Treatment of Cognitive Impairment After Poststroke Depression
A Double-Blind Treatment Trial

Mahito Kimura, MD; Robert G. Robinson, MD; James T. Kosier, BS

Background and Purpose—Patients with poststroke major depression have a greater severity of cognitive impairment than nondepressed patients even when matched for size and location of stroke lesion. Prior treatment studies have consistently failed to show an improvement in cognitive function even when poststroke mood disorders responded to antidepressant therapy. We examined the response of cognitive function to treatment with nortriptyline or placebo in a double-blind trial.

Methods—Patients with major (n=33) or minor (n=14) depression participated in a double-blind treatment study with nortriptyline or placebo. They were examined for change in depressive mood, measured by the Hamilton Rating Scale for Depression (HAM-D), and change in cognitive impairment, assessed by the Mini-Mental State Examination (MMSE), after treatment with nortriptyline or placebo. Cognitive treatment response, as measured by the MMSE, was compared between patients whose depression did and did not respond to treatment.

Results—Patients whose poststroke depression remitted (predominantly associated with nortriptyline treatment) had significantly greater recovery in cognitive function over the course of the treatment study than patients whose mood disorder did not remit (predominantly associated with placebo treatment).

Conclusions—Our findings support the contention that poststroke major depression leads to a “dementia of depression.” Prior studies failed to show an effect of treatment because the effect size was too small. Successful treatment of depression may constitute one of the major methods of promoting cognitive recovery in victims of stroke. (Stroke. 2000;31:1482-1486.)

Key Words: cerebrovascular disorders • cognitive disorders • depression • drug therapy

For many years, investigators have recognized in elderly patients a relationship between depressive disorder and cognitive impairment.1–4 If this cognitive impairment improves with treatment of depression, it is called pseudodementia or dementia of depression.1–4 In 1986, we first identified a similar phenomenon in elderly patients with poststroke depression.5 The cognitive impairment occurred only in patients with major depression and predominantly after left hemisphere stroke.6 Subsequently, House et al7 found that patients with major depression or any other DSM-III (Diagnostic and Statistical Manual of Mental Disorders, third edition) axis I diagnosis at 1 month after stroke had significantly more cognitive impairment than patients with no axis I diagnosis. In addition, for patients with left hemisphere lesions, there was a significant correlation between severity of cognitive impairment and Beck Depression Inventory score, whereas the correlation was nonsignificant in the right hemisphere.7 Similar findings have also been reported by Morris et al8 and Andersen et al.9

In spite of this general concurrence of findings, all prior double-blind treatment trials have failed to show an improvement in cognitive function among patients with poststroke depression who were given active antidepressant therapy.9–11 This finding led Andersen et al9 to suggest that the cognitive impairment may be the cause of depression. We subsequently refuted this hypothesis by demonstrating that among patients not treated for depression, there was a correspondence between depression and cognitive function. Depressed patients whose mood spontaneously improved over the first 3 months after stroke showed a significantly greater improvement in cognitive function than depressed patients whose mood did not improve, and similarly, depressed patients with spontaneous improvement in cognitive function showed an associated significant mood improvement.12 If poststroke cognitive impairment had caused depression, cognitive impairment would be expected to remain even if mood improved. We therefore sought to examine whether improvement in cognitive function is associated with successful treatment of

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poststroke depression. We combined data from our prior double-blind treatment studies of poststroke depression and compared patients whose depressive disorder did and did not respond to treatment.

