Prevention and Treatment of Poststroke Depression With Mirtazapine in Patients With Acute Stroke

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Background and objective: Poststroke depression is one of the most frequent complications of stroke, affecting approximately 20% to 40% of all patients. In spite of the importance of this neuropsychiatric disorder, little attention has been given to the prevention of poststroke depression. The purpose of this study was to examine whether prophylactic treatment with the antidepressant mirtazapine in patients with acute stroke given from day 1 after the incidence prevents poststroke depression.

Method: Patients with ischemic stroke received either 30 mg mirtazapine or no antidepressant medication from day 1 after the stroke in an open, randomized study design. Data were collected from August 2001 to December 2002. Seventy patients were enrolled in the study and were reexamined on days 7, 44, 90, 180, 270, and 360 using neurologic, functional, and depression rating scales. Those poststroke patients who developed depression (DSM-IV criteria) but had been randomly assigned to the nontreatment group were given the antidepressant mirtazapine after the diagnosis of depression had been established.

Results: Forty percent (14/35) of the nontreated patients and only 5.7% (2/35) of the patients who were treated with mirtazapine developed poststroke depression. Altogether, 16 patients developed poststroke depression, 15 of whom remitted after initiation of treatment with mirtazapine.

Conclusion: Mirtazapine significantly reduced the rate of poststroke depression in patients with acute stroke. The study also demonstrated that this antidepressant was highly effective in treating poststroke depression.

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Poststroke depression is one of the most frequent neuropsychiatric complications of ischemic stroke. Various studies have reported that depressive syndromes occur in approximately 20% to 40% of poststroke patients,[1–9] but nevertheless remain underdiagnosed and undertreated. This underdiagnosis is particularly important since the development of poststroke depression correlates with higher mortality and impaired functional recovery after stroke and is associated with a poor quality of life.[8,10–15] A variety of antidepressants have been shown to effectively lessen depressive symptoms after stroke, among them heterocyclics like nortriptyline,[16,17] imipramine,[18] and mianserin[18] and selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and citalopram.[1,17,19–21] Recently, a double-blind, placebo-controlled study[22] demonstrated the efficacy of sertraline to reduce poststroke depression rates.

Although there is consensus that poststroke depression should be treated as soon as possible, little attention has been given to its possible prevention. So far, 3 studies[22–24] have addressed this question. One[23] investigated mianserin in 100 stroke patients during 1 year but failed to show a significant difference in the frequency of major depression between the treated and the placebo groups; in that study, patients were eligible if they had an ischemic stroke within the last 30 days. The second study[24] examined the preventive effects of nortriptyline and fluoxetine given for 3 months in a total of 48 patients. Only patients who had had either an ischemic stroke or an intracerebral hemorrhage and who had suffered from stroke within 6 months prior to enrollment were eligible to participate in the study. Both nortriptyline and fluoxetine appeared to be effective in preventing poststroke depression, although results were ambiguous.

A recent double-blind, placebo-controlled study[22] reported the efficacy of sertraline in preventing the development of depressive symptom clusters in patients who had been diagnosed with stroke within 4 weeks prior to study inclusion. However, to our knowledge, there is no study yet examining a truly prophylactic potency of an antidepressant in poststroke depression. Thus, we began to administer the antidepressant mirtazapine the first day after stroke in a modern setting of a specialized stroke unit. This newer antidepressant had also not yet been investigated in the treatment of poststroke depression.

Hence, the purpose of this study was to test the efficacy of mirtazapine in the prophylaxis and treatment of poststroke depression. Mirtazapine is a tetracyclic antidepressant with serotonergic and noradrenergic activity and a relatively low incidence of anticholinergic effects, which makes it a particularly suitable drug for stroke patients. Mirtazapine is given once daily, usually at bedtime due to its sedating effects.

METHOD

Patients

From August 2001 to December 2002, 1060 patients with an acute stroke were initially treated in a modern setting in the specialized stroke unit of the Department of Neurology of a large academic medical center in Ludwigshafen, Germany, serving an area with approximately 500,000 inhabitants. Of these 1060 admissions, 742 patients had suffered an ischemic stroke. Approximately two thirds of these patients did not fulfill the inclusion criteria for our study (Table 1), and 177 patients refused participation. Thus, 70 patients were enrolled in the study.

