Double-Blind Comparison of Sertraline and Placebo in Stroke Patients With Minor Depression and Less Severe Major Depression

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Background: Poststroke depression is a frequent condition and important to treat. The aim of this trial was to study the efficacy and tolerability of sertraline.

Method: In 4 Swedish stroke centers, 123 patients (aged 70.7 ± 9.9 years) were enrolled during the period September 1998 to January 2001 in a randomized, double-blind, placebo-controlled 26-week trial, at a mean of 128 ± 97 days (range, 3–375 days) after stroke, if they fulfilled DSM-IV criteria of major depressive episode (N = 76) or minor depressive disorder (N = 47). The primary efficacy variable was a change in depression assessed by the Montgomery-Åsberg Depression Rating Scale. The Emotional Distress Scale (EDS) was administered and the occurrence of emotionalism and quality of life (QoL) were assessed, as well as neurologic recovery. Efficacy analyses were intention-to-treat, short-term (week 6) and long-term (week 26).

Results: Of the 123 patients, 62 were treated with sertraline (50–100 mg/day) and 61 with placebo. Both groups improved substantially, with no differences between the treatments, either for major depressive episode or minor depressive disorder, or for short- or long-term antidepressant effect and neurologic outcome. EDS revealed a better outcome with sertraline at week 6 ($p < .05$). At week 26, the improvement in QoL was better in sertraline patients ($p < .05$) and there was a trend for emotionalism ($p = .07$). No serious side effects were seen.

Conclusion: Poststroke depression as measured by a conventional depression rating scale improved over time irrespective of treatment. Positive effects specific to sertraline were identified in emotional distress, emotionalism, and QoL. The study indicates that poststroke emotional reactions comprise depression and other domains susceptible to pharmacologic therapy.

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Up to one third of poststroke patients seem to suffer from a clinically significant depression, but the prevalence varies considerably between studies.[1,2] Two forms of poststroke depression, major and minor, have been reported.[3] Besides the emotional discomfort, depressive symptoms appear to have bearings on the patient's ability to rehabilitate successfully.[4] In a 10-year follow-up, Morris et al.[5] reported that patients who had been depressed in the acute phase of stroke were 3 times more likely to die, and House et al.[6] found a trend toward increased mortality. A 9-year follow-up of patients included in a short-term randomized placebo-controlled trial (RCT) with nortriptyline or fluoxetine after stroke intriguingly showed a difference in long-term survival in favor of active treatment.[7] In poststroke depression, an increased risk of suicide has also been reported.[8] The presence of depressive and anxiety symptoms also has negative effects on the quality of life.[9,10]

Comparatively few RCTs of antidepressant drugs have been made in stroke patients. Short-term studies, with relatively few patients, have been reported for nortriptyline,[11,12] citalopram,[13] and fluoxetine.[12,14] One long-term

study was made by continuing a short-term trial for those who responded during the acute phase[13]; otherwise, previous antidepressant long-term drug studies, few in number, have been preventive.[15] The effect of antidepressant drugs on poststroke rehabilitation has also been studied specifically.[12,16,17]

Although there are indications that antidepressant drugs have positive effects on both depressive symptoms and recovery from stroke-related symptoms, the evidence is very limited and to some extent conflicting[18]; most studies have concentrated on the short term, 6 to 12 weeks. Our study was designed as a 26-week trial and aimed to assess the effects of sertraline, a selective serotonin reuptake inhibitor (SSRI).

METHOD

This 26-week, double-blind, placebo-controlled study of sertraline was carried out on an outpatient basis from September 1998 to January 2001 at 4 stroke centers throughout Sweden. Ethics committee approval was obtained. The patients gave their informed, written or, if unable to write, witnessed consent after receiving information, written and verbal. The study was also approved by the Medical Products Agency (Uppsala, Sweden) and conducted in accordance with the Helsinki Declaration and good clinical practice.

Patients

Patients ≥ 18 years of age who developed symptoms of depression at any time within the first 12 months after a stroke, defined according to the World Health Organization criteria,[19] could be entered in the study. All patients were hospitalized during the acute phase of the index stroke and investigated according to routine procedures, including computed tomography (CT) scan. Most of the study patients did not develop their depression during the acute phase of the stroke and were therefore included in the trial on an outpatient basis.

Inclusion criteria were either major depressive episode according to DSM-IV criteria[20] or minor depressive disorder according to DSM-IV research criteria,[20] and a Montgomery-Åsberg Depression Rating Scale (MADRS)[21] score of ≥ 10. Criteria for major depressive episode were used with the exception of the D-criterion (the depressive symptoms should not be due to a medical condition) and the time criterion (the symptoms should have been present during the same 2-week period). The corresponding exceptions were applied to the criteria for minor depressive disorder. Exclusion criteria were apparent difficulties in adhering to the study protocol including a severe impairment of the ability to communicate, acute myocardial infarction, psychiatric illnesses other than depression, significant risk of suicide, antidepressant drug treatment during the month before the study start, current use of any psychotropic medication (with the exception of small daytime doses of benzodiazepines or zopiclone, zolpidem, or benzodiazepines for night sedation), and current use of opiate analgesic drugs. All CT scans were consistently reviewed, with assessment of type of lesion and arterial supply area. The frontal pole involvement was defined according to Starkstein et al.[22] For comparison of the included patients to population-based series, the Oxfordshire Community Stroke Project classification[23] and the Swedish National Quality Register for Stroke Care (Riks-Stroke)[24,25] were used.