Subjects and Methods

Two groups of patients studied at different times were included in this double-blind treatment study. The first group consisted of 50 patients at the Montebello Rehabilitation Hospital in Baltimore, Md, with acute thromboembolic or intracerebral hemorrhagic infarction who were identified as depressed and were willing to participate. These patients had a mean age of 57.6 ± 12.0 years; 70% were white, 50% were male, and 51% were in Hollingshead social class IV or V. The second group consisted of 56 patients at the Younkers Rehabilitation Unit of Iowa Methodist Hospital in Des Moines, Iowa, with a subacute thromboembolic or hemorrhagic cerebral infarct who were identified as depressed and were willing to participate. These patients had a mean age of 67.1 ± 11.2 years; 83% were white, 57% were male, and 40% were in Hollingshead social class IV or V. Detailed neurological and psychiatric examinations were performed on all patients, excluding only those who had decreased levels of consciousness, dementia, or aphasia that significantly limited their verbal comprehension. After informed consent was obtained, all patients were assessed by fully trained psychiatrists using the semistructured interview of the Present State Examination. All patients were assessed by fully trained psychiatrists using the semistructured interview of the Present State Examination.13 All patients were required to have a diagnosis of mood disorder based on DSM-IV criteria14 for “depression due to stroke with major depressive episode” or “minor depression” (ie, DSM-IV research diagnosis) on the basis of the symptoms elicited by the Present State Examination and to be treated with nortriptyline or placebo. Severity of depression was measured with the 17-item Hamilton Rating Scale for Depression (HAM-D).15 Cognitive impairment was assessed with the Mini-Mental State Examination and to be treated with nortriptyline or placebo. Severity of depression was measured with the 17-item Hamilton Rating Scale for Depression (HAM-D). Cognitive impairment was assessed with the Mini-Mental State Examination (MMSE).16 Scores may range from 0 to 30, with lower scores indicating greater impairment. Reliability and validity of these instruments in patients with stroke have been demonstrated in prior publications.17–19 For the present study, patients with no depression diagnosis (n = 37) or with scores below 10 on the HAM-D (n = 10) at initial evaluation were excluded from analysis. In addition, there were 12 patients (Baltimore, n = 5; Iowa, n = 7) who dropped out during the treatment study. This left 47 patients who met criteria for major depression (n = 33) or minor depression (n = 14) and completed the treatment trial, who constitute the subjects of this study.

Neurological Evaluation

Neurological evaluations for all patients were performed with the standardized examination and rating criteria from the Stroke Data Bank.20 All neurological evaluations and CT scan readings were performed with the investigator blind to the findings on the psycho-pathological examination. Lesion volume was calculated from the ratio of the largest cross-sectional area of the lesion to the cross-sectional area of the brain at the level of the body of the lateral ventricle.5

Drug Protocol

The patients participating in the treatment study were given nortriptyline or placebo in a single daily dose at bedtime. Patients were randomly assigned to either active treatment or placebo. Both the patients and examiners were unaware of which treatment was given. In the first group (ie, Baltimore patients), patients were given 20 mg/d for 1 week, 50 mg/d for 2 weeks, 70 mg/d for 1 week, and 100 mg/d for the last 2 weeks of the study. They were evaluated before treatment began and at 2-week intervals during the 6-week treatment period. Patients in the second group (ie, Iowa patients) were given 25 mg/d for 1 week, 50 mg/d for 2 weeks, 75 mg/d for 3 weeks, and 100 mg/d for the last 6 weeks of the study. They were evaluated before treatment began and at 3-week intervals during the 12-week treatment period. In the present study, we analyzed the 2 groups by combining their data according to the dosage of nortriptyline, ie, the

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics for Nortriptyline and Placebo Groups</th>
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<tbody>
<tr>
<td>Diagnosis, n</td>
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<tr>
<td>Major depression</td>
</tr>
<tr>
<td>Minor depression</td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Right-handed</td>
</tr>
<tr>
<td>Married</td>
</tr>
<tr>
<td>Hollingshead class IV or V</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
</tr>
<tr>
<td>Time since stroke, mean ± SD, d</td>
</tr>
<tr>
<td>Family psychiatric history*</td>
</tr>
<tr>
<td>Personal psychiatric history</td>
</tr>
<tr>
<td>Personal alcohol abuse history</td>
</tr>
</tbody>
</table>

Values are number (percentage) unless otherwise indicated.

*Significant difference, χ² = 9.39, P = 0.0060.

evaluations of weeks 0 (0 mg), 2 (50 mg), 4 (70 mg), and 6 (100 mg) in the first group were considered approximately equivalent to those of weeks 0 (0 mg), 3 (50 mg), 6 (75 mg), and 9 (100 mg) in the second group, respectively.

