

## PAPER

# Longitudinal course of depression symptoms in multiple sclerosis

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**Background:** Despite the high lifetime prevalence of depression in multiple sclerosis (MS), its longitudinal course is poorly understood.

**Objective:** To examine the longitudinal course of and reliable change in different depression symptom clusters in MS, and the longitudinal association of interferon beta treatment and coping with depression symptoms.

**Methods:** 53 MS patients were examined at two time points three years apart on the Beck Depression Inventory (BDI) and the Chicago Multiscale Depression Inventory (CMDI).

**Results:** Correlations from time 1 to time 2 for BDI, CMDI-total, CMDI-evaluative scale, and CMDI-vegetative scale were all highly significant, and reliable change indices reflected little change over time. In contrast, the correlation over time for the CMDI-mood scale was significantly lower ( $p < 0.05$ ) than the CMDI-evaluative and CMDI-vegetative scale correlations, and over 40% of patients showed reliable change. Patients who improved in their mood showed increased use of active coping, while patients who worsened showed decreased active coping strategies; the latter were also significantly more likely to have been taking interferon beta drugs at both time points than patients who did not change in their mood functioning.

**Conclusions:** Mood symptoms of depression are significantly more variable over time than neurovegetative or negative evaluative symptoms in MS patients. Decreased use of active coping strategies may put patients at risk of increased depressed mood, whereas increased use of active coping may result in decreased depressed mood longitudinally. Interferon beta use may put patients at risk of increases in depressed mood.

Lifetime prevalence estimates of depression in multiple sclerosis (MS) patients are high, typically falling around 50%.<sup>1,2</sup> Although numerous studies have examined depression in MS cross sectionally,<sup>3-5</sup> few have examined it longitudinally. Schreurs and colleagues<sup>4</sup> found that Beck Depression Inventory (BDI) ratings over a one year period were highly correlated ( $r = 0.72$ ). Using the Hamilton Depression Rating Scale, Amato and colleagues found that MS patients showed a mild increase in depression relative to controls over a four year period,<sup>6</sup> but then remained stable through a 10 year follow up study.<sup>6</sup>

Several other studies have examined depression in MS longitudinally in the context of immunomodulatory treatment. Findings from these studies suggest that depression in MS is sometimes related to treatment with interferon beta drugs,<sup>7-9</sup> but not related in other studies,<sup>10,11</sup> and appears to be relatively stable over time<sup>10,12</sup> (but see Borrás *et al*).<sup>13</sup> However, given that these treatment studies were clinical trials, it is unclear what the natural history of depression would be in a mixed community sample of MS patients.

One limitation of all longitudinal depression studies in MS is that none has examined reliable change over time on a patient by patient basis. Existing studies have typically compared means or mean changes over time, or examined correlations between scores longitudinally. Although such data are illuminating, they can obscure significant individual variability. Identifying the proportion of patients who change significantly over time in MS is important in order to gain an appreciation of the natural history of depression symptoms in MS. Additionally, gaining an understanding of factors that might account for change should provide clues for guiding more effective treatments. Another limitation of longitudinal work on depression in MS is that all studies have used global indices of depression that do not distinguish between

different depression symptom clusters, such as those relating to mood, negative evaluative, and neurovegetative features.<sup>14</sup> Distinguishing among components of depression is important, given the hypothesised overlap between MS symptoms and neurovegetative symptoms of depression<sup>15-18</sup> (but see Aikens *et al*).<sup>19</sup> Additionally, it may be that different depression symptom clusters show different patterns of change over time.

