CME Effect of relapses on development of residual deficit in multiple sclerosis

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Abstract—*Objective:* To determine the percentage of patients with residual deficits following multiple sclerosis (MS) exacerbations and the magnitude of those deficits using a database of pooled placebo patients from clinical trials. *Methods:* A database of patients assigned to the placebo group in several randomized clinical trials was queried to determine those patients with Expanded Disability Status Scale (EDSS) and Scripps Neurologic Rating Scale assessments prior to, at the time of, and after an acute exacerbation of MS. The extent of deficit present at these time points was compared to determine the acute effect of exacerbations and the degree of persistent disability. *Results:* Forty-two percent of patients had residual deficit of at least 0.5 and 28% had residual of ≥1.0 EDSS units, at an average of 64 days after an exacerbation. The results were reproduced across subsequent exacerbations and were sustained over time. The subgroup of patients with measurable change in EDSS during the exacerbation had more extensive residual impairment on the follow-up visits. Similar results were seen when the Scripps score was examined. *Conclusion:* MS exacerbations produce a measurable and sustained effect on disability.

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Multiple sclerosis (MS) is a chronic disorder of the CNS where the accrual of impairment and disability occurs via two mechanisms. In patients with relapsing forms of MS, worsening may occur by incomplete recovery from acute exacerbations, that is, step-wise worsening. In progressive forms of MS, worsening may also occur by gradual, inexorable deterioration in the absence of acute exacerbations, that is, progression.[1,2] With either mechanism, the result over time is increased impairment/disability. The biologic mechanisms underlying these two patterns are not fully understood. The recent results of clinical trials in secondary progressive MS suggest that there may be different pathogenic mechanisms in MS: an inflammatory mechanism for relapses and a more degenerative mechanism for progressive disease. Either mechanism may produce relatively permanent clinical signs via either impaired/blocked conduction through demyelinated segments or acute axonal transaction. Irrespective of the mechanism, increasing impairment/disability of any cause is inherently unhealthy for patients and thus a valid therapeutic target for treatment of MS.

Prior studies[3] demonstrate that exacerbations in the first year after diagnosis have predictive validity on future disability, more recently confirmed for lower levels of disability.[4]

To address the issue of the direct effect of exacerbations on subsequent disability, we examine in this article the view that exacerbations cause measurable amounts of cumulative damage. Obtaining such data has been impeded in the past by the absence of reliable baseline evaluations prior to each acute exacerbation. The advent of modern clinical trials provides the opportunity to analyze the effects of exacerbations, as all patients have standardized evaluations at fixed intervals (usually 3 or 6 months) as well as at the time of acute exacerbation.

Methods and materials. *Obtaining data sets.* In 1994, the National Multiple Sclerosis Society USA's (NMSS) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis appointed a Task Force on Clinical Outcomes Assessment to focus on quantitative functional measures as components of a composite outcome measure and to develop specifications for a "meta-analysis" of primary and secondary outcomes assessments in existing MS clinical and historical data sets that would provide an objective basis for developing the recommended multidimensional outcome assessment tool.[5,6] Members of the NMSS Task Force identified existing longitudinal data sets from MS clinical trials and natural history studies that contained both clinical and functional measures. A listing of the 16 contributors to the data repository used in these analyses with the primary type of patients included in each data set has been published.[7] Placebo data from one additional study were added to the database after the task force completed its work and were available for this analysis (Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis).

Restrictions and agreements. The task force gave its commitment to the depositors of data that only variables that appeared in at least two different data sets would be used in order to increase generalizability and to guarantee that the source of the data could be masked as well as ensure the focus of analyses would be on the development of the outcome measure and not reassessment of clinical trial results. Furthermore, only the placebo arms of the clinical trials were used to ensure the appropriate focus and estimation of changes with limited impact from treatments. Thus, the data to be used in this meta-analysis are derived from the placebo groups of at least two clinical trials to be adherent to these restrictions.

