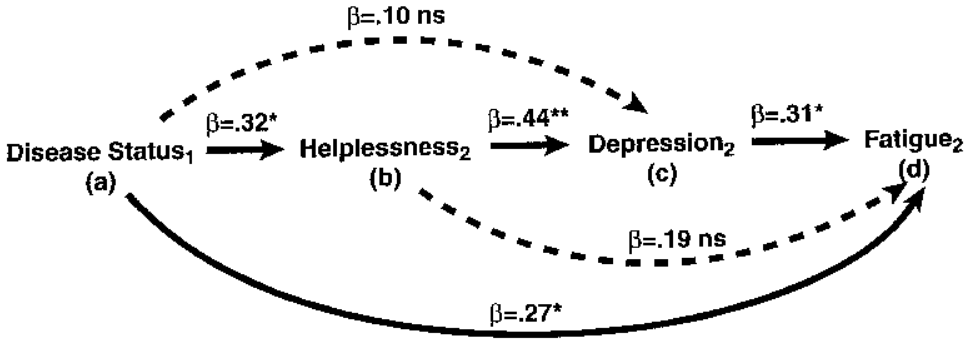


*Figure 4*. Longitudinal model with Time 1 disease status and Time 2 helplessness, depression, and fatigue.
* $p < 0.05$; ** $p < 0.01$.

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*Table 5*. Longitudinal multiple regression analysis predicting Time 2 fatigue with Time 1 disease status and mediators.

| Step | Variable | df | $R^2$ | $R^2$ Change | F | ß[a] | ß[a] | $sr^{2\,a}$ | $sr^{2\,b}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | T1 Antidepressants | (8,72) | 0.298 | — | 3.82* | 0.19 | 0.14 | 0.023 | 0.100 |
| | T1 Sedatives | | | | | –0.38 | –0.21 | 0.022 | 0.006 |
| | T2 Steroids | | | | | 0.21 | 0.05 | 0.034 | 0.001 |
| | T2 Antidepressants | | | | | –0.02 | 0.13 | 0.000 | 0.010 |
| | T2 Benzodiazepines | | | | | 0.18 | 0.07 | 0.024 | 0.003 |
| | T2 NSAID | | | | | 0.21 | 0.00 | 0.028 | 0.003 |
| | T2 Sedatives | | | | | 0.42 | 0.27 | 0.028 | 0.011 |
| | T2 Hormones | | | | | 0.10 | 0.11 | 0.005 | 0.006 |
| 2 | T1 Disease status | (3,69) | 0.417 | 0.12 | 4.72** | — | 0.31* | — | 0.043 |
| | T1 Helplessness | | | | | — | 0.15 | — | 0.014 |
| | T1 Depression | | | | | — | 0.13 | — | 0.010 |

[a] At Step 1; [b] at Step 2. * $p < 0.05$; ** $p < 0.01$.

*Table 6*. Multiple regression analysis predicting Time 2 fatigue with Time 1 disease status and Time 2 mediators.

| Step | Variable | df | $R^2$ | $R^2$ Change | F | ß[a] | ß[a] | $sr^{2\,a}$ | $sr^{2\,b}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | T1 Antidepressants | (8,72) | 0.298 | — | 3.82** | 0.19 | 0.12 | 0.023 | 0.008 |
| | T1 Sedatives | | | | | –0.38 | –0.28 | 0.022 | 0.012 |
| | T2 Steroids | | | | | 0.21 | 0.00 | 0.034 | 0.000 |
| | T2 Antidepressants | | | | | –0.02 | –0.20 | 0.000 | 0.025 |
| | T2 Benzodiazepines | | | | | 0.18 | 0.05 | 0.024 | 0.002 |
| | T2 NSAID | | | | | 0.21 | 0.06 | 0.028 | 0.002 |
| | T2 Sedatives | | | | | 0.42 | 0.32 | 0.028 | 0.016 |
| | T2 Hormones | | | | | 0.10 | 0.05 | 0.055 | 0.001 |
| 2 | T1 Disease status | (3,69) | 0.496 | 0.198 | 9.03*** | — | 0.27* | — | 0.033 |
| | T2 Helplessness | | | | | — | 0.19 | — | 0.018 |
| | T2 Depression | | | | | — | 0.31* | — | 0.049 |

[a] At Step 1; [b] at Step 2. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

researchers[15,16,22]. Significant differences emerged when the same model was tested cross sectionally, and then longitudinally, after a period of 3 months had elapsed between testing periods. Cross sectional findings provided substantial confirmation for the full model in which disease status was hypothesized to contribute to fatigue directly, and indirectly, by being related to higher helplessness and depression. These findings revealed that disease status, helplessness, and depression contributed unique variance to fatigue, with depression sharing the most variability with fatigue scores. Zonana-Nacach, *et al*[15] also found that helplessness was independently associated with SLE fatigue. The result that depression correlated with fatigue converges with data reported by Krupp, *et al*[3] and Wang, *et al*[9]; however, in contrast to those investigations, our research revealed that, at one point in time, higher disease activity and SLE helplessness also were uniquely associated with fatigue. Moreover, the data supported the plausibility of indirect mechanisms linking disease status with fatigue through helplessness and depression. The health status-to-helplessness-to-depression pathway has been found in research into RA[19] and fibromyalgia[20]. The role of depression as mediating the influence of disease activity on fatigue has also been repeated by McKinley, *et al*[16]. As per Baron and Kenny[34], our findings provided evidence of partial mediation, rather than full mediation, because the relationship between disease status and depression was still significant after taking into account the role of helplessness, and the relationship between helplessness and fatigue remained significant after taking into account the role of depression. The role of helplessness and depression as mediational variables explaining the association between disease activity, mood disturbance, and fatigue in SLE merits further research.

