Citalopram Versus Sertraline in Late-Life Nonmajor Clinically Significant Depression: A 1-Year Follow-Up Clinical Trial

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Objective: The aim of this study was to compare over 1 year the effect of sertraline and citalopram on depressive symptoms and cognitive functions of nondemented elderly patients with minor depressive disorder and subsyndromal depressive symptomatology.

Method: We recruited 138 consecutive nondemented outpatients of either sex, aged ≥ 65 years, who were classified as meeting research criteria for minor depressive disorder or subsyndromal depressive symptomatology using the Structured Clinical Interview for DSM-IV. Subjects were assigned to receive citalopram 20 mg/day (66 patients) or sertraline 50 mg/day (72 patients) orally for 1 year. Patients were assessed at baseline and after 1, 2, 3, and 6 months and at 1 year by raters masked with regard to patients' treatment assignments. The Hamilton Rating Scale for Depression, the Geriatric Depression Scale, and the Global Assessment of Functioning were administered to assess the course of depressive symptoms and social functioning during the study. Cognitive measures included Trail Making Test-Parts A and B, Wechsler Memory Scale, Mini-Mental State Examination, and a verbal fluency test. Data were collected from March 2000 to March 2003.

Results: The overall completion rate was 72%. Both treatments induced a significant, sustained, and comparable improvement in depressive symptoms and in social functioning. Nearly half of the subjects in the 2 groups achieved remitter status at study endpoint. Significant within-group improvements also were observed in all cognitive measures. Both drugs were well tolerated during the whole study period.

Conclusion: Our results suggest that sertraline and citalopram can improve depressive symptoms and cognitive functions of minor depressive disorder and subsyndromal depressive symptomatology in elderly nondemented patients.

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Depression in the elderly is associated with serious health consequences, such as increased mortality related to suicide and medical illness, amplification of disability due to medical and cognitive disorders, and increased health care use and burden.[1] Although major depression is the most studied and well-defined depressive syndrome, it is clear from the emerging literature that nonmajor forms of clinically significant depression, and particularly minor depressive disorder and subsyndromal depressive symptomatology, are responsible for considerable psychosocial impairment and functional compromise.[2–4]

Minor depressive disorder is now included in the DSM-IV-TR[5] as a "potential category," with a set of diagnostic research criteria proposed for further studies. The essential feature of the disorder is 1 or more periods of depressive symptoms that are identical to major depressive episodes in duration (2 weeks or longer), but that involve fewer than 5 symptoms and less impairment.

Subsyndromal depressive symptomatology is operationally defined as any 2 or more simultaneous symptoms of depression present for most or all of the time for at least 2 weeks, associated with evidence of social dysfunction, occurring in individuals who do not meet criteria for the diagnosis of minor, major, or dysthymic depressive disorder.[6]

Although all levels of depressive symptom severity are observed in the over 65 years age group, there is an emerging consensus, based on both community and clinical populations, that the predominant form of depression in the elderly population is subthreshold to major depres-

sion.[7,8] This is particularly true in medical and primary care settings, where older persons are most likely to be seen and treated.[2,9,10]

The literature pertaining to the neurobiology and neuropsychology of clinically significant nonmajor depression is limited. In a magnetic resonance imaging (MRI) study, Kumar and colleagues[11] demonstrated that patients with late-onset minor depression had smaller prefrontal lobe volumes than age-matched nondepressed control subjects. Preliminary unpublished observations suggest that in domains such as verbal recall, executive functioning, processing speed, maintenance of set, and working memory, elderly patients with minor depression have neuropsychological impairment levels that fall between those of patients with major depression and control subjects.[4] Polysomnographic findings in patients with subthreshold depression demonstrated shortened rapid eye movement (REM) latency, increased REM sleep, redistribution of REM to the first part of the night, classic diurnality, high rate of family history of mood disorders, and positive response to antidepressant medication and sleep deprivation.[12] These findings seem to indicate that patients with nonmajor forms of depression present with specific neurobiological and neuropsychological substrates that are comparable with the major depression group but significantly different from control subjects.

There is abundant evidence in the literature that pharmacotherapy is an effective treatment for major depressive disorder in the elderly.[13,14] In particular, selective serotonin reuptake inhibitors (SSRIs) appear to be as efficacious as traditional agents but more tolerable and easier to use in geriatric depressed patients.[15]

Despite the high prevalence and associated functional impairment, the benefit of depression-specific treatment for minor depressive disorder and subsyndromal depressive symptomatology remains controversial. To date, evaluations of treatment in clinically significant nonmajor depression are limited in number, and this is particularly true for elderly patients.[16,17] To our knowledge, in the only study focused exclusively on older persons,[18] paroxetine showed moderate benefit for depressive symptoms and mental health functioning in severely impaired elderly patients with minor depression.