Processing and pooling data sets. Data sets were received on magnetic media, archived, and examined to ensure that basic data

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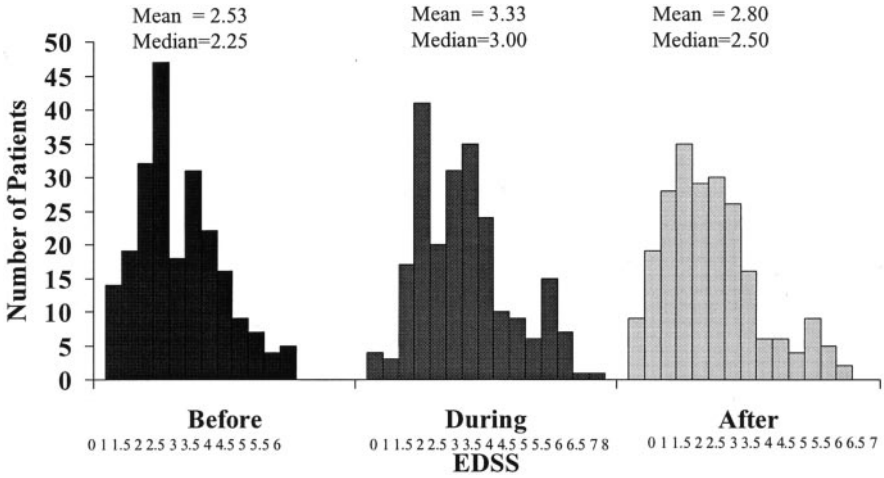

Figure 1. Distribution of Expanded Disability Status Scale (EDSS) scores before, during, and after an exacerbation. There is a shift toward increased scores on the "during" and "after" assessments.

could be used. Data dictionaries were catalogued to provide documentation for all data received and variables renamed into common terminology so that similar definitions would be used to define variables in as much as this was possible.

For this study, we queried this database for placebo patients with relapsing–remitting MS who had Kurtzke Expanded Disability Status Scale[8] (EDSS) and Scripps Neurologic Rating Scale scores[9] at the time of an exacerbation as well as before and after the exacerbation. We utilized the data to estimate the worsening produced by each exacerbation by comparing the baseline assessment as measured by the closest disability assessment preceding the exacerbation with the subsequent regular evaluations of the EDSS and Scripps scores as per the trial protocol. The definition of an exacerbation was as defined in the protocols of the clinical trials utilized and at a minimum required that a neurologist declare an event an exacerbation, but did not necessarily require a change in EDSS. Secondary progressive patients were not included, so as to avoid confusion between the residual deficit from an exacerbation and underlying progressive disease.

To find the purest cohort of patients in which to examine the issue of residual effects of exacerbations, we included only patients who had measures before, during, and after an exacerbation. A further restriction was that the assessment after the exacerbation had to occur at least 30 days from the time of the "during-exacerbation" assessments. In addition, the "after-exacerbation" measurement for an initial exacerbation could not be taken during or following a subsequent exacerbation. Thus, we believe these restrictions provide a conservative estimate of the true effects of each exacerbation, using the intraexacerbation visit as a measure of the acute deficit produced by an exacerbation and the postexacerbation visits as measures of the residual effects of the exacerbation.

Changes in EDSS and Scripps scores from before to after an exacerbation were assessed using paired *t*-tests and paired nonparametric tests on the first and subsequent exacerbation episodes. Correlations (Pearson and Spearman) were used to assess the relationships between the triads (before, during, and after the exacerbation) of disability measures (EDSS and Scripps scores). Regression analyses were used to assess changes in residuals between groups measured at different times after exacerbation.

Results. A total of 224 patients met the following criteria for inclusion in this study: They were placebo group patients contributed to the task force data set who had at least one exacerbation with both EDSS and Scripps Neurologic Rating Scale data available prior to the exacerbation, at the time of the exacerbation, and following the exacerbation. All exacerbations of the patients meeting this definition were included, but our analyses focus primarily on the first exacerbation to ensure independent responses among the assessments. Confirmation of the pattern of residual deficits is examined over subgroups with subsequent exacerbations to understand the reproducibility of the findings.