Statistical Analysis

Parametric data were analyzed with t tests (2-tailed), repeated-measures ANOVA, and ANCOVA. Descriptive statistics calculated for these data were means and standard deviations. In general, parametric data were used when the data were normally distributed. Assessment of MMSE scores demonstrated a normal distribution for both active-treatment and placebo-treated patients at initial evaluation and at follow-up. Nonparametric data were analyzed with χ² tests (with Fisher’s exact test, if sample sizes were prohibitively small).

Results

Changes of Mood and Cognitive Function in Double-Blind Treatment Study

Of the 47 patients who were evaluated, 21 were randomly assigned to nortriptyline and 26 were assigned to placebo. The demographic characteristics of these patient groups are shown in Table 1. The only intergroup difference was the significantly higher frequency of family psychiatric history in the nortriptyline group than in the placebo group (ie, the nortriptyline group improved more quickly than the placebo group).

Planned comparisons revealed that the nortriptyline group was significantly more improved than the placebo group at the 75-mg dose (t = −2.34, P = 0.024) and 100-mg doses (t = −2.60, P = 0.013) (Table 3). On the basis of having a greater than 50% reduction in HAM-D score and no longer
TABLE 2. Stroke Characteristics and Neurological Findings for Nortriptyline and Placebo Groups

<table>
<thead>
<tr>
<th>Stroke type</th>
<th>Nortriptyline (n=21)</th>
<th>Placebo (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct</td>
<td>18 (85.7)</td>
<td>21 (80.8)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3 (14.3)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Lesion location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>9 (42.9)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>4 (19.0)</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Bilateral or brain stem</td>
<td>8 (38.1)</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Lesion volume, mean±SD</td>
<td>(n=12)</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>9.2±6.8</td>
<td>10.2±9.7</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological deficits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor deficit</td>
<td>15 (71.4)</td>
<td>17 (65.4)</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>8 (38.1)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Visual field deficit</td>
<td>6 (28.6)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>5 (23.8)</td>
<td>8 (30.8)</td>
</tr>
</tbody>
</table>

Values are number (percentage) unless otherwise indicated.

meeting criteria for major or minor depression, the response rate was 76% for the nortriptyline group and 31% for the placebo group. In contrast, repeated-measures ANOVA of the MMSE scores showed no significant group effect but a significant time effect ($F_{3,108}=5.62$, $P=0.0013$) and no significant group-by-time interaction. There were no significant intergroup differences in MMSE scores at each dose (Table 3).

Relationship of Treatment Response to the Change in Cognitive Function

We next examined the relationship between the change in cognitive function and treatment response. Patients were divided into responder (n=24; major depression=15, minor depression=9) and nonresponder (n=23; major depression=18, minor depression=5) groups based on the criteria above. The responder group included 16 patients treated with nortriptyline and 9 with placebo. The nonresponder group included 5 patients treated with nortriptyline and 18 with placebo. There were no significant differences between the responder group (18.33±4.23) and the treatment-failure group (17.00±3.87) in their baseline HAM-D scores. There were no significant differences between the 2 groups in demographic characteristics, stroke characteristics, or neurological findings. We also examined the change in MMSE scores between groups. Repeated-measures ANOVA of the MMSE scores demonstrated a significant group-by-time interaction ($F_{3,108}=4.45$, $P=0.0055$) (ie, cognitive function in the responder group recovered more quickly than in the treatment-failure group). Planned comparisons revealed that the responders had significantly higher (less impaired) MMSE scores than the nonresponders at nortriptyline doses of 75 mg/d ($t_{41}=-2.17$, $P=0.036$) and 100 mg/d ($t_{41}=-2.34$, $P=0.024$) (Table 4). Although some placebo patients (n=8) were in the responder group, there were significantly more nortriptyline-treated patients in this group (n=16) than in the nonresponder group (n=5) ($\chi^2=7.90$, $P=0.0032$). In addition, there were no significant differences in the number of patients treated for 12 weeks in the responder (n=6) compared with the nonresponder (n=8) groups ($\chi^2=0.53$, $P>0.75$). We also used intention-to-treat methods in analyses that included the 12 patients who withdrew from the study. Repeated-measures ANOVA of the MMSE scores continued to show a significant group-by-time interaction ($F_{3,116}=3.94$, $P=0.0097$).

