# Sertraline treatment of post-stroke major depression: an open study in patients with moderate to severe symptoms

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**Summary**

**First-ever stroke patients (n=20) with a DSM-IV diagnosis of major depressive disorder (MDD) were included in an open-label study and received a single oral dose (50-100 mg) of the selective serotonin reuptake inhibitor sertraline. At days 0, 7, 14, 28, 42, and 56, a psychometric test battery comprising the Hamilton rating scales for depression and anxiety, the Mini Mental State Examination and the Barthel Index was administered. At the endpoint, 9 (45%) of the subjects were no longer depressed, 4 (20%) presented minor depression, and 7 (35%) still suffered from MDD. Considering the whole group of treated patients, depression and anxiety symptoms were found to decrease continuously and cognitive and functional performances to improve continuously during the treatment. Furthermore, differences between the values recorded by the treatment responders and non responders at the end of follow up were highly significant ($p<0.02$ for all comparisons). This report suggests that sertraline treatment of post-stroke MDD could be effective and well tolerated. However, non responders to the treatment are at risk of poor outcome. Double blind studies with a greater number of patients are necessary to confirm these preliminary results.**

*KEY WORDS: anxiety, cognition, depression, sertraline, stroke.*

## Introduction

Depression and anxiety are very common features of neurological diseases (1,2), appearing, in particular, to be the most common complications of stroke (1). Given that these neuropsychiatric disorders can impair cognitive level and activities of daily living (ADL), especially during the first months after the acute event, appropriate treatment is often required to improve the rehabilitation outcome (1,3).

Some studies have shown that the tricyclic nortryptiline is an effective treatment of post-stroke depression (PSD) and improves depression, anxiety, cognition and ADL functions (4-7). Other studies investigating the selective serotonin reuptake inhibitors (SSRIs) fluotexine (8) and citalopram (9) have indicated that these new generation antidepressants may have a role in the treatment of PSD. However, data currently available on comorbid anxiety in PSD are insufficient (i.e., only one study comparing nortriptyline and fluoxetine (5) has investigated this issue), while data on cognition are discordant (1,5,8).

The problem of treating elderly patients with tricyclic antidepressants, especially subjects with comorbid neurological, cerebrovascular and cardiovascular diseases, has been widely debated in the literature (2,10). Even though it seems that nortriptyline could be effective in patients with PSD (4), clinicians often maintain that SSRIs are safer in elderly depressed patients (2,11). In addition, tricyclics are associated with a higher rate of contraindications to treatment than SSRIs (12). Unfortunately, the efficacy of one drug that is potentially safe and effective in the treatment of mood and anxiety disorders, namely sertraline, has so far been studied only in relation to stroke-associated lability of mood (13) and, indirectly, in post-stroke patients with major depressive disorder (MDD) (14). There are various reasons why sertraline might be considered a first-line drug in the treatment of post-stroke depression and anxiety syndromes: its linear pharmacokinetic profile (15,16), its mild inhibition of cytochrome P450 isoenzyme systems (16,17), its low potential for pharmacokinetic drug interaction (17,18), its anti-platelet effects (19), its good tolerability (16,17) and the resulting mortality benefits after stroke (19). This last issue is particularly important because previous scientific literature has stated that depression is a risk factor for later stroke morbidity and mortality, possibly due to low compliance with disease management protocols and/or increased rates of vascular disease (20). These two mechanisms could be aetiological factors in patients with PSD, too. Hence, it could be argued that antidepressant drugs with good cardiovascular effects may both improve depression and reduce stroke severity. In addition, the well-documented dopamine action of sertraline (21) may act by improving the patients' cognitive level, which is very often impaired in the post-stroke period, especially when symptoms of depression are present (22).

This open-label study of sertraline treatment of PSD patients was conducted in order to investigate the drug's possible effectiveness on neuropsychiatric symptoms of depression and anxiety, and its effects on ADL functions and global cognitive levels during the rehabilitation period, considering both the overall group of pa-

tients and the responders and non responders to the antidepressant treatment.

## Materials and methods

*Treated subjects*

The subjects were recruited at the IRCCS Fondazione Santa Lucia Hospital, a neuro-rehabilitation centre serving the population of central and southern Italy. The data from 13 of these patients have been partially analysed in another recent study (14). The inclusion criteria were:
i) first-ever stroke diagnosis according to the Stroke Data Bank (23); in particular, the diagnosis of stroke was based on the clinical history and magnetic resonance or computerized tomography findings;
ii) time elapsed since the acute event (>14 days and <6 months);
iii) DSM-IV diagnosis of MDD as obtained from the Structured Clinical Interview for DSM-IV–Patient edition (SCID-P–DSM-IV) (24) administered to the patients and, when necessary, to the caregivers;
iv) moderate to severe symptoms of depression, reflected in scores >14 on the Hamilton Rating Scale for Depression-17 items (HRSD) (25).
The exclusion criteria were:
i) severe aphasia or cognitive deficit;
ii) a previous history of head trauma or other neurological disease(s);
iii) major medical illness(es);
iv) a personal or family history of psychiatric illness, evinced by the SCID administered to the patients and the caregivers.

