

Depression during Exacerbations in Multiple Sclerosis:
The Importance of Uncertainty

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Abstract

The following correlates of depression were examined in a sample of 166 patients with clinically definite relapsing-remitting (N = 140) or secondary progressive (N = 26) multiple sclerosis: (a) the present state of the patients' illness (i.e., whether or not they were currently experiencing an exacerbation of their symptoms); (b) their level of uncertainty concerning their illness; and (c) their strategies for coping with their illness. A current exacerbation in symptoms, greater uncertainty of illness, and greater use of emotion-centered forms of coping were all related to depression. Multivariate analyses revealed that uncertainty of illness played a pivotal role as a mediating variable. Exacerbations in illness appeared to heighten patients' levels of uncertainty, and it was largely through this heightened uncertainty that the increases in depression came about.

Introduction

The lifetime prevalence of clinical depression in patients with MS is estimated to be about 50%.¹ As with many autoimmune diseases, one of the hallmarks of MS for most patients is its highly variable course. Because of this variability, investigators should consider the present state of the patient's illness when studying psychological correlates of depression in MS. The few studies that have done so indicate that patients currently experiencing an exacerbation have higher levels of emotional distress^{2,3} and use more emotion-centered coping strategies.^{4,5} The goal of the present study is to replicate and extend these findings -- our focus being upon two general psychological correlates of depression in MS: coping and uncertainty.

The instrument commonly used to study coping in MS patients is the Ways of Coping Questionnaire, which distinguishes between problem-focused and emotion-focused coping.⁶ Problem-focused coping involves taking actions to change the environment or oneself in order to solve the problem that is the source of distress. Emotion-focused coping involves efforts directed toward managing the negative emotions associated with the stressor. In circumstances where the stressor affords little opportunity for direct intervention, individuals tend to resort to emotion-focused coping, and in particular, this form of coping is common in stressful situations involving health problems.^{7,8} Emotion-focused coping has been found to correlate with psychological distress and depression in patients with various chronic medical conditions,^{9,10} including MS.¹¹⁻¹³ Correlations with problem-focused coping are lower in magnitude and seldom attain significance.

Analyses of MS patients' responses to the Ways of Coping questionnaire have revealed factors that generally resemble emotion-focused and problem-focused coping. For example, Wineman, Durand, and McCulloch distinguished between

emotional respite and cognitive reframing¹⁴, and we recently identified two factors involving passive avoidant and active constructive coping.⁴ As in the case of emotion-focused coping itself, emotional respite and passive avoidant coping are positively related to depression.^{15,16} Cognitive reframing and active constructive coping are negatively related to depression, but the correlations are weaker and these factors do not emerge as significant predictors when examined within multiple regression models.¹⁶

Thus, studies of both healthy individuals and patients with MS have distinguished two general coping strategies: one centered on emotions and characterized by a certain passivity with regard to the stressor itself; the other, more problem-centered and active. The purest examples of these strategies are embodied by two subscales of the Ways of Coping, escape-avoidance and planful problem solving. These scales have often been singled out in studies concerning the relationship between coping and depression in MS patients. Both Mohr et al.¹⁵ and Jean et al.¹² showed depression in MS patients to be positively related to escape-avoidance and negatively related to planful problem solving. Furthermore, in one of the few prospective studies in this area, escape-avoidance was the only subscale from the Ways of Coping that contributed to the prediction of subsequent depression in patients with MS.¹⁷

The variable course of MS undoubtedly contributes to the substantial amount of uncertainty patients have concerning their illness, and yet surprisingly few studies have examined uncertainty in conjunction with MS. Using a combined sample of patients with MS and spinal cord injuries, Wineman, Durand, and Steiner found greater emotion-focused coping among patients with high uncertainty and more problem-focused coping among those with no uncertainty of illness.⁸ To our

knowledge, there have been no studies directly examining the relationship between uncertainty and depression in MS patients.