Longitudinal findings illustrated a different pattern, emphasizing the value of examining prospective relationships among model constructs. In contrast to the cross sectional findings, longitudinal data supported the primacy of disease status as a predictor of fatigue over time. Although Time 1 disease status shared common variance

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with Time 1 helplessness and Time 1 depression, disease status proved to be the only predictor of fatigue 3 months later. Helplessness and depression were not associated with fatigue over time. The second longitudinal analysis revealed that prior disease status remained a predictor of fatigue when it competed with Time 2 depression. Although laboratory data were not used in the assessment of disease activity, the item measuring fatigue was removed from the SLAM, thus eliminating the possibility that the relationship between SLAM scores and fatigue was due to measurement artifact. Overall, these findings agree with data reported by Wysenbeek, *et al*[4], Taylor, *et al*[14], and Zonana-Nacach, *et al*[15], who found disease activity contributed to fatigue in SLE, but diverge from the results of Krupp, *et al*[3] and Wang, *et al*[9], who found depression, and not disease activity, to be correlated with fatigue.

However, since the contribution of disease activity to subsequent fatigue was modest, the possibility cannot be ruled out that other psychosocial factors may influence fatigue over time. Aaronson, *et al*[35] and Smets, *et al*[36] have noted that fatigue is a multidimensional construct, involving a combination of biomedical, psychological, and motivation components. Disease activity, depression, and helplessness may affect different aspects of fatigue, making the use of multidimensional measures of fatigue an important methodological improvement in future research.

Longitudinal data also revealed that disease status predicted subsequent helplessness, which in turn was related to depression. The effects of disease status on depression were fully mediated by helplessness, in that disease status evidenced no independent relationship with depression. Similarly, regression findings also showed that helplessness at Time 2 was related to fatigue only through depression. Helplessness at Time 2 shared no unique variance with fatigue. The pattern of these results indicates that while helplessness may not predict fatigue directly, it may be a critical factor in explaining fatigue through its effects on depression. The data did not substantiate the longitudinal effect of depression on fatigue; however, the contribution of depression to fatigue may be more immediate, as reflected in the significant within-time relationships that were found between these variables at both Time 1 and Time 2.

These findings suggest that improvement in fatigue should result from early and aggressive biomedical treatment of SLE disease processes and symptoms. Effective treatment may mitigate fatigue directly, and prevent the development of a vicious cycle that may lead to dysfunctional illness beliefs and mood disturbance that may interfere with successful biomedical treatment and exacerbate disease activity over time. In addition, interventions should be directly targeted at reducing helplessness beliefs in the face of SLE. Cognitive-behavioral treatment strategies and psychoeducational strategies that enhance perceived control over the illness and engender active coping efforts may be particularly beneficial[37] as suggested by the findings of other investigators[15,22]. Reduction in helplessness in patients who receive such interventions may be responsible for improvement in depression and physical symptomatology[38].

## Conclusions

The study possessed some notable strengths and advantages over previous research. This investigation adopted a theoretical model that allowed disease status and psychological variables to be integrated in the prediction of fatigue. In addition, a longitudinal design permitted examination of the predictive efficacy of model variables, thus avoiding interpretational problems between predictors and outcomes that have limited previous cross sectional research. Further, the research adopted validated measures of fatigue and all psychological constructs, and the use of the SLAM as an objective, global measure of SLE disease status, administered by a clinical rheumatologist.

However, it is important to acknowledge some methodological limitations and to exercise caution in interpreting the results of this research. Despite the longitudinal perspective, the correlational nature of this study prevented causal significance from being ascribed to model predictors of fatigue. Although the path-analytic framework examined direct and indirect associations between constructs, causal mechanisms could not be substantiated by the data. In addition, a longer followup period with a larger sample size is recommended in order to study change in the adjustment to SLE, and to obtain a firmer grasp of the interrelationships among the variables that were studied. A period of 3 months may be insufficient to examine the role of depression in SLE, or how change in disease status may predict corresponding alterations in psychological functioning or fatigue. Finally, this research did not screen for the presence of fibromyalgia, which in recent research has been found to occur in a subset of patients with SLE and contribute variance to fatigue[12,14].

SLE is a complex medical condition with confusing physical and psychological symptomatology; thus, the origins of fatigue in SLE are difficult to identify and interpret. Based on this research, the continued use of multivariate models in which the role of disease related and psychosocial processes in fatigue can be analyzed independently and interactively over time is warranted. This approach is highly suitable for studying the development and maintenance of symptoms that may result from disease related and psychological factors.

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