Study Design

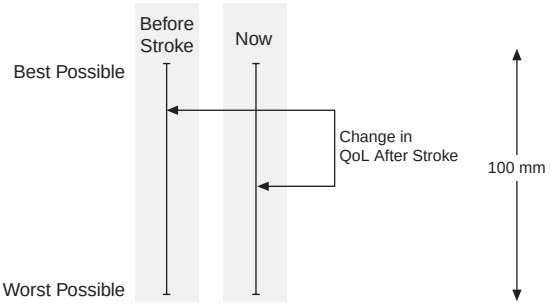
A centralized randomization procedure was applied. The Central Pharmacy in Stockholm kept the randomization list. Each center pharmacy received a consecutive series of presealed treatment packages. Once a patient had been found eligible, without contraindications, a randomization number was allocated, the main center was contacted, and the patient was entered in the trial. All randomization numbers and all treatment packages were accounted for. Patients received double-blind identical capsules of either sertraline 50 mg or placebo, once a day, as a starting dose. After 4 weeks, in lack of sufficiently improving antidepressant effect, the dose could be increased to 2 capsules in the morning, at the investigator's discretion. If the patient experienced side effects after dose increase, the intake could be reduced to the initial level. Compliance was checked using pill counts. To be allowed to continue trial treatment after the assessment at week 6, both sertraline and placebo patients had to display a decrease of at least 20% of the baseline MADRS score. After 6 weeks, during the continuation phase of the study, patients could discontinue if, in the investigator's opinion, an adequate clinical response had not been observed.

Efficacy and Safety Evaluations

The MADRS (see Appendix 1) was assessed by trained research nurses at baseline and at weeks 2, 4, 6, 8, 12, 18, and 26. A MADRS rating was also carried out at week 1, based on a telephone interview. Joint ratings were carried out prior to the study start and repeated at a mid-study meeting. The corating sessions displayed good interrater consistency with a coefficient of variance of 8.1%. The Clinical Global Impressions-Severity of Illness scale (CGI-S),[26] the Clinical Global Impressions-Improvement scale (CGI-I),[26] and the Emotional Distress Scale (EDS)[27] (Appendix 1) were administered on the same occasions as MADRS, as were the Scandinavian Stroke Supervision Scale (SSSS)[28] measuring neurologic deficit, the Barthel Index[29] measuring activities of daily living (ADL), and a modified version of the Udvalg for Kliniske Undersøgelser side effect rating scale.[30] Presence of emotionalism—increased tearfulness and pathologic crying—was recorded as a dichotomous variable.

The question "Do you experience an increased tearfulness beyond control?" was put to the patient at baseline and at weeks 6 and 26. The corresponding question, about the patient, was put to the relatives. The inquiry was completed by observations made by the research nurses. The patient's global subjective rating of change in quality of life (QoL) was measured according to a validated visual analog scale technique[9] (Figure 1).

Figure 1. Measurement of Quality of Life (QoL) According to a Visual Analog Scale Technique[a]



[a]At every point of assessment, the patient marks the perceived QoL before stroke on the left bar and the present one on the right bar. The difference in millimeters indicates the relative deficit in well-being.

Statistics

The primary outcome variable was change in MADRS score from baseline to weeks 6 and 26. Week 6 was predefined as the end of the acute phase of treatment. Efficacy analyses were based on the intention-to-treat (ITT), last-observation-carried-forward population, comprising all randomized patients. In addition, response and remission rates were calculated for those patients who completed the study. Response was defined as ≥ 50% decrease in the MADRS score. Remission was defined as a MADRS score < 10. Differences in rates of response and remission were tested by the χ^2 test, or in case of small frequencies, by Fisher exact test. The same tests were used to evaluate the hypothesis of other variables in contingency tables. Statistical comparisons for the assessment of differences between groups on continuous variables were made with Student t test and analysis of variance. Correlation coefficients were calculated according to both Pearson and Spearman. The study employs multiple hypotheses testing, in which each hypothesis was analyzed separately, and the existence of patterns in, and the consistency of, the results were considered in the analysis. All analyses were carried out with the SAS statistical system (release 8.02, SAS Institute, Inc., Cary, N.C.), and the 5% level of significance was considered.