With these considerations in mind, the first specific aim of our study was to evaluate the consistency of depression symptom clusters longitudinally. Based upon results from the few existing longitudinal studies of depression in MS,<sup>10,11</sup> we hypothesised that the correlation of depression scores between time points would be large in magnitude. Because some research has suggested that interferon beta-1b<sup>7</sup> (but see Feinstein *et al*)<sup>10</sup> and interferon beta 1a<sup>8</sup> (but see Patten and Metz<sup>11,12</sup>) may be related to depression, a second (exploratory) aim was to examine whether an increase in depression symptoms is associated with interferon beta use. Coping has been shown to be associated with depression in MS in previous reports.<sup>14,20</sup> As such, a third aim was to examine coping, in particular whether increases in maladaptive coping and decreases in adaptive coping would co-vary with increased depression symptoms over time.

Although in the light of the longitudinal stability of depression scores reported in previous work it was expected that depression symptom scores from our study would also be stable, because no existing study has examined the stability of different clusters of depression symptoms over time, this part of the study was considered exploratory.

**Abbreviations:** BDI, Beck Depression Inventory; CMDI, Chicago Multiscale Depression Inventory; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis

**Table 1** Summary of participant characteristics at time 1 and time 2

| Variable                               | Mean T1 | SD T1  | Mean T2 | SD T2  |
|--|---------|--------|---------|--------|
| CMDI mood scale <i>t</i> scores        | 49.2    | 7.6    | 51.5    | 11.9   |
| CMDI evaluative scale <i>t</i> scores  | 51.5    | 12.7   | 49.6    | 11.7   |
| CMDI vegetative scale, <i>t</i> scores | 61.2    | 13.8   | 61.9    | 13.9   |
| CMDI total <i>t</i> scores             | 54.7    | 10.9   | 55.6    | 11.4   |
| Beck Depression Inventory (BDI)        | 10.2    | 7.4    | 8.5     | 5.6    |
| Age (years)                            | 46.6    | 7.6    | 49.5    | 7.7    |
| Education (years)                      | 14.9    | 2.3    | 15.4    | 2.5    |
| Kurtzke (1983) EDSS                    | 4.5     | 1.4    | 4.7     | 1.6    |
| Symptom duration (years)               | 14.0    | 9.4    |         |        |
| Diagnosis duration (years)             | 7.6     | 5.9    |         |        |
|  | n (T1)  | % (T1) | n (T2)  | % (T2) |
| BDI depressed*                         | 26      | 49     | 20      | 38     |
| Sex                                    |         |        |         |        |
| Male                                   | 12      | 23     |         |        |
| Female                                 | 41      | 77     |         |        |
| Clinical course                        |         |        |         |        |
| Relapsing-remitting                    | 31      | 58     |         |        |
| Secondary progressive                  | 15      | 28     |         |        |
| Primary progressive                    | 6       | 11     |         |        |
| Progressive relapsing                  | 1       | 2      |         |        |
|  | n (T1)  | % (T1) |         |        |
| Diagnostic category                    |         |        |         |        |
| Clinically definite                    | 49      | 92     |         |        |
| Clinically probable                    | 3       | 6      |         |        |
| Laboratory supported definite          | 1       | 2      |         |        |

For most variables, n=53.

\*Patients falling in the "mild-moderate" BDI depressed range or above.

BDI, Beck Depression Inventory; CMDI, Chicago Multiscale Depression Inventory; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

## METHODS

### Participants

A subset of 53 of the 77 MS participants diagnosed as having definite or probable MS based on the criteria of Poser *et al.*,<sup>23</sup> and described in detail elsewhere,<sup>22</sup> completed testing at time 2 approximately three years after their initial participation. Each MS participant was diagnosed as having definite or probable MS on the basis of the Poser criteria by a board certified neurologist who also determined disease course using standard criteria.<sup>21</sup> Duration of illness from symptom onset and from diagnosis, and neurological disability using Kurtzke's Expanded Disability Status Scale (EDSS)<sup>24</sup> were also assessed.

All participants provided informed written consent and were treated in accordance with the ethical standards of the American Psychological Association. The research was approved by the Institutional Review Board at Washington State University in Pullman, Washington.