*Neuropsychiatric, cognitive and functional assessment*

Two clinical psychiatrists, trained until they demonstrated an inter-rater reliability of 0.80 (κ coefficient) for all the psychometric tests used and unaware of the aims of the study, randomly interviewed the patients. They used the SCID-P at baseline (day 0) and at the end of the follow up (day 56) to establish the DSM-IV diagnoses of MDD and minor depression (MIND). The same psychiatrists administered, at days 0, 7, 14, 28, 42, and 56, a psychometric test battery comprising: the HRSD to assess symptoms of depression, the Hamilton Rating Scale for Anxiety-14 items (HRSA) (26) to assess symptoms of anxiety, the Mini Mental State Examination (MMSE) (27) to assess the global cognitive level, the Barthel Index (BI) (28) for functional evaluation of ADL, and the Clinical Global Impression Scale (CGI) (29). A clinical neurologist assessed neurological symptoms at baseline.

*Treatment regimen*

After the baseline evaluation, the patients received a single oral dose (50mg) of the SSRI sertraline daily at 9.00 a.m. At day 28 of treatment, it was decided to raise the dosage from 50 to 100 mg in the 9 patients deemed, on the basis of clinical findings (i.e., CGI global severity score ≥ 4, global improvement score ≥ 3 and efficacy index rated as mild or unmodified), to be non responders to the antidepressant.

Two of the original 22 patients entering the study discontinued the treatment after the fourth evaluation (day 28) because of adverse events, respectively arrhythmia and seizure. The first event was deemed "not related" to the treatment and "unlikely" to be attributable to the treatment. The second event was deemed "related" to the treatment and a relationship with the latter was considered "possible". When treating post-stroke patients it is, in fact, important to bear in mind that coexistent diseases are very common (30) and that adverse events are often not related to the psychiatric pharmacological treatment. No patients discontinued treatment because of side effects and at no time-point of treatment did side effects interfere with the functions of the patients as assessed by the CGI. Thus, 20 patients treated with sertraline were considered in this study. Their sociodemographic and clinical characteristics are described in Table I.

Table I - Sociodemographic and baseline clinical variables of 20 inpatients with post-stroke MDD.

| Characteristics | Mean±SD |
|---|---|
| Age (years) | 66.7±11.3 |
| Education (years) | 10.3±5.1 |
| Time elapsed since the acute stroke (days) | 85.3±64.8 |
| HRSD-17 items | 21.75±5.82 |
| HRSA-14 items | 22.45±7.50 |
| MMSE | 19.60±8.85 |
| BI | 41.00±32.59 |
| | n. (%) |
| Gender (female) | 13 (65) |
| Marital status (married) | 18 (90) |
| Side of stroke | |
| bilateral | 2 (10) |
| right | 9 (45) |
| left | 9 (45) |
| Lesion location | |
| cortical | 6 (30) |
| subcortical | 10 (50) |
| mixed | 4 (20) |
| Ischaemic lesion | 17 (85) |
| Neurological symptoms | |
| motor weakness | 20 (100) |
| sensory symptoms | 17 (85) |
| visual field deficit | 2 (10) |
| aphasia | 7 (35) |

Abbreviations: MDD=major depressive disorder; HRSD= Hamilton Rating Scale for Depression; HRSA=Hamilton Rating Scale for Anxiety; MMSE=Mini Mental State Examination; BI=Barthel Index.

*Statistical analyses*

Student's t test was used to detect differences in means for continuous variables. Differences in HRSD, HRSA, MMSE and BI scores during sertraline treatment within the group of patients were tested for significance by using, for each score, a repeated measures analysis of variance (ANOVA) with time as a within subjects factor with six levels and Fisher's protected least significant difference (PLSD) post-hoc tests were performed in order to locate the time points at which mean values differed significantly from the baseline value.
Clinical response to treatment was defined as a >50% decrease in the depression score (as measured by HRSD) from baseline to the end of the follow up.