TABLE 3. Comparison of HAM-D and MMSE Scores for Nortriptyline and Placebo Groups

<table>
<thead>
<tr>
<th>Dose</th>
<th>Nortriptyline</th>
<th>Placebo</th>
<th>$P^*$</th>
<th>Nortriptyline</th>
<th>Placebo</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg</td>
<td>17.38±4.30</td>
<td>17.92±3.95</td>
<td>0.655</td>
<td>23.62±1.24</td>
<td>24.39±1.02</td>
<td>0.632</td>
</tr>
<tr>
<td>50 mg</td>
<td>12.81±3.86</td>
<td>13.27±4.79</td>
<td>0.723</td>
<td>24.95±1.10</td>
<td>24.76±1.07</td>
<td>0.903</td>
</tr>
<tr>
<td>75 mg</td>
<td>8.38±5.74</td>
<td>13.12±7.70</td>
<td>0.024</td>
<td>25.20±1.09</td>
<td>25.17±1.02</td>
<td>0.986</td>
</tr>
<tr>
<td>100 mg</td>
<td>5.33±6.24</td>
<td>11.08±7.81</td>
<td>0.013</td>
<td>26.47±1.14</td>
<td>25.44±1.14</td>
<td>0.540</td>
</tr>
</tbody>
</table>

Values are mean±SD. Total number in each group decreased because of missing data.

*Unpaired t test.

Change of Each Individual Item in the MMSE

Cognitive domains examined by the MMSE include orientation, registration, attention-calculation, recall, language, and visuomotor integrity. There was significantly greater improvement in both attention-calculation ($t_{41}=-2.15$, $P=0.038$) and recall ($t_{41}=-2.05$, $P=0.047$) items in the responders than in the nonresponders (Figure 1).

Comparison Between Nortriptyline-Treated Patients and Placebo Patients

If only nortriptyline-treated patients were used in the treatment-response group compared with all placebo patients in the treatment-failure group, there was still a significant group-by-time interaction ($F_{3,95}=2.96$, $P=0.036$), which in-
dicates that the failure to demonstrate cognitive improvement in prior treatment trials was not the result of nortriptyline drug effects such as sedation or impaired attention.

Among patients given nortriptyline, we compared responders (n=16) and nonresponders (n=5) using pretreatment MMSE scores as covariants. ANCOVA analyses of MMSE scores for patients responding to nortriptyline showed significantly greater improvement than the nortriptyline nonresponders at doses of 75 mg/d (F_{11}=2.39, P=0.0034) and 100 mg/d (F_{11}=21.79, P=0.0004). Among patients given placebo only (8 responders and 18 nonresponders), repeated-measures ANOVA also showed a significant group-by-time interaction (F_{17}=3.17, P=0.031), with the responders showing more improvement in cognitive function than the nonresponders.

Comparison Between Major Depression and Minor Depression

Because our previous publications have identified that cognitive impairment is associated with major but not minor depression, we wanted to determine whether major and minor depression show the same phenomenon of cognitive improvement with response to treatment. Among patients with major depression, responders (n=15) showed significantly greater improvement in cognitive function than nonresponders (n=18) (repeated-measures ANOVA of MMSE scores showed a significant group-by-time interaction; F_{19}=4.19, P=0.0087) (Figure 2). Among patients with minor depression (9 responders and 5 nonresponders), repeated-measures ANOVA of MMSE scores showed no significant group effect, time effect, or group-by-time interaction.

Discussion

This study confirmed that when we combined our prior controlled treatment data, administration of nortriptyline did not lead to significant group improvement in cognitive function as assessed by MMSE score in spite of significant group improvement in severity of mood. However, after dividing patients into groups based on whether or not they responded to treatment, we found that treatment responders showed significantly greater improvement in MMSE scores than patients who failed to respond to treatment.

Before further discussion of our results, it is important to acknowledge the methodological limitations of this study. First, our only measure of cognitive function was a brief, language-dominated examination, the MMSE. A more detailed neuropsychological battery would have documented whether cognitive improvement occurred in areas other than attention and recall and how many of these cognitive disorders met the diagnostic criteria for vascular dementia. Second, the combination of 2 patient groups that had different durations of treatment could have led to differential treatment response. We showed, however, that duration of treatment did not explain the improvement in cognitive function among the treatment responders. Third, the use of multiple comparisons could have led to type I errors identifying random findings as significant.