In the present study, the patients' present state of illness, the extent of their uncertainty concerning their illness, and their methods of coping were evaluated as correlates of depression. On the basis of previous studies, we expected that patients currently experiencing an exacerbation of symptoms would report greater levels of depression and use more emotion-centered forms of coping. However, clinical observations suggested that patients also experience heightened uncertainty concerning their illness at such times and that this uncertainty might play an influential role affecting their depression. This led to our particular interest in how uncertainty (or coping) interacted with exacerbations in the patient's illness to impact depression -- whether either of these psychological correlates might serve as a moderator or a mediator of the relationship between the present state of illness and depression. Multivariate models recommended by Baron and Kenny¹⁸ were used to examine the moderating and mediating effects of uncertainty and coping in exacerbating versus non-exacerbating patients.

Method

Subjects

One hundred eighty-nine patients attending regularly scheduled appointments in a multiple sclerosis clinic at the University of Kansas Medical Center were invited to participate in the study. We excluded patients with primary progressive MS since, by definition, this subtype is characterized from its outset by a progressive course without exacerbation periods. Four patients refused the request for participation, five did not provide useable data, and 14 failed to return the battery of questionnaires. The present sample consisted of 166 patients who met Poser et al.'s¹⁹ criteria for clinically

definite MS and were diagnosed with either relapsing-remitting (N = 140) or secondary progressive (N = 26) disease. Most of these patients turned in the battery at the end of their clinic appointment. Fifty-two return envelopes were distributed to individuals who could not complete the battery during their appointment, and 38 (73%) of these patients returned the battery by mail.

During the course of the clinic visit, the attending physician (SGL) recorded each patient's current level of disability using Kurtzke's²⁰ Expanded Disability Status Scale (EDSS), the subtype of MS, the patient's age at first diagnosis, length of illness, and current medications relating to MS.

The participants (27 males, 139 females) ranged in age from 16 to 80 ($M = 42.7$). Ninety-two percent were Caucasian, 4% African American, and 2% Hispanic. Four percent of the sample had not completed high school, 21% had completed high school, 40% had completed some college credit, 17% had completed a 4-year college degree, and 18% had undertaken graduate work or completed an advanced degree. Forty-six percent were currently employed or self-employed, 37% were unemployed, and 11% were retired. Sixty-seven percent of the participants were married, 16% divorced or separated, 3% widowed, and 14% single.

The age when the patient was diagnosed with MS ranged from 14 to 59 ($M = 34.9$), and the length of illness ranged from 1 to 43 years ($M = 7.9$). Scores on the EDSS ranged from 1.0 to 9.0 ($M = 3.5$). Eighty-three percent of the patients were taking one or more MS-related medications.

Two of the questions on the initial page of the battery were used to classify patients according to the present state of their illness: (a) "Do you have clear cut times when you experience exacerbations in your symptoms (i.e., times when symptoms are noticeably worse?); (b) "If yes, are you experiencing an exacerbation phase now?"

Five patients failed to respond to the first question and 24 responded "no" to this question. The remaining 137 patients were considered appropriate for subclassifying into the exacerbating and non-exacerbating subgroups since they all reported having experienced exacerbations in their illness. Two of these 137 patients failed to respond to the second question; 46 responded "yes" and were thus designated the exacerbating subgroup; and 89 responded "no" and were designated the non-exacerbating subgroup. In the correlational and regression analyses of this study, patient's present state of illness was treated as a dichotomous variable (i.e., 1 = non-exacerbating; 2 = exacerbating).

Measures

In addition to an initial page eliciting demographic and disease-related information, the battery of questionnaires included the following measures:

The Self-Rating Depression Scale (SDS).²¹ The SDS is comprised of 20 items reflecting common affective, cognitive-behavioral, and physiological symptoms of depression. Participants rated the frequency with which they had experienced each symptom during the recent past, using a scale from 1 (never or a little of the time) to 4 (most of the time). Several investigators have recommended that, in order to avoid spuriously inflating depression scores in samples of MS patients, depression questionnaires should be corrected for items that overlap with symptoms or other features of MS.^{22,23} In the present study, four such items were omitted from the scoring: "I get tired for no reason"; "My mind is as clear as it used to be"; "I find it easy to do the things I used to"; "I still enjoy the things I used to do." The ratings assigned to the remaining 16 items were summed, and this total was prorated to an equivalent score for the full 20-item questionnaire by multiplying by 5/4. These prorated depression scores had an internal consistency (Cronbach's alpha) of .76 and ranged

from 31 to 69 ($M = 46.0$; $S.D. = 7.2$). By way of comparison, Zung reported means of 26 for healthy persons, 51 for depressed psychiatric outpatients, and 59 for depressed psychiatric inpatients using the full questionnaire.²¹

The Uncertainty of Illness Scale (UIS).²⁴ The original UIS consisted of 30 items rated on a scale from 1 (strongly disagree) to 5 (strongly agree). Three items referring to inpatient care were omitted in an attempt to make the scale more suitable for the outpatient setting of the present study. A total score was derived by summing ratings on the 27 remaining items and had a standardized alpha of 0.91.