## Results

The SCID administered to the patients at the end of the follow up indicated that 9 (45%) of the subjects were no longer depressed, 4 (20%) were affected by MIND, and 7 (35%) still suffered from MDD.
Table II reports the mean HRSD, HRSA, MMSE and BI values of the stroke patients during the sertraline treatment.
Considering the whole group of treated patients, depression and anxiety symptoms were found to decrease continuously during the treatment. Repeated measures ANOVAs revealed a highly significant time effect for HRSD ($F=10.77$; $df=19,5$; $p<0.0001$), and HRSA ($F=3.72$; $df=19,5$; $p=0.004$) scores. Repeated measures ANOVAs applied to the MMSE and BI scores demonstrated that cognitive and functional (ADL) performances improved continuously during the antidepressant treatment ($F=2.31$; $df=19,5$; $p<0.05$ and $F=4.52$; $df=19,5$; $p=0.001$ respectively). Fisher's PLSD post-hoc tests clarified that, in the overall group of patients, changes between day 0 and subsequent time points reached statistical significance from day 14 in the case of the HRSD ($p=0.0005$) and HRSA ($p=0.0133$), from day 28 in the case of the MMSE ($p=0.0171$), and from day 7 in the case of the BI (0.0366).

*Responders and non responders*

On the basis of clinical response to the antidepressant treatment, 10 (50%) of the treated subjects were classified as responders at the end of the follow up.
Baseline values of HRSD and HRSA did not differ between responders (21.9±6.1 and 20.2±4.7 respectively) and non responders (21.6±5.8 and 24.7±9.2 respectively).
Table III (see over) shows the MMSE and BI values of the responders and non responders and describes statistical differences.
Considering the overall results of the responders and of the non responders at the end of follow up, it is interesting to note that both MMSE and BI scores differed between the two groups.
Finally, comparisons performed separately in the two groups, i.e., the patients who were responders and those who were non responders to the antidepressant treatment, revealed that only the treatment responders recorded statistically significant differences in MMSE and BI values at later timepoints vs MMSE and BI values at baseline. In particular, ADL improved from day 7 ($p=0.0444$), while improvement of global cognitive level became significant at day 56 ($p=0.0185$).

## Discussion

In this exploratory study, the effectiveness of the SSRI sertraline on depression, anxiety, cognitive level and ADL functions in a sample of patients with post-stroke MDD was analysed. The main finding was that, in the whole group of subjects, reduction of clinically-rated depression and anxiety was apparent from day 14 of treatment. Furthermore, the improvement of ADL func-

Table II - Mean HRSD, HRSA, MMSE and BI scores of 20 post-stroke MDD inpatients during sertraline treatment.

| Day of treatment | Scale (mean ± SD) | | | |
|---|---|---|---|---|
| | HRSD | HRSA | MMSE | BI |
| 0 (baseline) | 21.7±5.8 | 22.4±7.5 | 19.6±8.8 | 41.0±32.6 |
| 7 | 20.9±5.8 | 22.5±7.6 | 20.4±8.4 | 50.0±33.3* |
| 14 | 16.3±5.6* | 17.6±8.2* | 21.1±9.0 | 53.7±32.1 |
| 28 | 14.4±6.0 | 18.3±10.6 | 22.1±7.5* | 55.2±36.0 |
| 42 | 15.4±8.2 | 18.8±12.2 | 22.0±6.9 | 55.7±36.6 |
| 56 (end of follow up) | 13.2±7.1 | 16.2±10.5 | 22.5±7.1 | 59.2±34.8 |

Abbreviations: SD=standard deviation; MDD=major depressive disorder; HRSD=Hamilton Rating Scale for Depression; HRSA=Hamilton Rating Scale for Anxiety; MMSE=Mini Mental State Examination; BI=Barthel Index.
Repeated measures ANOVA (Fisher's PLSD post-hoc comparisons): * first statistically significant improvement ($p<0.05$) vs day 0.

tions was even more rapid, being apparent from day 7, while cognitive impairment improved from day 28 of treatment. On the basis of DSM-IV psychiatric diagnoses present after the 56 days of sertraline treatment here investigated, 45% of patients were found to have recovered totally, 20% to present "residual" depression (i.e., MIND), and 35% still to be affected by MDD. Globally, the treatment was well tolerated: no side effect interfered with the patients' functions and this favourable profile is in accordance with the finding of a previous randomized, double-blind, study of late-life depression associated with vascular disease (31).

Interestingly, when the clinical response was defined as a greater than 50% decrease in HRSD score from baseline to the end of follow up, cognitive level and ADL functions were found to improve in the 10 responders. On the contrary, the 10 non responders did not show improvements in these areas and were still very impaired at the end of follow up.