Inclusion criteria were having suffered an acute ischemic stroke diagnosed clinically and confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) scan. Additionally, patients had to be able to give written, informed consent, could not be currently using antidepressants, and could not have been depressed within 2 weeks prior to the stroke. Patients had to be older than 18 years and, in the case of women, not pregnant or breastfeeding. Fertile women had to use a safe method of contraception. The patients were required not to have aphasia that would interfere with the psychiatric examination. All patients received maximum stroke care as needed, including systemic thrombolysis if applicable. Drugs that may induce depression (e.g., particular calcium channel blockers) were not given. The patients were randomly assigned alternately either to the group receiving 30 mg mirtazapine once daily at bedtime (group A) or to the group receiving no antidepressant medication (group B); each group consisted of 35 patients.

Table 1. Inclusion Criteria

Ischemic stroke
Written informed consent
Age > 18 years
Not pregnant or breastfeeding
In fertile women, safe contraception
No depression 2 weeks prior to stroke
No use of antidepressants currently or 2 weeks prior to stroke
No severe aphasia interfering with psychiatric exploration

Assessment of Depression and Neurologic Status

All patients underwent neurologic and psychiatric examinations on admission and at days 7, 44, 90, 180, 270, and 360. After discharge, patients were visited either at home or in rehabilitation or long-term facilities, or they returned to our outpatient clinic if possible.

Neurologic status was assessed with the National Institutes of Health Stroke Scale (NIHSS)[25] and the Scandinavian Stroke Scale (SSS).[26] The Rankin Scale,[27] Global Assessment of Functioning (GAF),[28] and Barthel Index[29] were used to assess functional status. Depression was defined as a major depressive episode using the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria and a score of 16 or higher on the 17-item Hamilton Rating Scale for Depression (HAM-D).[30] A semistructured interview[31] was used to assess the absence or presence of a major depressive episode, and the severity of depression was assessed with the HAM-D[30]; response was defined as a reduction of > 50% in the HAM-D score.

All examinations and interviews were performed by a psychiatrist and a neurologist. The patients received maximum stroke care according to the recommendations of the European Stroke Initiative (EUSI).[32]

Treatment Protocol

The patients randomly assigned to group A received 30 mg mirtazapine orally once daily at bedtime from day 1 poststroke. Compliance was checked at follow-up and also with routine telephone contact with the patient and his or her family between the follow-up visits. Patients who developed depression received an increased dose of 45 mg mirtazapine and were then followed up at an interval of 21 days. If depression persisted in spite of dosage increase for 4 weeks, they were excluded from the study.

Patients who were not given mirtazapine poststroke (group B) were followed up with exactly the same schedule as patients in group A. In cases where poststroke depression was diagnosed, patients were started on 30 mg mirtazapine for at least 3 weeks. The dose was increased to 45 mg if depression persisted. In cases where depression did not improve with 45 mg of mirtazapine during 4 weeks, patients were excluded from the study. The study was approved by the local ethics committee, and all patients gave written, informed consent.

Statistical Analysis

Baseline and demographic characteristics were analyzed using appropriate test procedures, such as the Mann-Whitney and the χ^2 tests. The major aim of the study was to determine whether mirtazapine may prevent the occurrence of a depression following a stroke. This involved the comparison of proportions, which was done using a χ^2 test. Here the limit for type I error was set to 0.025, since this comparison constitutes an interim analysis of the study.

As a measure of effect, the risk difference together with a 95% confidence interval was calculated. A supplemen-

Table 2. Baseline Characteristics of Poststroke Patients in Group A (mirtazapine, N = 35) and Group B (no antidepressant treatment, N = 35) at Enrollment in the Trial

Variable	Group A	Group B
Age, mean (SD), y	66.4 (10.1)	63.5 (11.36)
Gender, N, M/F	24/11	23/12
NIHSS score, mean	4.9	5.1
NIHSS score in patients who developed poststroke depression, mean	6.0	7.3
Infarct localization, N (%)		
Middle cerebral/anterior cerebral artery	21 (60.0)	31 (88.5)
Posterior cerebral artery	4 (11.4)	1 (2.8)
Vertebral/basilar artery	10 (28.5)	3 (8.5)
Infarct etiology (TOAST criteria), N		
Small-vessel thrombotic	21	19
Cardioembolic	3	11
Atherothromboembolic	8	4
Other	1	1
Unknown	2	0