The population appeared representative of relapsing–remitting MS patients: average age of 35.2 years (range 18 to 50 years), mostly Caucasian (96.8%), and mostly women (72.3%), with a baseline mean EDSS score of 2.5 (range 0 to 6, SD = 1.4).

Figure 1 shows the distribution of EDSS scores before, during, and after the first exacerbation. Two hundred twenty-four subjects had at least one exacerbation. Seen in this figure is the upward shift or increases in the EDSS score from before to during to after the exacerbation evi-

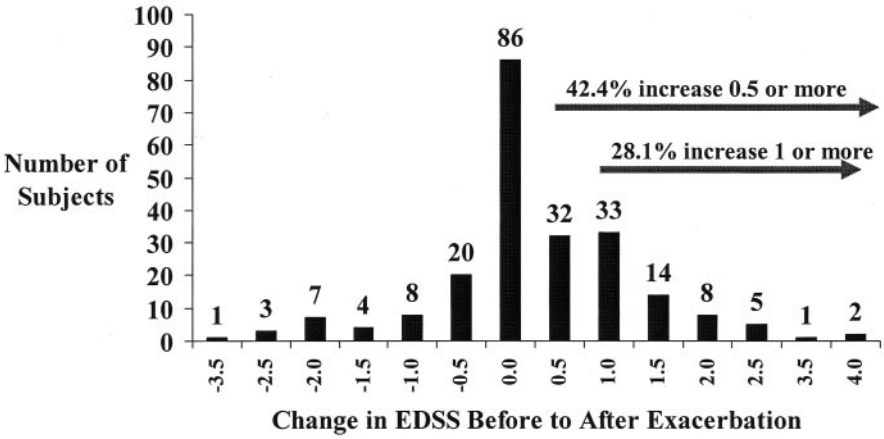

Figure 2. The net change in Expanded Disability Status Scale (EDSS) score from before an exacerbation to after. Forty-two percent of patients demonstrate measurable residual.

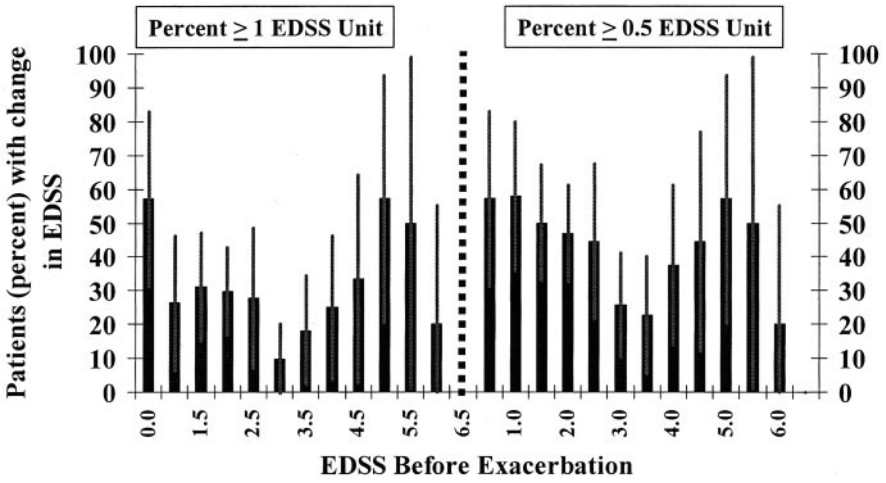

Figure 3. Percentage of patients with change in Expanded Disability Status Scale (EDSS) score (≥1 or ≥0.5 point) before to after exacerbation by EDSS level before the exacerbation and 95% CI. There is a small, but significant, negative correlation between pre-exacerbation EDSS and residual dysfunction.

denced by the increased number of patients in the upper levels of the EDSS and fewer at the lowest levels.