Although there are similarities between geriatric and nongeriatric depression with regard to phenomenology and other clinical features, there are also important differences, such as cognitive and medical aspects, that need to be considered in the independent study of elderly patients.[19–21] However, no published study to date has investigated cognitive disabilities and the effect of antidepressant treatment on cognitive functions in patients with minor depressive disorder and subsyndromal depressive symptomatology.

The aim of the present study was to compare the effect of 2 SSRIs, sertraline and citalopram, on depressive symptoms and cognitive functions in nondemented elderly patients with minor depressive disorder or subsyndromal depressive symptomatology in a long-term single-blind trial lasting 1 year. We also investigated the safety and the overall tolerability of both drugs.

METHOD

This study was conducted at the Department of Neurosciences, Psychiatric Section, University of Turin, Turin, Italy. Over a 3-year period, we recruited 138 consecutive elderly outpatients with minor depressive disorder or subsyndromal depressive symptomatology of either sex, aged 65 years or older. Minor depressive disorder was defined as feeling sad or "blue" or anhedonic plus at least 1 other symptom of a major depressive episode as presented in the DSM-IV-TR list of symptoms. Subsyndromal depressive symptomatology was defined as having 2 or more symptoms of a major depressive episode excluding the A criteria for major depressive episode as defined by DSM-IV-TR (feeling sad, blue, or anhedonic). The diagnoses of minor depressive disorder and subsyndromal depressive symptomatology were assigned to subjects who met these criteria on the Structured Clinical Interview for DSM-IV Disorders (SCID)[22] and were confirmed by 2 expert clinicians (P.R., E.R.), who were also involved in patient treatment assignment.

Subjects had to present a baseline total score of 10 or more[4] on the 17-item Hamilton Rating Scale for Depression (HAM-D).[23] The exclusion criteria included any other current Axis I or Axis II psychiatric disorder, impairment and decline of global cognitive functions detected through Mini-Mental State Examination (MMSE),[24] a score of ≥ 12 on the Alzheimer's Disease Assessment Scale-Cognitive Subscale,[25] and any acute or unstable medical or neurologic condition that might interfere with safety or the interpretation of results. In addition, patients were excluded if they had taken any psychotropic medication within 1 month before entering the study.

Written informed consent was obtained from all participants after the trial procedures and possible side effects of the treatment had been fully explained to the subjects. The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Data were collected from March 2000 to March 2003.

At study entry, demographic information, medical history, characteristics of the current symptomatology, and psychiatric and family history were obtained. Moreover, full physical and neurologic examinations and measurement of vital signs were performed.

According to the study protocol, patients fulfilling the inclusion criteria were alternatively allocated to 1 of 2 therapeutic arms: citalopram 20 mg/day or sertraline 50 mg/day, configuring a quasirandomized trial. Both study drugs were orally administered in the morning for 1 year.

No other psychoactive drugs were allowed during the treatment period. Stabilized treatments for concomitant systemic diseases were allowed in both groups.

All patients were scheduled for 6 visits over 1 year, occurring at baseline and after 1, 2, 3, and 6 months and at 1 year. Visits took place in the outpatient setting of our clinic and included symptom and cognitive assessments, a review of adverse effects, and clinical management. During the medication trial, patients were not receiving any specific psychological treatment.

Patients were assessed by 2 psychiatrists and 2 psychologists who were masked with regard to the patient's treatment assignment, and patients were instructed not to reveal their current treatment to these investigators. In an attempt to reduce interrater variability, all raters were trained to administer the psychometric tools according to common standards prior to study enrollment.

Clinical measurements included both interviewer-rated and patient-rated instruments: HAM-D, Geriatric Depression Scale (GDS),[26] and DSM-IV-TR Global Assessment of Functioning (GAF).[5] We used 2 different rating scales for depressive symptoms—1 clinician-rated and the other self-rated—in order to strengthen any conclusions drawn from score changes during active treatment.