RESULTS

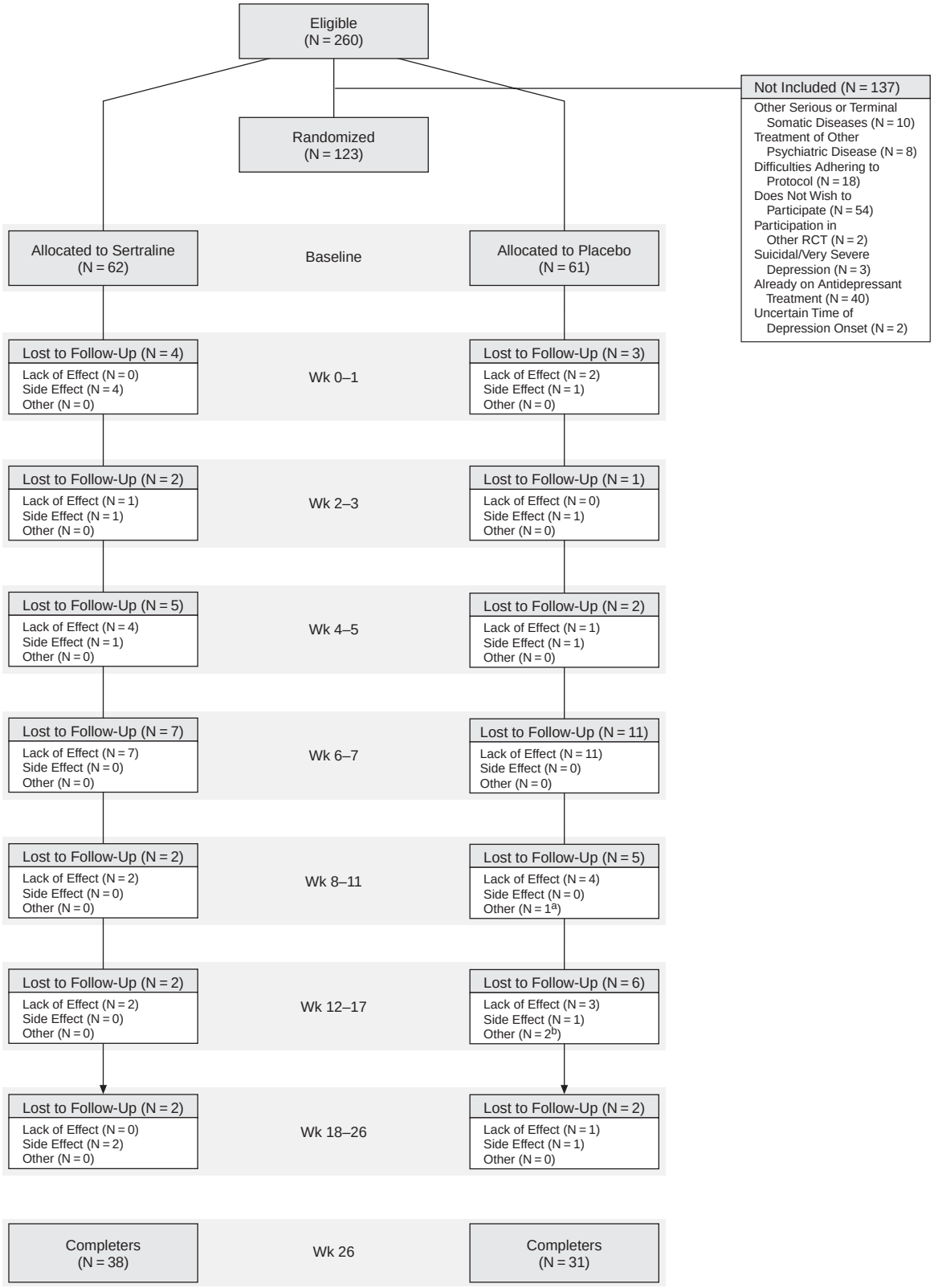
A total of 260 patients were considered eligible for the trial, representing 7% of the total cohort of stroke patients during the study period, and 123 were subsequently randomized at a mean ± SD of 128 ± 97 days (range, 3–375 days) (Figure 2). The nonincluded patients (N = 137) were older than those randomized (aged 74.2 vs. 70.7 years; $p < .05$), and a higher proportion had the diagnosis of major depressive episode (79.8% vs. 61.8%; $p < .05$). For 15% of the included patients, depression occurred when the patients were still at hospital and a mean of 17 days after stroke onset. For the remaining 85%, the mean interval after stroke onset was 147 days, and in all these patients the depression occurred after discharge from their hospital stay for the index stroke. The patients with an early onset of depression were significantly more disabled (Barthel Index 79 vs. 96; $p < .05$). The comparison between the early- and late-onset depression patients revealed no difference in the severity or subtype of depression, neither at baseline nor as to the depression regression, as measured after 6 months. Demographic and baseline characteristics of the ITT population are shown in Tables 1 and 2.