Participants were recruited from neurologists and MS support groups in the northwestern United States. Participants were excluded if they had a history of substance abuse or nervous system disorder other than MS; had severe motor or visual impairment that might substantially interfere with questionnaire completion; had a premorbid history of a learning disability; or were experiencing a clinical exacerbation at either time point.

### Measures

#### Chicago Multiscale Depression Inventory (CMDI) and Beck Depression Inventory

The CMDI<sup>16</sup> is a self report questionnaire that was specifically designed for use in MS and other medical patient groups and has vegetative, mood, and evaluative scales consisting of 14 items each. Examinees are asked to rate on a scale of 1 to 5 the extent to which each word or phrase (for example, "sad," "glum," "low," for the mood subscale; "worthless," "a failure," "unwanted," for the evaluative subscale; "easily awakened," "exhausted," "poor appetite" for the vegetative

subscale) describes them during the past week, including today, where 1 is "not at all" and 5 is "extremely." Total scores for each scale are computed by simply summing together the participants' scores. To facilitate their interpretation, we further converted these raw scores into *t* scores using healthy control norms from Nyenhuis and colleagues' validation study of the CMDI.<sup>16</sup> Participants also completed the BDI.<sup>15</sup>

### COPE

The COPE is a 52 item scale designed to measure a variety of coping styles used in response to stressful events.<sup>26</sup> Consistent with previous work<sup>26</sup> with this scale and with the approach we took in cross sectional studies,<sup>27</sup> we divided the COPE inventory into adaptive ("active coping") and maladaptive ("avoidance coping") clusters. The "active coping" index combined the active coping, planning, and suppression of competing activities subscales. The "avoidance coping" index included the subscales for mental disengagement, behavioural disengagement, and denial.

**Table 2** Reliable change in depression scores from time 1 to time 2

|                 | Unchanged  | Decreased depression | Increased depression |
|-----------------|------------|----------------------|----------------------|
| BDI             | 42/53, 79% | 8/53, 15%            | 3/53, 6%             |
| CMDI-total      | 38/53, 72% | 6/53, 11%            | 9/53, 17%            |
| CMDI-evaluative | 42/53, 79% | 7/53, 13%            | 4/53, 8%             |
| CMDI-vegetative | 46/53, 87% | 0/53, 0%             | 7/53, 13%            |
| CMDI-mood       | 31/53, 58% | 8/53, 15%            | 14/53, 26%           |

All reliable change indices calculated using formulas and guidelines suggested by Spear.<sup>28</sup> Values required for reliable change in original scale units (*t* values for CMDI scales, raw scores for BDI): CMDI-total, >7; CMDI-vegetative, >14; CMDI-mood, >5; CMDI-evaluative, >9; BDI raw, >7. BDI, Beck Depression Inventory; CMDI, Chicago Multiscale Depression Inventory.

### Medication measure

Because relatively few patients were taking the interferons (19%,  $n = 10$ ), patients taking either type (beta 1a or 1b), assessed through self report, were combined in the data analysis.

### Procedure

Participants completed the measures described as part of a longitudinal study of MS. A brief psychosocial interview was conducted on the same day, and prior to, the testing and administration of depression symptom questionnaires. The COPE was mailed to participants for completion a few days before the testing day.

### Data analytic strategy

SPSS 12.0 for Windows was used to analyse the data. For the first specific aim—to evaluate the linear association of depression symptom clusters longitudinally—we calculated the Pearson product-moment correlations between CMDI mood, negative evaluative, and neurovegetative symptoms and BDI scores at two time points three years apart. Also for this aim, we calculated reliable change scores from time 1 to time 2 for all depression indices using an adaptation<sup>28</sup> of a reliable change index originally proposed by Jacobson and Truax.<sup>29</sup> Reliable change indices allow for the calculation of change in scores that is reliable, that is, not simply caused by the error inherent in the particular measure being examined. Following Speer's guidelines,<sup>28</sup> we also used estimated true scores at time 1 for all depression indices because of evidence for regression to the mean. We derived Cronbach's  $\alpha$  from the current sample for the reliability indices used in calculating true score estimates.