The patients were administered 5 cognitive measures. Trail Making Test-Part A (TMT-A),[27] which requires subjects to connect a series of consecutively numbered circles scattered about a page, was used to measure psychomotor speed. Trail Making Test-Part B (TMT-B)[27] was used to assess executive functioning and requires subjects to connect a series of numbered and lettered circles, alternating between the 2 sequences, allowing assessment of mental flexibility in managing more than 1 stimulus at a time and in shifting the course of an ongoing activity. Semantic retrieval was estimated by a verbal fluency test (VF),[28] in which the patient is asked to name as many words belonging to a specific category (animals, colors, fruits, towns) as possible; 2 minutes are allowed for each category. Wechsler Memory Scale (WMS)[29] was used to measure memory and learning abilities. The MMSE was used to evaluate global cognitive performance. Each research tool was administered at baseline and at each follow-up visit.

The clinical safety of treatment was assessed by spontaneous notification and an open-ended inquiry of adverse events, a full physical examination, and measurement of vital signs at each visit. Adverse events and drug compliance were carefully monitored throughout the study. Patients were withdrawn from the trial if they requested discontinuation or by the physician on account of an adverse event, lack of efficacy, or uncooperativeness.

All data were analyzed by means of SAS System V.8.2 (Cary, N.C.). Quantitative variables are expressed as mean and 95% confidence interval, and qualitative variables are expressed as absolute value and percentage, unless otherwise noted. Group comparisons on baseline demographic and clinical characteristics (sex, age, onset of depression before or after age 60 years, employment, diagnosis) used Kruskal-Wallis test for continuous variables and χ^2 test for categorical variables to test lack of balance between groups.

Changes in the continuous outcome measures were assessed by comparing the pooled results of groups at each follow-up assessment with the baseline results in order to evaluate the overall effect of the medications, and between groups at any follow-up by means of a multivariate, linear, regression model for repeated measures, with time, treatment, and their interaction as covariates.[30] The categorical variables, such as remission rate and incidence of adverse events, were compared between the 2 groups using the χ^2 test or the Fisher exact test when appropriate. Remission was defined by a final HAM-D score of less than 7. Remission rates were calculated using the intention-to-treat analysis, i.e., selecting the set of patients who were assigned to treatments and received at least 1 evaluation after baseline assessment. Baseline HAM-D observations for patients who withdrew prematurely from the study were carried forward to endpoint. All statistical tests were 2-sided.

RESULTS

Table 1 shows the demographic and clinical characteristics of the study population. A total of 138 patients (39 women and 99 men) were recruited. Sixty-six patients (16 women and 50 men) were assigned to treatment with citalopram 20 mg/day, and 72 subjects (23 women and 49 men) were assigned to treatment with sertraline 50 mg/day.

Contact was maintained with all patients, and any dropouts from the 2 groups were recorded. The mean completion rate was 72%. Ten patients in the citalopram group (6 patients before and 4 patients after the second assessment) and 8 patients assigned to sertraline treatment (all before the second assessment) stopped because of adverse reactions. Dropouts due to adverse reactions were similar for the 2 treatment groups: 7 patients stopped for nausea, 1 for headache, and 2 for dizziness in the citalopram-treated group, whereas in the sertraline-treated group, 5 patients were withdrawn for nausea, 1 for headache, and 2 for dizziness.

Eight patients who received citalopram and 12 who received sertraline dropped out of the trial for inadequate compliance (2 for lack of efficacy and 6 for unknown reasons in the citalopram group and 4 for lack of efficacy and 8 for unknown reasons in the sertraline-treated patients). All noncompliant patients withdrew after the second assessment.

Table 2 shows the assessment data for the 2 treatment groups at baseline. No significant between-group differences were detected on any baseline demographic or

Table 1. Demographic and Clinical Characteristics of 138 Nondemented Elderly Patients Who Received Citalopram or Sertraline

Variable	Citalopram (N = 66)	Sertraline (N = 72)	Statistic[a]	p Value
Gender, male/female, N	50/16	49/23	1.0075	.315
Age, y, mean (95% CI)	72.4 (71.0 to 73.8)	71.9 (71.0 to 73.8)	0.2806	.5963
Employment, yes/no, N	13/53	14/58	0.0014	.970
Diagnosis, N			3.4869	.062
Minor depressive disorder	38	30		
Subsyndromal depressive symptomatology	28	42		
Onset of depression, age, N			0.0267	.8702
≤ 60 y	22	26		
> 60 y	44	46		

[a]For gender ratio, employment, diagnosis, and onset of depression, the statistic is the χ^2 test with df = 1. For age, the statistic is the Kruskal-Wallis test with df = 1.