The residual effects of the exacerbation as measured by the net difference from the EDSS before to after the exacerbation for all patients meeting the inclusion criteria for this analysis are shown in figure 2. The residual deficit was 0.27 (median 0) EDSS unit, with an SD of 1.04 ($p < 0.0001$). Forty-two percent of the patients experienced residual deficit as measured by the EDSS from before the exacerbation to the first nonexacerbation measure at least 30 days following the onset of the exacerbation. In 28% of the patients, there was an increase by ≥1 point on the EDSS. The average time between the exacerbation and the after-exacerbation measure was 64 days (median 63 days, minimum 32 days, and maximum 140 days). The average duration from before to after was 114 days (median 98 days, minimum 34 days, and maximum 231 days).

Figure 3 shows the percentage of patients with residual deficit of 1 or 0.5 point by the pre-exacerbation EDSS level. There is a slight but significant negative correlation between the residual and EDSS level prior to the exacerbation (Spearman $r = -0.20$, $p = 0.002$). Figure 4 shows the residual (mean change) percentage with at least a 1- and 0.5-point change in EDSS by number of months after exacerbation measured from the time of the last assessment during the 30-day window around the exacerbation to the time of the next routinely scheduled assessment. There is no recovery trend that would indicate that these residual increases in EDSS subsequent to an exacerbation are due to artifacts of measuring the residual while the exacerbation is recovering ($p = 0.22$).

To evaluate the extent to which the residual deficits were enduring, we examined the second postexacerbation measure for each individual. Sixty-three of the 224 patients had a second scheduled EDSS determination recorded in the data sets (those with intervening exacerbations were excluded to avoid overestimating the impact of an exacerbation by including second events; other patients are lost because they reached the end of the clinical trial prior to the exacerbation follow-up determination). Of those, 36.5% had measurable residual deficits on EDSS. The results are similar for this assessment as with

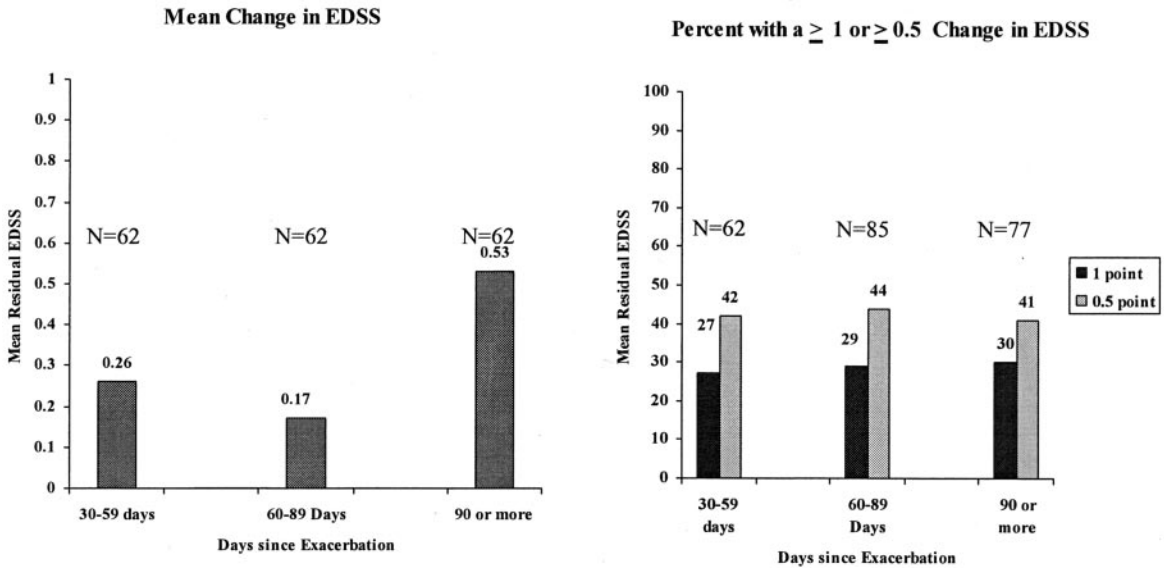

Figure 4. Mean change and percentage with ≥1-point Expanded Disability Status Scale (EDSS) change (black columns) and ≥0.5-point change (gray columns) in EDSS score from before to after exacerbation by time between exacerbation and follow-up. The residual from the exacerbation and the percentage with residual do not diminish with time.