The Ways of Coping (WOC).⁶ The WOC consisted of 65 items describing a variety of coping strategies which people use to deal with stressful events. Participants were asked to identify the coping strategies they used to deal with their multiple sclerosis. They responded to each item using a scale from 1 (not used) to 4 (used a great deal). The WOC was scored to yield four measures of emotion-centered coping (emotion-focused coping, emotional respite, passive avoidant coping, and escape-avoidance) and four measures of problem-centered coping (problem-focused coping, cognitive reframing, active constructive coping, and planful problem solving).

Results

Table 1 presents the means for patients currently experiencing or not experiencing an exacerbation in their symptoms. The two subgroups did not differ in age, education level, age at diagnosis, or disability status. However, exacerbating subjects had been diagnosed with MS for a longer duration than non-exacerbating patients ($t = 2.1$, $df = 119$, $p = .042$). Exacerbating subjects also had higher scores on depression, uncertainty of illness, passive avoidant coping and escape-avoidance coping, and these differences remained significant when differences in duration of illness were controlled through an analysis of covariance (depression: $F = 8.4$,

$df = 1, 101, p = .005$; uncertainty: $F = 11.1, df = 1, 104, p = .001$; passive avoidant coping: $F = 8.8, df = 1, 101, p = .004$; escape-avoidance: $F = 6.6, df = 1, 110, p = .012$).

Insert Table One About Here

As shown in Table 2, depression scores were significantly related to current exacerbations in patients' illness ($r = .31, p = .001$), elevations in their levels of uncertainty ($r = .47, p < .001$), and use of emotion-centered coping strategies (r 's from .22 to .43). Depression scores were also correlated with most of the problem-centered coping measures, but these correlations were lower in magnitude (r 's from -.14 to -.22).

Insert Table Two About Here

For purposes of brevity, before presenting the remaining results, it is useful to reduce the number of coping variables. As indicated above, depression was significantly related to all measures of emotion-centered coping, and exacerbating patients had significantly higher scores on both passive avoidant coping and escape-avoidance. While either of these latter two measures could be chosen (the results being the same for either), escape-avoidance is featured in the remainder of this section. Escape-avoidance was chosen because it was the coping measure most highly correlated with depression, as well as figuring prominently in other studies of coping with MS.^{12,15,17}

As illustrated in Figure 1, substantial intercorrelations were found between the patients' present state of illness, uncertainty, and use of escape-avoidance coping, and this raises the issue of the relative contributions of these variables as predictors of depression. Such questions are best answered through multiple regression analyses in which uncertainty, coping, and present state of illness are entered as predictors.

Insert Figure One About Here

When entered simultaneously, the three predictors together accounted for 26% of the variance in depression (adjusted $R^2 = .26$, $F = 12.9$, $df = 3, 99$, $p < .001$). Uncertainty of illness ($\beta = .23$, $t = 4.0$, $p < .001$) and escape-avoidance coping ($\beta = .26$, $t = 2.9$, $p = .005$) were both significant predictors of depression, although present state of illness was not ($\beta = .06$, $t = 0.7$, $p = .51$). The finding that the patients' present state of illness is no longer significantly related to depression is indicative that either or both of the other two variables (i.e, uncertainty, escape-avoidance coping) might be serving as moderating or mediating variables linking present state of illness to depression.

In regression analyses, moderator variables are represented as interaction terms computed by multiplying the relevant predictor variables. In accordance with Baron and Kenny¹⁸, the interaction term is entered after the individual predictors, and the test of the moderator variable is based upon the increase in variance accounted for (ΔR^2) by the interaction term. The increase in variance accounted for by the interaction of present state and uncertainty was not significant ($\Delta R^2 = .008$, $F = 1.1$, $df = 1,103$, $p = .29$); nor was the increase in variance accounted for by the interaction of present state and escape-avoidance coping ($\Delta R^2 = .007$, $F = 1.0$, $df = 1,107$, $p = .32$). Neither uncertainty nor escape-avoidance coping was serving as a moderator variable.