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, TOAST = Trial of Org 10172 in Acute Stroke Treatment.

tary explorative analysis investigated potential prognostic factors, other than treatment, for the occurrence of poststroke depression. This was done using binary logistic regression with age, gender, and the NIHSS score as potential additional covariates. Model selection was based on a stepwise selection procedure using the Akaike information criterion. For these analyses, the significance level was set to the usual p value of ≤ .05. All statistical analyses were performed using SAS 8.1 software.[33]

RESULTS

Sample Characteristics

The characteristics of the 2 patient groups are presented in Table 2. Two patients in group A dropped out because of side effects (sedation and dizziness), and 2 patients refused further participation due to other reasons. Two patients in group B refused further participation and dropped out.

One patient died, and 1 was lost to follow-up. Mean age was 66.4 years in group A and 63.5 years in group B. The male-to-female ratio was similar in both groups. The localization of cerebral infarcts was determined with CT and in most cases also with MRI. Sixty percent (N = 21) of group A and 88.5% (N = 31) of group B patients had middle cerebral/anterior cerebral artery infarcts; 28.5% (N = 10) of group A and 8.5% (N = 3) of group B had vertebral/basilar artery infarcts; 11.4% (N = 4) of group A and 2.8% (N = 1) of group B patients had posterior cerebral artery infarcts. Stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[34] is also listed in Table 2. The majority of strokes in both groups were due to small-vessel disease, followed by strokes of cardioembolic origin.

Stroke severity at admission as determined by NIHSS score was 5 in both treatment groups. Overall, no significant difference in the above-mentioned characteristics between the treatment groups was found.

Development of Poststroke Depression

According to DSM-IV criteria, 14 (40%) of 35 patients in the nontreated group developed poststroke depression, whereas in the treatment group, only 2 (5.7%) of 35 cases of depression were observed. The corresponding value of the χ^2 test statistic was 11.67, df = 1, p = .001; the corresponding risk difference equaled –34.3% (95% confidence interval = –52.2% to –16.3%).

Eight patients became clinically depressed 1 to 4 weeks poststroke, 5 patients 2 to 3 months poststroke, and 2 patients 4 to 6 months after the stroke. In only 1 patient did depression occur 9 months poststroke. In general, neurologic and functional deficits were less in nondepressed patients in comparison with depressed patients (Table 3). Although 4 patients became clinically depressed directly after stroke onset, they greatly improved psychopathologically during the following 2 weeks; thus, they did not fulfill the duration criterion for a major depressive episode. However, they were included nevertheless since they met all symptomatic cross-sectional criteria.

All 14 nontreated patients who developed poststroke depression and were then treated with 30 mg of mirtazapine responded to the antidepressant medication. One patient in this group needed a 45-mg daily dose. Two patients in group A also developed poststroke depression; of these, only 1 responded to the dose augmentation of 45 mg.

Prognostic Factors

Using a stepwise selection procedure, "antidepressant" and "degree of severity of stroke" (NIHSS score at hospitalization) were identified as prognostic factors for the development of poststroke depression. The odds ratio for the "antidepressant" effect was 0.069 (95% CI = 0.012 to 0.389). For the effect of severity of stroke, the odds ratio was 1.22 (95% CI = 1.04 to 1.45). Age and gender did not turn out to have an impact on the occurrence of depression.

DISCUSSION

This study is the first to investigate the prophylactic effects of an antidepressant immediately (day 1) poststroke. The patient sample was homogeneous since only stroke patients with ischemic stroke were included, and all received the same standardized maximum stroke care as defined by the EUSI criteria.