Table 3 and Figure 3 illustrate the results of the ITT analysis of the antidepressant outcome. The MADRS score decreased substantially in both treatment groups, with no significant differences between them at 6 and 26 weeks, both for all patients and for major and minor depressed patients separately. As there were no significant differences between major depressive episode and minor depressive disorder with respect to all the different outcome measures, the results will be reported for the complete group. Among those who completed 6 weeks and 26 weeks of treatment, respectively, 56% and 76% in the sertraline group and 46% and 78% in the placebo group responded. The corresponding percentages for remission were 59% and 81%, and 51% and 87%. No significant correlation was found between antidepressant effect and lesion location. In keeping with the MADRS results, an improvement from baseline to weeks 6 and 26 was observed in CGI-S for both sertraline- and placebo-treated patients, with no significant difference between the treatment groups. Neither did the mean CGI-I scores at weeks 6 and 26 differ between the groups.

At week 6, 11 patients (18%) in the sertraline group and 6 patients (10%) in the placebo group had dropped out of the study (Figure 2). At week 26, an additional 13 patients (21%) in the sertraline group and 24 patients (39%) in the placebo group had been withdrawn. Of the 54 patients prematurely withdrawn, 30 had a major depressive episode and 17 a minor depressive disorder. Lack of antidepressant effect was the reason for exclusion in 38 cases and side effects in 13. The dropout patients had a higher mean ± SD baseline MADRS score than the completers (20.7 ± 6.1 vs. 18.1 ± 5.8; $p < .05$).

The dose was increased from 50 to 100 mg/day for 48% of the patients in the sertraline group, and for 59% of the placebo patients a corresponding increase, from 1 to 2

Figure 2. Flow Diagram of Subjects' Progress Through the Trial



[a]One patient died from pneumonia.
[b]One patient died from a new stroke during the study, and 1 patient discontinued due to general discomfort.
Abbreviation: RCT = randomized placebo-controlled trial.

Table 1. Baseline Characteristics of the ITT Population (N = 123)

Characteristic	Sertraline (N = 62)	Placebo (N = 61)	p Value
Age, mean ± SD, y	70.7 ± 9.7	70.7 ± 10.1	NS
Range	47–86	52–89	
Male, %	51.6	44.3	NS
Hospitalized at baseline, %	15.2	16.7	NS
Previous cerebrovascular event, %	30.0	29.5	NS
Stroke type, %			
Hemorrhagic	6.4	11.5	NS
Ischemic	93.5	88.5	NS
Brain lesion location, % (N = 120)			
Left hemisphere	56.6	33.3	< .05
CT finding, %[a]			
Left frontal pole	4.8	4.9	NS
Left posterior pole	21.0	14.8	NS
Right frontal pole	8.1	9.8	NS
Right posterior pole	22.6	32.8	NS
Bilateral	0	1.6	NS
Lesion nonvisible	43.5	36.1	NS

[a]According to Starkstein et al.[22]
Abbreviations: CT = computed tomography, ITT = intention to treat, NS = not significant.

Table 2. Baseline Depression and Neurologic Findings in the ITT Population

Variable	Sertraline (N = 62)	Placebo (N = 61)	p Value
Type of depression, %			
Major depressive episode	66.1	57.4	NS
Minor depressive disorder	33.9	42.6	NS
Previous depressive episode, %	13.3	19.7	NS
Stroke to diagnosis of depression, mean ± SD, d	137.3 ± 101.4	119.0 ± 92.5	NS
Neurologic deficit, mean ± SD, SSSS[a] (N = 107)	10.4 ± 3.6	10.6 ± 3.7	NS
Barthel Index, mean ± SD, total score	90.7 ± 19.6	90.2 ± 18.4	NS
MADRS, mean ± SD, total score	18.9 ± 6.1	19.6 ± 6.1	NS
CGI–Severity, mean ± SD, total score	3.9 ± 1.0	3.9 ± 0.9	NS

[a]Minimal function score 29; maximal function score 7 (Rödén-Jüllig et al.[28]).
Abbreviations: CGI = Clinical Global Impressions scale, ITT = intention to treat, MADRS = Montgomery-Åsberg Depression Rating Scale, NS = not significant, SSSS = Scandinavian Stroke Supervision Scale.

capsules, was made. For patients treated with sertraline, the mean ± SD daily dose was 76.4 ± 25.2 mg at week 6 and 67.1 ± 24.0 mg at week 26; in the placebo group, the corresponding figures were 75.9 ± 25.2 mg and 77.6 ± 25.3 mg, respectively. The incidence of side effects at any time during the 26 weeks is presented in Table 4.