The most significant finding from this study was that for the first time, we showed in a double-blind, controlled treatment trial that patients with stroke had partially reversible cognitive dysfunction when their depressive disorder was successfully treated. Because the cognitive impairment involved more than 1 area of cognitive function (ie, memory and attention), it suggests that this disorder is probably a dementia of depression. This finding also supports our contention that poststroke depression produces a cognitive impairment but refutes the hypothesis posed by Andersen et al that the cognitive impairment produces the depression.

One might logically wonder why this improved cognitive function related to mood improvement was not noted in the prior treatment studies that documented improved mood with active treatment of poststroke depression. We believe the answer to this question is related to effect size. Nortriptyline treatment of depression, as demonstrated in the present study, produced a mean change of 12.1 points on the HAM-D, or a 69.5% decline, compared with a 36.8% (6.8 points) decline in the placebo group. The effect size was 0.71. When this effect size is compared with the effect of nortriptyline on MMSE (ie, 9.6% [1.8 points] for active treatment and 5.6% [1.3 points] for placebo treatment; effect size 0.16), it would take a group size of 598 to demonstrate a significant effect of nortriptyline on cognitive function with an 80% probability. By dividing patients on the basis of response to treatment, the effect on MMSE was 17.2% (3.0 points) for responders and only 1.3% (0.14 points) for nonresponders, for an effect size

Figure 1. Mean change scores in individual items in MMSE for treatment responder (n=24) and nonresponder (n=23) groups. Error bars represent standard errors of the mean (SE). *P<0.05 (unpaired t test).

Figure 2. Change of MMSE scores in patients with poststroke major depression during treatment study. Treatment responders (n=13) showed significantly greater improvement in cognitive function than nonresponders (n=18) (P=0.0087). Error bars represent standard errors of the mean (SE).
of 0.96. This allowed a significant difference to be detected with a group size of only 47.

The other major finding from the present study was that improved cognitive function was related to mood improvement and not to nortriptyline itself. Approximately one third of the patients responding to treatment were taking placebo and showed the same cognitive improvement as patients taking nortriptyline. This suggests that cognitive impairment was associated with the mechanism of depression and was not a parallel phenomenon of depression with a separate mechanism. In other words, nortriptyline could have affected 2 different neurophysiological mechanisms: one related to depression and one related to cognitive impairment. The fact that mood improvement with placebo was associated with the same cognitive improvement as nortriptyline suggests that the mechanism of depression, not the mechanism of nortriptyline, was responsible for the cognitive improvement. This lends further support to the hypothesis that poststroke major depression causes a dementia of depression.

Another interesting finding was that improved mood led to improvement in specific cognitive domains. It is known that the cognitive domains most likely to be defective after stroke are memory, orientation, language, and attention.21 On the other hand, patients with functional (ie, no known brain lesion) depression and dementia of depression have been shown to perform poorly on cognitive tasks involving memory and concentration.22,23 Thus, our findings are consistent with the cognitive deficits found in patients with functional depression and therefore provide additional validation that the mechanism of depression, not the mechanism of nortriptyline, was responsible for the cognitive improvement. This lends further support to the hypothesis that poststroke major depression causes a dementia of depression.

Finally, our previous studies5-24 demonstrated that cognitive impairment was associated with major but not minor depression. We therefore did not expect to see any significant improvement in cognitive function among patients whose minor depression responded to treatment. This hypothesis was supported when we analyzed patients with minor depression separately. This finding is also consistent with our previous suggestion that minor depression has a different pathophysiological mechanism than poststroke major depression.25

In conclusion, this study has demonstrated that an impairment associated with stroke can be significantly improved by treatment of poststroke depression. This finding adds greater urgency to the need to identify and treat depression in patients who have suffered a stroke. Any treatment method that improves mood should improve cognitive function in patients with poststroke depression. Thus, treatment of depression may constitute one of the major methods of improving cognitive recovery in victims of stroke.

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References
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