This article presents the results of an interim analysis, after which further recruitment was stopped. The study showed that mirtazapine was remarkably effective in preventing poststroke depression in patients with acute

Table 3. Neurologic, Functional, and HAM-D Test Scores in Patients With or Without Poststroke Depression (PSD) During the Observation Period[a]

	Admission		Day 7		Day 90		Day 180		Day 360	
Measure	With PSD	Without PSD	With PSD	Without PSD	With PSD	Without PSD	With PSD	Without PSD	With PSD	Without PSD
GAF	88	87.3	77.9	89.3	77.5	89.9	80.6	92.4	84.3	94.7
NIHSS	7	4.5	5.7	3.1	3.69	1.3	3.73	1	3.3	1.4
SSS	43.2	48.8	46.4	52.3	50.1	55.3	51.3	57.2	51.9	54.6
Rankin Scale	3.54	3.0	3.1	2.0	2.46	1.5	2.27	1.13	2.5	1.4
Barthel Index	56.2	69.5	68.3	85	84.2	91.1	91.5	95.7	86.1	90.4
HAM-D, mean (range)[b]	…	3.0 (0–15)	…	2.1 (0–21)	…	1.9 (0–14)	…	1.3 (0–10)	…	0.87 (0–6)

[a]Values are means unless otherwise noted.
[b]Mean (range) HAM-D scores in patients with PSD were 18.6 (16–23) at diagnosis and 8.3 (5–16) after treatment.
Abbreviations: GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, NIHSS = National Institutes of Health Stroke Scale, SSS = Scandinavian Stroke Scale.

stroke. The efficacy analysis suggested that prophylactic treatment with mirtazapine may prevent 34 cases of depression per 100 stroke patients.

One previous small study about prevention of poststroke depression that also demonstrated a beneficial effect of antidepressants[24] compared fluoxetine and nortriptyline versus placebo. Poststroke depression occurred in 20% of the fluoxetine- and 7.7% of the nortriptyline-treated group. In contrast to our study, patients who had had a stroke within 6 months from enrollment were included. Another study by Palomäki et al.,[23] which failed to show a beneficial prophylactic effect of mianserin, had a mean interval of 14.3 days from stroke to beginning of mianserin. Finally, a recent placebo-controlled study[22] that included patients who had suffered an ischemic or hemorrhagic stroke during an interval of 4 weeks prior to enrollment demonstrated a significant efficacy of sertraline to reduce depressive symptom clusters; only 10% of the sertraline-treated patients developed depression, but 30% of the placebo-group developed depression. In our study, which was not placebo-controlled but was strictly randomized, an even lower proportion (5.7%) of mirtazapine-treated patients became clinically depressed, and a higher percentage (40%) of nontreated patients developed poststroke depression.

One possible hypothesis regarding the high effectiveness of mirtazapine in our study may be related to the fact that the drug was given very early, beginning on day 1 poststroke. The effectiveness of an antidepressant may be better in a situation of acute brain damage when stress-induced neurohormonal (glucocorticoids) and neurotransmitter (excitatory amino acids) changes may endanger neuronal integrity. It seems plausible that mirtazapine may be most effective in such a "toxic" situation.

The second major result of this study was that mirtazapine proved to be effective in treating poststroke depression. The incidence of poststroke depression within the untreated group was similar to those in previously published studies,[1–9] and all depressed patients in group B showed a significant reduction of depressive symptoms and in the HAM-D score. To our knowledge, this is also the first study to examine the effectiveness of mirtazapine in patients with poststroke depression.

The drug was well tolerated; among the few side effects, mild sedation was the most frequent. No serious side effect was observed, and the rate of patients who dropped out because of untoward effects was remarkably low.

A logistic regression analysis regarding age, gender, and severity of stroke as potential risk factors for the development of poststroke depression while adjusting for antidepressive treatment showed that among these, only the NIHSS score at admission was significant. This finding is in accordance with various other studies, although the role of female gender is discussed somewhat inconsistently.[35–37] Stroke localization and infarct etiology did not play a role as a prognostic factor, as described previously.[38]

However, the limitations of our work have to be mentioned. The obvious shortcoming is that our study was done in an open, randomized fashion. From our point of view, however, the results of this trial are so convincing that they can hardly be explained by the patients' knowledge of their treatment status.

The majority of studies examining treatment of poststroke depression, including the 3 previously published prophylaxis studies,[22–24] were done in the setting of rehabilitation facilities. Our study suggests that poststroke depression should also be considered and taken seriously in acute stroke care units, since prophylactic antidepressant treatment may be highly beneficial.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft).

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