Alternatively, uncertainty (or escape-avoidance coping) might serve as a mediating variable interposed between the patients' present state of illness and depression. Baron and Kenny¹⁸ cite three criteria that must be satisfied to demonstrate a mediating variable. Stated in terms of the present study, (a) the present state of illness must be significantly related to uncertainty (or escape-avoidance coping), (b) the present state of illness must be significantly related to depression, and

(c) the relationship between present state of illness and depression must decline substantially or become nonsignificant when uncertainty (or escape-avoidance coping) is included as a predictor.

As already noted (Table 1), exacerbating patients have significantly higher scores than non-exacerbating patients on uncertainty and on escape-avoidance coping, and these differences remain significant even after the two subgroups are equated with respect to duration of illness. The point biserial correlation is .33 ($p < .001$) between present state of illness and uncertainty and .21 ($p = .018$) between present state of illness and escape-avoidance coping. The first criterion is satisfied with respect to both of the suggested mediating variables.

To evaluate the second and third criteria, depression scores were first regressed on present state of illness alone and then on present state and uncertainty (or escape-avoidance coping). The focus of these analyses was the standardized regression coefficient (i.e., β) for present state of illness. If this coefficient was significant in the simple regression, the second criterion was met, and if this coefficient declined substantially or became nonsignificant when the multiple regression was performed, the third criterion was satisfied. The coefficient for present state of illness was significant in the simple regression ($\beta = .31$, $t = 3.4$, $p = .001$); present state of illness is significantly related to depression. When escape-avoidance coping was included in the multiple regression, the coefficient for present state of illness showed only a slight decline and remained significant ($\beta = .23$, $t = 2.6$, $p = .010$). However, when uncertainty rather than escape-avoidance coping was included in the multiple regression, the coefficient for present state of illness declined substantially and was no longer significant ($\beta = .096$, $t = 1.1$, $p = .29$). Uncertainty of illness clearly meets the

criteria for a mediating variable. On the other hand, escape-avoidance coping appears to function as an independent predictor of depression.

Discussion

Patients in the present study were classified into currently exacerbating and non-exacerbating subgroups on the basis of self report. Although previous studies concerning the psychological impact of exacerbations have likewise relied on patients' self report, the accuracy of these reports is always open to question. We attempted to refine the classification of the current sample by eliminating patients with primary progressive MS from the exacerbating and non-exacerbating subgroups and by asking a series of questions pertaining to patients' present state of illness. To be placed in the exacerbating subgroup, patients had to affirm that they had experienced clear-cut exacerbations associated with their illness and that they were experiencing such an exacerbation at the present time. Objective criteria for establishing a current exacerbation (e.g., an increase of .5 in EDSS within a 24-hour period) have been proposed, but to employ such criteria in the present study would still have involved patients' retrospective reports concerning the onset of their current exacerbation. Nevertheless, reliance upon self report for classifying patients' present state of illness poses the possibility that those with greater emotional distress and uncertainty are also more likely to perceive minor changes in their symptoms as exacerbations.

Each of the three central variables examined in this study was significantly related to the level of depression reported by patients with MS. Patients currently experiencing an exacerbation of their symptoms, those reporting a high degree of uncertainty concerning their illness, and those using more emotion-centered forms of coping in conjunction with their illness all reported significantly greater depression. Furthermore, we found that patients currently experiencing an exacerbation of their

symptoms had greater uncertainty concerning their illness and resorted to the use of more avoidant forms of coping than non-exacerbating patients.

Most of these associations have been reported by other investigators. With respect to coping, we replicated other studies showing positive relationships between the use of emotion-centered forms of coping and emotional distress in MS patients.^{11-13,15,17} With respect to present state of illness, we replicated previous studies showing greater emotional distress^{2,3} and greater use of passive avoidant coping⁴ during exacerbations in the patient's illness.

The most noteworthy finding of the present study, however, involves the central role of uncertainty in mediating the relationship between patients' present state of illness and their level of depression. Uncertainty clearly satisfied the three criteria set forth by Baron and Kenny¹⁸ as a mediating variable. The effects of patients' current state of illness on depression are indirect and mediated through uncertainty.