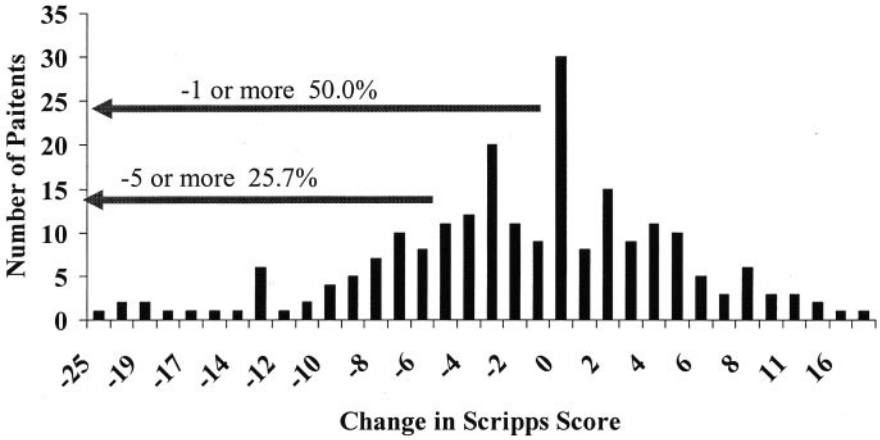

Figure 5. Effect of exacerbation on the Scripps score, demonstrating residual in 50% of patients.

the first, with a residual deficit of 0.24 EDSS unit and an average of 113 days after onset (during measurement of the first exacerbation), suggesting a degree of permanence to the residual.

In 137 patients, there was a second exacerbation recorded that fulfilled the criteria for our analysis. In those subjects, there was a residual deficit of 0.44 (median 0) ($p < 0.0001$, SD = 1.06), measured 69 days after the exacerbation (median 63 days, minimum 31 days, and maximum 168 days). Measurable deficit occurred in 46% of these exacerbations. Thirty of these patients had a second postexacerbation visit (after the second recorded exacerbation) with a mean residual of 0.38 ($p = 0.0073$) at 133 days following the exacerbation, with 43% showing residual.

Similar results are seen using the Scripps Neurologic Rating Scale (figure 5). Fifty percent of all patients experienced residual as assessed by the Scripps score compared with the 42% based on the EDSS. The mean residual was −1.1 points (SD 6.3; $p < 0.0001$). Nine percent of the patients exhibited a residual ≥10-point drop in Scripps score. The results were similar for the second exacerbation where 63% of the patients exhibited residual deficit on the Scripps compared with 46% using the EDSS. The Scripps score was more sensitive than the EDSS in detecting residual deficits ($p = 0.02$, χ^2 analysis).

Within the study cohort described above, 84 patients had no worsening of EDSS from before to during the exacerbation (but still met their original clinical trial protocol-defined definition for an exacerbation). This subgroup likely lessened our ability to measure overall change in the entire cohort. Of the remaining 140 who had a worsening of EDSS during the exacerbation visit, 57% showed residual deficit of 0.57 (SD 0.93) an average of 65 days after the exacerbation visit. Thirty-seven of the 140 patients had a second postexacerbation visit at an average of 161 days after the exacerbation. Of these, 54% showed residual deficit with a mean worsening of 0.45 EDSS unit. The Scripps score analysis of these 140 patients reveals residual worsening of −2.5 points in 58.3% at the first postexacerbation visit.