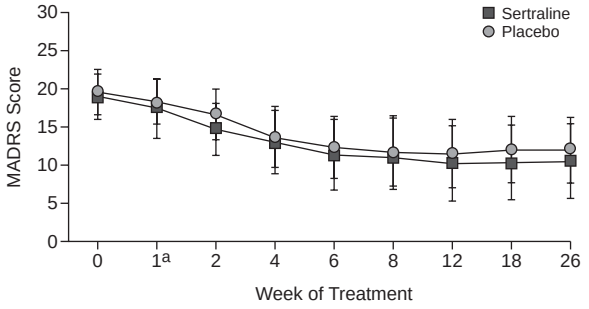
An assessment of the therapeutic outcome according to the EDS showed a significantly more pronounced amelioration in the sertraline-treated group at week 6 (Figure 4). At week 26, the outcome for sertraline was numerically better but not statistically different from placebo ($p < .1$). Of the items in the EDS that are not included in the MADRS (see Appendix 1), "hostile feelings" improved most during treatment, specifically for the sertraline group.

Table 3. Baseline and Endpoint MADRS Scores (mean ± SD) in Patients With Major or Minor Depression Treated With Sertraline or Placebo (intention-to-treat population, last-observation-carried-forward analysis)

	Major Depressive Episode			Minor Depressive Disorder		
Weeks of Treatment	Sertraline (N = 41)	Placebo (N = 35)	p Value	Sertraline (N = 21)	Placebo (N = 26)	p Value
0	20.8 ± 6.2	22.6 ± 6.2	NS	15.2 ± 3.6	15.5 ± 2.6	NS
6	12.4 ± 9.6	13.5 ± 8.1	NS	9.1 ± 6.2	10.8 ± 7.4	NS
26	11.5 ± 10.5	12.6 ± 8.9	NS	8.4 ± 7.3	11.1 ± 8.1	NS

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale, NS = not significant.

Figure 3. Changes in MADRS Scores (mean ± SD) for Sertraline- and Placebo-Treated Patients With Poststroke Depression (intention-to-treat population, last-observation-carried-forward analysis)



[a]Week 1 = telephone interview.
Abbreviation: MADRS = Montgomery-Åsberg Depression Rating Scale.

Quality of life improved during the entire treatment period on sertraline as well as on placebo; at the end of the study, however, the outcome was significantly better for patients treated with sertraline (Figure 4). QoL was statistically significantly correlated ($p < .05$) with the EDS score, both at baseline and during the trial and for both treatment groups.

The ADL performance was generally good already when the patients developed their depression and were included in the study, and did not improve. The same applies to the neurologic deficit as measured by SSSS. There was no significant difference between the treatment groups.

The occurrence of emotionalism diminished during the trial for patients treated with sertraline and was unchanged in patients treated with placebo. There was a trend toward a difference at week 26 ($p = .07$).

DISCUSSION

In this long-term study of patients with either major or minor poststroke depression, a high rate of amelioration

was found at week 26. The antidepressant outcome did not differ between sertraline- and placebo-treated patients, regardless of whether the depression was major or minor. Outcome assessed by the EDS as well as by global QoL was significantly better in the sertraline group.

The lack of a difference in antidepressant effect between the 2 treatment alternatives is the most striking finding of the present study. Specifically, the response rate in the placebo-treated patients was as high as in the actively treated patients. The length of the placebo-controlled study may have restricted enrollment to less severely depressed patients, in whom the placebo effect is known to be greater[31]; the placebo effect in itself can thus not be overlooked. The response rate for sertraline at both week 6 and week 26 was of about the same magnitude as in 2 long-term studies of sertraline in depressed psychiatric patients,[32,33] as well as in a very large, but short-term, placebo-controlled sertraline study[34] of elderly depressed patients. Note, moreover, that in 2 large SSRI studies in elderly, depressed patients,[34,35] the differences between drug and placebo were very small. Findings from other sertraline studies on depression do not indicate that a higher dose than used in our study would have improved the results.[36]

There are only a few RCTs in poststroke depression reported before, and comparisons between the studies are complicated by differences in trial design. In a 12-week trial by Robinson et al.,[12] neither the SSRI compound fluoxetine nor placebo did well in contrast to the norepinephrine reuptake–inhibiting tricyclic compound nortriptyline. On the other hand, in a study by Wiart et al.,[14] fluoxetine gave a better outcome than placebo. In a comparison between citalopram and placebo,[13] citalopram did better only for those who became depressed after the sixth week after stroke. It is, however, noteworthy that in another previous study of nortriptyline a significantly better outcome compared to placebo was reported.[11]

Neither the uneven lateralization between the treatment groups in our series nor the lateralization or the intrahemispheric location of the brain lesion was found to influence the treatment results. In the treatment series reported by Andersen et al.,[13] the effect of citalopram did not differ with the side of the brain lesion in a smaller subgroup defined by CT. The predictive implication of the lateralization, as well as of the intrahemispheric location of the brain lesion, for the occurrence of depression is unclear, and so is the relationship between brain lesion location and the effect of antidepressant treatment. The Robinson group[22] in the 1980s suggested an association between anterior pole lesions in the left hemisphere and poststroke depression, but this could not be confirmed in a more recent systematic review by Carson et al.[37]

While neurologic recovery paralleled the effects on depression in the study by Robinson et al.,[12] no such relationship was found either in our study or in the studies by Lipsey et al.[11] and Wiart et al.[14] The inclusion of neurologically less impaired patients might explain the difference in findings in our study.