To address the second specific aim, to examine whether an increase in depression symptoms is associated with interferon beta use, we used a  $\chi^2$  analysis to examine the proportion of patients in the reliable change groups (increased, decreased, stayed the same for depression symptom status) using interferon beta treatment at both time points. For the third aim,<sup>14, 30</sup> to examine whether change in depression status co-varied with changes in coping strategies over time, we used repeated measures analysis of variance (ANOVA) with *reliable change group* as the between groups factor and *time* as the repeated measures factor. The active coping index was the dependent variable in one analysis and the avoidance coping index in the other. Additionally, we used active coping at time 1 and time 2 as covariates in the avoidance coping analysis, and avoidance coping at time 1 and time 2 as covariates in the active coping analysis. Tukey post-hoc tests were used to follow up any significant group effects.

### RESULTS

The 53 patients who participated in the study at time 2 were compared with the 23 patients who did not return for testing on all of the variables listed in table 1 using *t* tests for continuous variables and  $\chi^2$  analyses for categorical variables. None of these analyses was statistically significant, indicating that there were no systematic differences between participants who returned for testing versus those who did not.

Table 3 Interferon beta use

|                       | Time 1     | Time 2     | Both time points |
|-----------------------|------------|------------|------------------|
| Using interferon beta | 11/53, 21% | 17/53, 32% | 10/53, 19%       |

Means and standard deviations for the CMDI scales, the two BDI measures, and the demographic and illness variables are listed in table 1.

For the first specific aim, to evaluate the consistency of depression symptom clusters longitudinally, because 25 correlations were calculated (each of the four CMDI scales plus the BDI correlated with one another at each time point), a Bonferroni correction to control for possible inflated type 1 error was applied. Thus a *p* value of 0.002 was required for statistical significance. The correlations between depression index scores from time 1 to time 2 were as follows: BDI,  $r = 0.62$  ( $p < 0.001$ ); CMDI-total,  $r = 0.61$  ( $p < 0.001$ ); CMDI-mood,  $r = 0.39$ , ( $p < 0.005$ ); CMDI-evaluative,  $r = 0.70$  ( $p < 0.001$ ); and CMDI-vegetative,  $r = 0.69$  ( $p < 0.001$ ). Fisher's *r*-to-*z* transformations showed that the CMDI-mood scale correlation over time was significantly lower than CMDI-evaluative ( $t(53) = 2.28$ ,  $p < 0.05$ ) and CMDI-vegetative ( $t(53) = 2.18$ ,  $p < 0.05$ ) scales.

Also relating to the first specific aim, before conducting the reliable change calculations we evaluated the possibility of regression to the mean in scores over time following Speer's guidelines.<sup>28</sup> Specifically, difference scores using time 1 and time 2 scores were calculated and this difference score was correlated with patients' scores on the same index at time 1. For all depression indices, this correlation was statistically significant ( $p < 0.05$ ), indicating evidence for regression to the mean. As a result,<sup>28</sup> we adjusted participants' time 1 scores by calculating their estimated true scores accordingly before calculating reliable change indices. This method involved adjusting the observed score for a participant by multiplying the reliability coefficient for the index by the difference of the sample mean subtracted from the observed score, and then adding the sample mean to that product. To then calculate reliable change, we subtracted participants' time 1 adjusted true score from their time 2 score on each index, then divided by the standard error of the difference of the index at time 1. Table 2 outlines these reliable change results for the depression indices.

Because the largest percentage of participants showed reliable change on the CMDI-mood scale, we examined our second and third aims only in the context of reliable change groups derived from this scale. For the second specific aim, to examine whether an increase in depression symptoms is related to interferon beta use, we found that 43% of the participants (six of 14) in the "increased depressed mood" group were taking an interferon beta drug at both time points, whereas only 10% (three of 31) in the "unchanged" group and 13% (one of eight) in the "decreased depressed mood" group were taking these drugs at both time points.