Discussion. The data presented here reveal that exacerbations in MS produce a worsening on average of 0.24 to 0.57 point on the EDSS and 1.0 to 2.5 points on the Scripps scale. For the reasons described above, we believe these are conservative estimates. If the residual were due only to observing the recovery process from the exacerbation, we would expect the proportions with residual to be higher among the measures taken during earlier months, and this is not the case. There was no significant trend for the percentage with residual to decrease over time and no significant change in the size of the residual. These residual changes are present whether we used the first postexacerbation visit (up to 3 months after the exacerbation, mean time 64 days) or subsequent evaluations. Further, 42% of patients maintained residual deficit measured ≥1 month after their exacerbation, and this did not materially change over time. If we include only those subjects that demonstrate a worsening in EDSS during the exacerbation visit (as is commonly required in current clinical trials), the degree of residual (0.57) and the percentage with residual (57%) increase. In this relapsing–remitting MS population, this would suggest that the change we are measuring comprises not transient, fully reversible effects from the exacerbation but rather a more lasting stepwise accrual of deficit. A carefully controlled repeated examination study assessing the process of recovery would be very valuable to characterize the precise time course of residual deficit. The data developed in this report should be useful for modeling the behavior of patients with relapsing forms of MS in future clinical trials.

Three of the four pivotal clinical trials leading to approved agents for treating relapsing–remitting MS utilized reduction in relapse rate as their primary outcome measure,[10-12] and in the fourth, relapse rate reduction was an important secondary outcome measure.[13] A more recent article[14] concluded that exacerbations were not related to progression. The conclusions of this article seem inconsistent with the benefits demonstrated by actual treatment trials in the primary outcome as well as coherence in benefit on related outcomes such as EDSS analyses and MRI measures. Several potential explanations may account for these apparently conflicting views. First is the fact that their analysis was conditional on having reached a certain level of disability. This condi-

tioning on achieving a particular level of disability and ignoring the path to this event may limit the conclusions that can be drawn. Their analyses show that once one reaches a particular level on the Disability Status Scale (DSS; which measures change by 1-point increments, rather than the 0.5-point increments of the EDSS), the impending gradual decline is not impacted by prior exacerbation differences. This does not mean that exacerbations are unimportant in the course of disease, only that the course of disease may not differ after a particular level of disability has been reached, irrespective of how one arrived at this point. Another analysis by the same group confirms this finding, showing important covariates influenced times to various points on the DSS (4, 6, and 7).[4] However, none of these covariates predicted the time from DSS 4 to higher levels. It is also possible that the pathogenic mechanisms underlying worsening in MS may differ at various stages of MS. The development of biologically based disease course descriptions should allow for determining these distinctions.

It could also be argued that because most MS patients experience exacerbations during the course of their illness and because the EDSS is a nonlinear scale, the impact of the exacerbation on progression cannot easily be seen. We showed that there is an inverse correlation ($r = -0.20$) between the EDSS level and size of the residual effect of the exacerbation. We also know that as the EDSS increases, there is a tendency for the number of exacerbations to decrease or at least not to be measurable; thus, it may be that the lack of a relationship between long-term progression and the simple count of the number of exacerbations may be the insensitivity of the EDSS to measure the excess progression attributable to exacerbations in the later stages of MS.

The data presented here do not allow analysis of the relative effect of stepwise worsening, as produced by acute exacerbations, compared with gradual progression on the outcome of the various clinical trials. The data in the clinical trials in this database were not collected in a manner to allow examination of this question. However, there was no reported transition from relapsing–remitting MS to a secondary progressive MS in these trials. In all the recent successful relapsing–remitting MS clinical trials, there was either clear evidence of, or a trend toward, slowed accrual of disability. This would support the contention that reducing relapses should improve overall disability.

These results suggest that acute exacerbations of MS have a measurable and sustained effect on accrued impairment/disability in MS. Therefore, consistent with the evidence among the various trials of therapies for relapsing–remitting MS, treatment modalities that reduce the frequency of relapses should be beneficial for patients independently of whether they affect the progressive phase of the illness.

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