Table 4. Incidence of the Most Frequent Side Effects (> 8%)

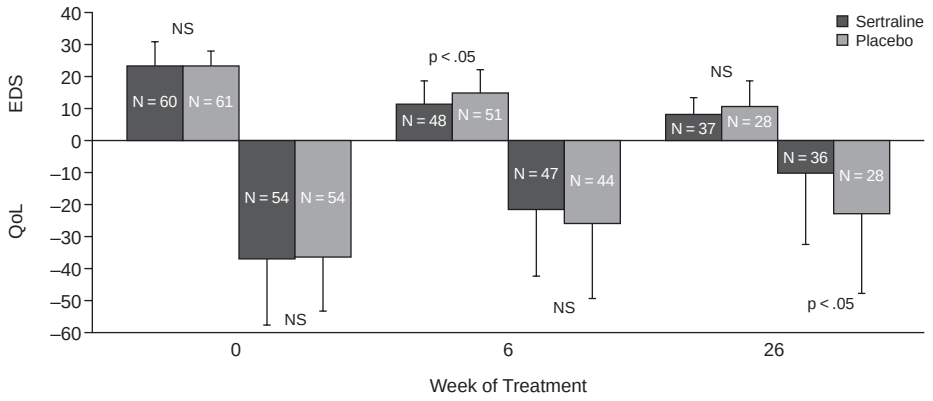
Adverse Event	Incidence, % Sertraline (N = 62)	Placebo (N = 61)
Dry mouth	23.6*	7.4
Diarrhea	23.6*	9.3
Emotional indifference	9.1*	0
Nausea	21.8	14.8
Tremor	12.7	7.4
Constipation	14.5	9.3
Increased dream activity	14.5	9.3
Weight loss	17.4	13.3
Postural hypotension	13.0	9.3
Dyspepsia	20.0	16.7
Dizziness	14.5	13.0
Edema	12.7	11.3
Increased sweating	16.4	17.0
Weight gain	15.2	15.6
Headache	14.5	16.7
Reduced duration of sleep	9.1	18.5

*$p < .05$.

Stroke seems to be frequently followed by different types of disturbances in emotional behavior.[38] Pathologic crying is a common and, in severe cases, disabling manifestation of poststroke emotional lability. SSRIs are known to have different emotional stabilizing effects.[39] In a recent Cochrane review,[40] it was shown that antidepressants can reduce the frequency and severity of crying and laughing episodes. One of the studies included in the review was a placebo-controlled trial, by Burns et al.,[41] which showed that sertraline exerted a positive effect on emotionalism, in particular on tearfulness. It is therefore very likely that the tendency to an effect of sertraline on emotionalism in our patients represents a real effect and not a chance finding. Our finding of a positive effect on emotional distress, as identified by the EDS, is also interesting. Compared with MADRS, EDS mirrors additional discomfort that, just like emotionalism, possibly is more related to the brain lesion. Our findings that symptoms of depression, as measured by a conventional depression rating scale, were alleviated over time irrespective of treatment, while sertraline lessened the EDS and in particular the experience of hostile feelings, may also reflect a stabilizing effect of sertraline. These findings underscore the importance of broadening the assessment of emotional reactions after stroke. Our study also indicates a positive effect of sertraline on perceived QoL, and the QoL correlated with a decrease in emotional distress symptoms as measured by EDS. An advantage to a global QoL assessment is that it contains domains that are specific for each individual.[9]

To elucidate the question of which patients our findings apply to, a comparison with the Swedish National Quality Register for Stroke Care (Riks-Stroke) was car-

Figure 4. Changes in Emotional Distress Scale (EDS) Score (mean ± SD) and Perceived Change in Quality of Life (QoL) (mm VAS) (mean ± SD) in Patients Treated With Sertraline or Placebo (observed cases)



Abbreviations: NS = not significant, VAS = visual analog scale.

ried out and showed that the mean age of our patients lies below the national mean of 75.5 years. The genders were equally distributed in the register and in our series. Physical and ADL functioning in our patients equal the median value of approximately 80% to 90% independent after 3 months found in Riks-Stroke.[24,25] As for types and severity of brain lesions, our series contains all types of severity of stroke as described by the clinical classification method from the Oxfordshire Community Stroke Project.[23] However, the material is dominated by the least severely struck.