Before discussing the results it is important to draw attention to the limitations of the study, i.e., the relatively small number of subjects included, the use of an open-label treatment procedure, and the assessment of cognitive level using the MMSE, which is able to provide information only on the global cognitive level. Also, unlike the patients considered in other studies, who suffered from mild to moderate depression (5,6) and were less cognitively (5,6,8) and perhaps less functionally (5,6,8,9) impaired than our subjects, the subjects included here presented moderate to severe symptoms of depression and were cognitively and functionally quite severely impaired. Thus, the results of this study should be considered cautiously and should not be generalized to all patients with PSD. On the other hand, the homogeneity of the sample's characteristics increases the clarity of the results, which are in line with those of other studies in which cognitive level (6) and ADL functions (7) improved in responders to antidepressant treatment with nortryptiline and in patients treated with placebo whose depressive symptoms remitted. In addition, in other naturalistic studies, ADL functions (32) and cognitive performance (33) improved only in depressed subjects whose symptoms of depression remitted.

To better understand this issue, we must take into account the emergence, in the scientific literature on the relationship between PSD and cognitive impairment, of two opposite schools of thought: one considers depression as a secondary consequence of cognitive impairment (34), the other that the two are inter-linked and that cognitive impairment is clearly reduced when depression is treated successfully (6) or when depression regresses naturally (33). In addition, the concept that depression influences functional recovery has already been described (35). One recent paper, in particular, highlights the fact that untreated patients with PSD showed a poor rehabilitation outcome compared with patients treated with the antidepressant fluoxetine (36).

Thus, our study confirms the hypothesis that cognitive level and ADL functions improve during antidepressant treatment and after remission of PSD (6). Furthermore, given that improvement of cognition and ADL functions was observed only in the treatment responders, our results are in line with the theory of cognitive and functional deterioration related to primary depressive disorder (6,33,36).

However, it is worth making a consideration on the pharmacological mechanism of the SSRI here used, namely sertraline. Indeed, in previous studies, the SSRI fluoxetine has not appeared to be effective in reducing cognitive impairment in patients with PSD (5,8). It is thus possible that the dopaminergic action (i.e., dopamine reuptake inhibition) of sertraline (21) may partially explain the different action of these two SSRIs, fluoxetine and sertraline, on the cognitive performance in patients with PSD. These differing results may also

Table III - Cognition and ADL scores in 20 post-stroke MDD patients during sertraline treatment (10 responders and 10 non responders).

| Day of treatment | Scale (mean ± SD) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | MMSE | | Unpaired comparison | | BI | | Unpaired comparison | |
| | Responders | Non responders | t | p | Responders | Non responders | t | p |
| 0 (baseline) | 22.6±3.2 | 16.6±2.0 | 1.57 | 0.133 (NS) | 44.5±11.1 | 37.5±9.9 | 0.47 | 0.644 (NS) |
| 7 | 23.3±2.7 | 17.6±2.4 | | | 56.0±9.2* | 44.0±11.9 | | |
| 14 | 24.0±2.8 | 18.2±2.7 | | | 61.5±8.5 | 46.0±11.5 | | |
| 28 | 25.8±1.3 | 18.5±2.7 | | | 71.0±8.6 | 39.5±12.0 | | |
| 42 | 25.7±1.1 | 18.4±2.4 | | | 74.0±8.2 | 37.5±11.8 | | |
| 56 (end of follow up) | 26.7±1.1* | 18.3±2.4 | 3.21 | 0.005 | 77.0±7.5 | 41.5±11.4 | 2.60 | 0.018 |

Abbreviations: SD=standard deviation; NS=not significant; MDD=major depressive disorder; ADL=activities of daily living; MMSE=Mini Mental State Examination; BI=Barthel Index.
Repeated measures ANOVA (Fisher's PLSD post-hoc comparisons): * first statistically significant improvement ($p<0.05$) vs day 0.

be explained on the basis of effect size; in other words, previous failure to detect cognitive improvement may be due to small numbers of subjects included in the studies (6). This hypothesis is not, however, supported by our small-sample study. Our final hypothesis is that, in the event of sertraline treatment only, the drug's parallel actions on the serotonergic system – with the resultant improvement of the clinical dimension of depression – and on the dopaminergic system – with the enhancement of the dopaminergic transmission in cortical and subcortical sites (37,38) – may act by improving cognition. Regarding the effect of the antidepressant treatment on functional recovery, conceptually this may be due to the serotonergic action of the SSRIs. Indeed, previous studies have reported that the norepinephrine reuptake blocker maprotiline failed to improve functional recovery (35), while the SSRI fluoxetine did improve it (35,36). The results of the present study constitute further evidence that drugs acting on the serotonergic system may improve ADL functions.

In conclusion, this report suggests that sertraline treatment of post-stroke MDD could be effective and well tolerated in patients with moderate to severe depressive symptoms. However, future double-blind studies with longer follow up are necessary to confirm this evidence of sertraline efficacy in PSD. Furthermore, this study confirms that patients who are treatment non responders are at risk of poor outcome.

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