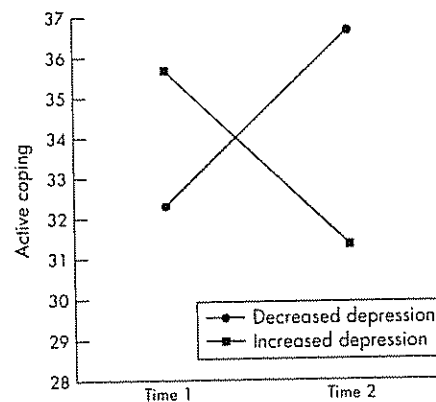


Figure 1 Depressed mood change groups as a function of changes in active coping.

Because the  $\chi^2$  test is thought to be less valid in cases where more than 25% of expected frequency cells in a matrix have an  $n$  value less than 5 (in this case two of six cells had expected counts less than 5), we used Fisher's exact test to compare the different groups. Using a Bonferroni test to adjust for the number of comparisons performed,  $\alpha$  was set at 0.017. Differences between the "decreased depressed mood" and "increased depressed mood" and also between the "decreased depressed mood" and "unchanged" groups were not statistically significant ( $p$  value = 0.19 and 1.0, respectively). In contrast, the difference between the "increased depressed mood" and the "unchanged" group was statistically significant,  $p = 0.01$ . Table 3 outlines the number of patients taking an interferon beta drug at each time point, in addition to the number of patients taking these drugs at both time points.

To evaluate the possible contribution of demographic, illness, and treatment variables to our group differences, we examined continuous demographic variables (for example, age, education, EDSS, disease duration) using one way ANOVA, and categorical variables (for example, sex, course type) using  $\chi^2$  analyses. There were no statistically significant differences between the mood change groups on any illness or demographic variable, in addition to utilisation of psychotherapy or pharmacological treatment for depression from time 1 to time 2. Because age is a potential confounder, given that younger patients are more likely to be depressed<sup>1</sup> and have a relapsing-remitting course (and therefore more likely to be receiving interferon beta treatment), we conducted several follow up analyses to evaluate the extent to which age may have contributed to our interferon beta findings. We compared age data in those patients taking interferon betas at both time points to those patients not taking interferon betas at either time point, correlated CMDI-mood scale scores at both time points with age, and compared CMDI-mood scale scores in secondary progressive versus relapsing-remitting patients. None of these analyses yielded statistically significant effects; thus it was not necessary to control for age statistically.

Analyses for the third specific aim, to examine whether change in depression status co-varied with changes in coping strategies over time, revealed a significant group  $\times$  time effect for active coping ( $F_{(2,44)} = 6.57$ ,  $p < 0.005$ ). Tukey post-hoc tests ( $p < 0.05$ ) showed that this effect resulted from the "increased depressed mood" group using significantly less active coping at time 2 (covariate adjusted mean = 31.31, SE = 1.68) compared with time 1 (covariate adjusted mean = 35.63, SE = 1.64), and the "decreased depressed mood" group using significantly *more* active coping at time 2 (mean = 36.60, SE = 2.21) compared with time 1 (mean = 32.27, SE = 2.16) (fig 1). A marginally significant group  $\times$  time effect was also found for avoidance coping ( $F_{(2,44)} = 2.90$ ,  $p < 0.10$ ).

## DISCUSSION

Our data indicated that global, neurovegetative, and negative evaluative measures of depression symptoms in MS were quite stable over time. These data are consistent with several other longitudinal MS studies examining depression.<sup>8, 9, 11, 12</sup> Our reliable change scores revealed that a large majority of patients displayed minimal change on these measures over three years. However, compared with neurovegetative and

negative evaluative symptoms, more patients showed reliable change in depressed mood over the three year interval.