The construct of uncertainty of illness has received relatively little attention in the literature concerning adjustment to disease. It has been shown to be associated with health-related quality of life in patients with gynecological cancer²⁵ and with both the use of emotion-centered coping²⁶ and emotional distress²⁷ in patients with heart disease. Furthermore, uncertainty concerning their spouse's illness appears to be a relevant construct affecting the health and well being of spousal caregivers²⁸, including those caring for a person with MS.²⁹

The present study indicates a more pivotal role for this construct in shaping the way patients with MS cope with and adjust to exacerbations in their illness. This finding might have been anticipated on the basis of patients' statements clearly implying that exacerbations in symptoms constitute times of heightened uncertainty. Patients often wonder about whether and to what extent the intensified symptoms will

abate, whether their chronic symptoms will be substantially augmented following the current exacerbation. Patients also tell us they wonder about what might have brought on the exacerbation, whether there were physical or psychological factors in their lives that played a role in evoking the flare-up. For example, 66% of the patients in the present study felt that exacerbations in their illness were "definitely" or "strongly" related to stress in their lives.

In brief, one of the challenges that patients frequently report involves coming to terms with the substantial amount of uncertainty accompanying the disease of multiple sclerosis. The present study indicates that their success in doing so may have an important bearing on their psychological adjustment to this disease. In light of these findings, health care providers should be aware of the importance of recognizing periods of heightened uncertainty in their patients and, wherever possible, reducing the uncertainty that accompanies exacerbations in their illness.

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Table 1

Comparison of Patients Experiencing and Not Experiencing
an Exacerbation of their Illness

		Current Exacerbation		t	df	p
		Yes	No			
<u>Patient and Disease-Related Variables</u>						
Age	M	42.09	41.39	0.39	119	
	S.D.	9.71	9.59			
Education	M	3.13	3.21	0.41	133	
	S.D.	0.93	1.18			
MS Age	M	33.60	35.12	0.94	133	
	S.D.	8.06	9.33			
Length of illness	M	8.60	6.14	2.05	119	.04
	S.D.	7.92	5.23			
Disability (EDSS)	M	3.52	3.33	.53	132	
	S.D.	2.21	1.92			

Table 1 (continued)

		Current Exacerbation		t	df	p
		Yes	No			
<u>Depression, Uncertainty, and Coping Variables</u>						
Depression	M	49.38	44.93	3.43	114	.001
	S.D.	7.25	6.39			
Uncertainty	M	51.71	44.35	3.83	118	<.001
	S.D.	9.74	9.82			
Emotion-focused coping	M	31.63	28.83	1.55	116	
	S.D.	9.15	9.20			
Emotional respite	M	5.42	4.64	1.32	126	
	S.D.	3.53	3.00			
Passive avoidant coping	M	38.44	32.99	2.52	113	.01
	S.D.	11.78	10.56			
Escape-avoidance	M	8.48	6.59	2.39	123	.02
	S.D.	4.41	4.03			
Problem-focused coping	M	17.02	17.26	0.20	120	
	S.D.	5.93	6.30			
Cognitive reframing	M	10.46	11.12	.75	120	
	S.D.	4.56	4.74			
Active constructive coping	M	27.37	29.41	1.02	115	
	S.D.	10.59	10.22			
Planful problem solving	M	9.45	9.68	0.30	120	
	S.D.	3.47	4.02			

Table 2

Bivariate Correlations between Depression, Present State of Illness, Uncertainty, and Coping

	Depression	
	r	p
Current Exacerbation (1 = no; 2 = yes)	.31	.001
Uncertainty	.47	<.001
<u>Emotion-Centered Coping</u>		
Emotion-focused coping	.22	.012
Emotional respite	.34	<.001
Passive avoidant coping	.28	.001
Escape-avoidance	.43	<.001
<u>Problem Centered Coping</u>		
Problem-focused coping	-.17	.049
Cognitive reframing	-.19	.027
Active constructive coping	-.22	.015
Planful problem solving	-.14	

Figure Caption

Figure 1. Intercorrelations among predictors of depression.

Note: * $p < .05$; ** $p < .01$; *** $p < .001$