Limitations

One weakness of this study is the high discontinuation rate at the end of the treatment period. The total rate at week 26 was 39% in the sertraline group and 49% in the placebo group. The rates were similar for both treatments and are similar to many other long-term studies. At week 6, the discontinuation rates are well in line with most short-term antidepressant trials, or even somewhat lower. A substantial contribution to the discontinuation rates came from the study design, whereby patients who had not shown the predefined minimal response of a 20% reduction of the baseline MADRS score by week 6 were withdrawn. Some of these patients may have been late responders, and their withdrawal may have masked a difference between drug and placebo. On the other hand, the response rate for sertraline was of a magnitude that could be expected. The consistent results from the ITT and completers analyses indicate that the findings of this study are more robust than the high long-term dropout rates might suggest.

Another weakness concerns the selection of patients who were less severely depressed, so that the results do not concentrate much on the effect of sertraline in more severely depressed stroke patients. On the other hand, the efficacy of antidepressants is rarely studied in minor depression, or in milder forms of major depression, although in clinical practice antidepressant drugs are being used more and more frequently for these particular categories of patients.

Stroke patients most certainly have different etiologies of their depressive symptoms. This might be more pronounced in a population consisting of patients who developed their depression at different time intervals after stroke. However, most of our patients were included about 3 months after stroke; only a minority were included either immediately after stroke or at the end of the year.

The proportion of 7% depressed patients out of the total stroke population seems to be small in comparison to results from epidemiologic studies.[1] It should, however, be kept in mind that a common limitation to depression treatment trials in stroke is that up to one half of the patients are not even primarily considered for inclusion due to communication difficulties and cognitive impairment.[42] In our treatment trial, patients suffering from more severe depressions were not considered, and by intention we did not include those patients who were discharged from the acute hospital to institutionalized care.

Strengths

A major strength of this study is the combination of a long-term duration and a placebo-controlled design. It is to our knowledge the first randomized controlled study of poststroke depression lasting for 6 months.

The patients in the present trial fulfilled criteria for either major depression or minor depression, i.e., those with only 2 to 4 symptoms specified in criterion A for major depression. The response to treatment did not differ be-

tween these groups, which may indicate that there is no qualitative difference between patients with fewer depressive symptoms and those with enough symptoms to qualify for a diagnosis of major depression.

A further strength of this study is that it also included instruments reaching beyond depressive core symptoms. Emotional reactions considered as induced by the brain lesion, and of specific interest in this population, were thereby investigated. Some of the instruments were chosen to capture more global and individualized measures.

CONCLUSION

The lack of a specific antidepressant effect of sertraline in this study does not, per se, preclude use of this drug in poststroke depressed patients, since many factors have to be considered, e.g., the severity of the depression. The frequent comorbidity of depression and other emotional reactions also has to be taken into account and point to the fact that an assessment of poststroke emotional symptoms should not be limited solely to a conventional depression rating. Finally, the study findings cannot, with regard to depressive symptoms, solely be interpreted as if no treatment is as good as active, since this has not been studied. In view of earlier findings of the devastating effect of a poststroke depression, the results in this study underscore the effect of attention and care.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft), zolpidem (Ambien), zopiclone (Lunesta).

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REFERENCES

1. Aben I, Verhey F, Honig A, et al. Research into the specificity of depression after stroke: a review of an unresolved issue. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:671–689
2. Berg A, Palomäki H, Lehtihalmes M, et al. Poststroke depression: an 18-month follow-up. Stroke 2003;34:138–143
3. Morris PL, Shields RB, Hopwood MJ, et al. Are there two depressive syndromes after stroke? J Nerv Ment Dis 1994;182:230–234
4. González-Torrecillas JL, Mendlewicz J, Lobo A. Effects of early treatment of poststroke depression on neuropsychological rehabilitation. Int Psychogeriatr 1995;7:547–560
5. Morris PL, Robinson RG, Andrzejewski P, et al. Association of depression with 10-year poststroke mortality. Am J Psychiatry 1993;150: 124–129
6. House A, Knapp P, Bamford J, et al. Mortality at 12 and 24 months after stroke may be associated with depressive symptoms at 1 month. Stroke 2001;32:696–701
7. Jorge RE, Robinson RG, Arndt S, et al. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. Am J Psychiatry 2003; 160:1823–1829
8. Stenager EN, Madsen C, Stenager E, et al. Suicide in patients with stroke: epidemiological study. BMJ 1998;316:1206
9. Ahlsiö B, Britton M, Murray V, et al. Disablement and quality of life after stroke. Stroke 1984;15:886–890
10. Golomb BA, Vickery BG, Hays RD. A review of health-related quality of life measures in stroke. Pharmacoeconomics 2001;2:155–185
11. Lipsey JR, Robinson RG, Pearlson GD, et al. Nortriptyline treatment of post-stroke depression: a double-blind study. Lancet 1984;1:297–300
12. Robinson RG, Schultz SK, Castillo C, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry 2000; 157:351–359
13. Andersen G, Vestergaard K, Lauritzen L. Effective treatment of poststroke depression with the selective serotonin reuptake inhibitor citalopram. Stroke 1994;25:1099–1104
14. Wiart L, Petit H, Joseph PA, et al. Fluoxetine in early poststroke depression: a double-blind placebo-controlled study. Stroke 2000;31: 1829–1832
15. Rasmussen A, Lunde M, Poulsen DL, et al. A double-blind, placebo-controlled study of sertraline in the prevention of depression in stroke patients [Erratum in Psychosomatics 2004;45:91]. Psychosomatics 2003;44:216–221
16. Reding MJ, Orto LA, Winter SW, et al. Antidepressant therapy after stroke: a double-blind trial. Arch Neurol 1986;43:763–765
17. Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke 1996;27:1211–1214
18. Hackett M, Anderson CS, House AO. Interventions for treating depression after stroke. Cochrane Database Syst Rev 2004;2:CD003437
19. World Health Organization. Cerebrovascular diseases: prevention, treatment, and rehabilitation. WHO Org Techn Rep Ser; 1971
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
21. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
22. Starkstein SE, Robinson RG, Price TR. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain 1987;110:1045–1059
23. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337:1521–1526
24. Stegmayr B, Asplund K, Hulter-Åsberg K, et al. Stroke units in their natural habit: can results of randomized trials be reproduced in routine clinical practice? Riks-Stroke Collaboration. Stroke 1999;30:709–714
25. Glader E-L. Stroke Care in Sweden: Hospital Care and Patient Follow-Up Based on Riks-Stroke, the National Quality Register for Stroke Care [dissertation]. Umeå, Sweden: University Medical Dissertations New