A larger proportion of patients who increased in their depressed mood over time were using interferon beta drugs at both time points compared with patients who did not change in their depressed mood. This increased depressed mood was not caused by any demographic or illness variable. Nonetheless, it is possible that other variables, not measured as part of this study, contributed more to patients' increased mood disturbance than interferon beta use. One possibility is that patients inclined to depressed mood to begin with were more likely to complain about illness related problems and, as such, physicians treating them may have been more likely to prescribe disease modifying drugs such as interferon beta preparations. A future study providing a more detailed analysis of treating physicians' reasons for prescribing interferon beta drugs could evaluate this possibility. As a caveat to these findings, it is important to note that the relationship between change in depressed mood status and interferon beta use was not linear. Significantly more patients in the increased depressed mood group displayed interferon beta use at both time points compared with the unchanged mood group, but not compared with the decreased depressed mood group.

The use of adaptive coping strategies co-varied with depression symptoms over time in our MS sample. Specifically, patients who increased reliably in their depressed mood also displayed significant *decreases* in their use of a more adaptive type of coping, active coping. Patients who decreased in their depressed mood displayed significant increases in active coping over time. Although the nature of our design cannot tease out causality, it may be that decreased use of active coping strategies over time leads to increases in depressed mood, and that increased use of these strategies has some protective value.

There were several limitations to our study. First, the sample size was relatively small, so any generalisations or clinical application regarding our data should be made with caution until replication occurs. Second, we did not use a clinician rating or diagnostic criteria to diagnose depression in the present study. As such, we did not study depression so much as depression symptoms. Related to this second limitation, some investigators maintain that self reported symptoms of depression on mood questionnaires primarily reflect emotional distress rather than clinical depression *per se*.<sup>13</sup> It is therefore possible that our self report depression symptom measures reflected generalised emotional distress. However, the differential proportion of participants increasing in CMDI-mood versus CMDI-evaluative and CMDI-vegetative scale scores over time suggests an alternative view. If our measures were all simply tapping the same generalised factor, such as emotional distress, then one might expect them to show comparable change over time. These caveats aside, it is important to acknowledge that the outcome of our study could have been different if interviewer/observer depression ratings had been made and it is possible that our measures were simply tapping into different degrees of generalised emotional distress. A third limitation concerned the fact that we did not evaluate whether patients were taking interferon beta drugs continually from time 1 to time 2. As such, it was not possible to determine the extent to which continuous versus sporadic use of such drugs may be related to increased mood disturbance in MS. Also, because our patient sample was relatively small, we combined use of interferon beta-1a and interferon beta-1b in our data analyses. A larger sample would have made it possible to analyse these agents separately to determine whether the use of one was differentially contributing to the effect found for the mood groups. A fourth limitation is that our exclusionary

<sup>1</sup>Degrees of freedom here are reduced because one participant did not complete the COPE at time 1 and another did not complete it at time 2. A third participant failed to complete at least half the items making up the active coping index, and a fourth participant completed less than half the questionnaire overall. As a result, these participants were excluded from the analyses.

criteria limit the generalisability of our findings only to patients fitting such a profile of exclusion. A final limitation is that the correlation between our depression symptom scales was undoubtedly inflated because we used the same measures at both time points. A future study could examine the relations between, for example, interview/observation based symptom ratings at one time point and questionnaire based ratings at the other to limit correlation inflation due to method overlap.

### Conclusions

Despite its limitations, our study makes several contributions to the MS literature. First, it is the first to examine the longitudinal course of different depression symptom clusters in MS. This approach was fruitful in that we discovered that mood symptoms of depression are considerably more variable over time than other core depression symptoms. Second, our mood change data revealed a close correspondence between increased mood disturbance and decreased active coping, in addition to interferon beta use. Although not demonstrating causality, the parallel relation between these variables over time suggests the intriguing possibility that a causal link might exist. Overall, our study reveals the power of longitudinal design in extending our knowledge of depression symptoms in MS and their correlates.

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