serie No 838, Umeå University; 2003
26. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
27. Wiholm BE, Åsberg M, Jacobsen K, et al. A rating scale for emotional distress in patients with malignant diseases. Acta Psychiatr Scand 1984; 70:378–388
28. Rödén-Jüllig Å, Britton M, Gustafsson C, et al. Validation of four scales for the acute stage of stroke. J Intern Med 1994;236:125–136
29. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–65
30. Lingjærde O, Ahlfors UG, Bech P, et al. The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand 1987;76(suppl 334):1–79
31. Montgomery SA. The failure of placebo-controlled studies. ECNP Consensus Meeting, September 13, 1997, Vienna, Austria. European College of Neuropsychopharmacology. Eur Neuropsychopharmacol 1999;9:271–276
32. Ekselius L, von Knorring L, Eberhard G. A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. Int Clin Psychopharmacol 1997;12: 323–331
33. Åberg-Wistedt A, Ågren H, Ekselius L, et al. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. J Clin Psychopharmacol 2000;20:645–652
34. Schneider LS, Nelson JC, Clary CM, et al. An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. Am J Psychiatry 2003;160: 1277–1285
35. Tollefson GD, Bosomworth JC, Heiligenstein JH, et al. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. Int Psychogeriatr 1995;7:89–104
36. Preskorn SH, Lane RM. Sertraline 50 mg daily: the optimal dose in the treatment of depression. Int Clin Psychopharmacol 1995;10:129–141
37. Carson AJ, MacHale S, Allen K, et al. Depression after stroke and lesion location: a systematic review. Lancet 2000;356:122–126
38. Carota A, Staub F, Bogousslavsky J. Emotions, behaviours and mood changes in stroke. Curr Opin Neurol 2002;15:57–69
39. Kemp AH, Gray MA, Silberstein RB, et al. Augmentation of serotonin enhances pleasant and suppresses unpleasant cortical electrophysiological responses to visual emotional stimuli in humans. Neuroimage 2004;22: 1084–1096
40. House AO, Hackett ML, Anderson CS, et al. Pharmaceutical interventions for emotionalism after stroke. In: The Cochrane Library, Issue 3, 2004. Chichester, England: Wiley
41. Burns A, Russell E, Stratton-Powell H, et al. Sertraline in stroke-associated lability of mood. Int J Geriatr Psychiatry 1999;14:681–685
42. Turner-Stokes L. Poststroke depression: getting the full picture. Lancet 2003;361:1757–1758

Appendix 1. Montgomery-Åsberg Depression Rating Scale (MADRS) and Emotional Distress Scale (EDS) Items

MADRS	EDS
Sadness (r)	Sadness (r)
Apparent sadness (o)	Apparent sadness (o)
Inner tension (r)	Inner tension (r)
Reduced sleep (r)	Reduced sleep (r)
Reduced appetite (r)	Reduced appetite (r)
Concentration difficulties (r)	
Lassitude (r)	Lassitude (r)
Inability to feel (r)	Inability to feel (r)
Pessimistic thoughts (r)	
Suicidal thoughts (r)	
	Aches and pains (r)
	Fatigability (r)
	Hostile feelings (r)
	Worrying over trifles (r)
	Labile emotional responses (o)
	Lack of appropriate emotion (o)
	Hostility (o)

Abbreviations: o = observed, r = reported.