Table 2. Assessment Data for the Citalopram and Sertraline Treatment Groups at Baseline[a]

Variable	Citalopram (N = 66)	Sertraline (N = 72)	Statistic[b]	p Value
Hamilton Rating Scale for Depression	12.9 (12.4 to 13.5)	12.9 (12.4 to 13.4)	0.0009	.9759
Geriatric Depression Scale	15.7 (14.6 to 16.8)	15.9 (14.5 to 17.4)	0.1547	.6941
Global Assessment of Functioning	64.3 (63.5 to 65.2)	64.6 (63.8 to 65.3)	0.1061	.7446
Mini-Mental State Examination	27.0 (26.5 to 27.6)	26.7 (26.0 to 27.3)	0.4658	.4949
Trail Making Test-Part A	86.3 (83.5 to 89.0)	86.5 (83.6 to 89.4)	0.0707	.7903
Trail Making Test-Part B	284.7 (257.9 to 311.5)	272.8 (247.2 to 298.4)	0.5094	.4754
Wechsler Memory Scale	82.3 (80.1 to 84.6)	80.2 (77.3 to 83.1)	1.7065	.1914
Verbal fluency test	12.9 (12.1 to 13.6)	12.5 (11.6 to 13.4)	0.9148	.3388

[a]All data are presented as mean (95% CI).
[b]For all variables, the statistic is the Kruskal-Wallis test with df = 1.

depression-related clinical variables or for symptom severity and cognitive performances.

Baseline cognitive assessment scores for patients involved in the study are contrasted with the Italian elderly general population data[28,31] in Table 3. In particular, our subjects had worse scores than archival normative data for VF and WMS.

Overall, both treatments induced a notable improvement of depressive symptoms during the trial. Significant decreases from baseline in HAM-D scores were observed for both groups of patients starting from month 1 and were sustained during the whole treatment period (Figure 1). No statistically significant differences were found at each assessment between the 2 treatments for this measure. At the end of the study, the mean total HAM-D score had fallen 55.0% in the citalopram group and 52.7% in the sertraline group. Analogous results were observed for the patient-rated GDS. For this scale, mean total scores at endpoint were 9.08 ± 5.57 for citalopram and 9.46 ± 4.45 for sertraline (β_2 = –0.0829, p = .8439).

No significant differences in achieving remission were observed at any timepoint between the 2 agents. After 1 month, 15% (10/66) of patients in the citalopram group and 22% (16/72) of patients in the sertraline group were classified as remitters (χ^2 = 0.886, df =1, p = .3466), whereas after 3 months, 35% (23/66) of the citalopram-treated group and 38% (27/72) of the sertraline-treated group achieved remitter status (χ^2 = 0.0957, df = 1, p = .7570). At the end of the follow-up, remission was achieved by 53% (35/66) of patients treated with citalopram and 42% (30/72) of patients treated with sertraline (χ^2 = 1.30, df = 1, p = .2537).

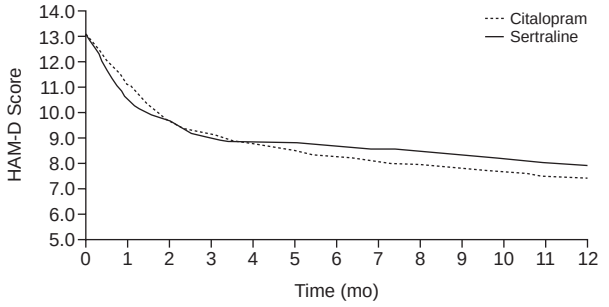
Table 3. Archival Normative Data for the Italian Elderly General Population Contrasted With Baseline Test Scores for 138 Nondemented Elderly Patients Involved in the Current Study[a–c]

Cognitive Test	Score
Trail Making Test-Part A	
Normative data (aged 70–79 y)	84.60 ± 23.76
Study sample	86.40 ± 11.70
Trail Making Test-Part B	
Normative data (aged 70–79 y)	336.80 ± 197.80
Study sample	278.50 ± 108.80
Verbal fluency test	
Normative data (aged 70–74 y)	16.42 ± 4.64
Study sample	12.70 ± 3.39
Wechsler Memory Scale	
Normative data, range	90–109
Study sample	81.20 ± 10.90

[a]Values expressed as mean ± SD unless otherwise specified.
[b]Data for the Italian general population from Spinnler and Tognoni[28] and Giovagnoli et al.[31]
[c]Mean age of the study sample: 72.1 y.

Both treatments were followed by within-group improvements in overall psychosocial functioning. From month 1 forward, statistically significant changes from

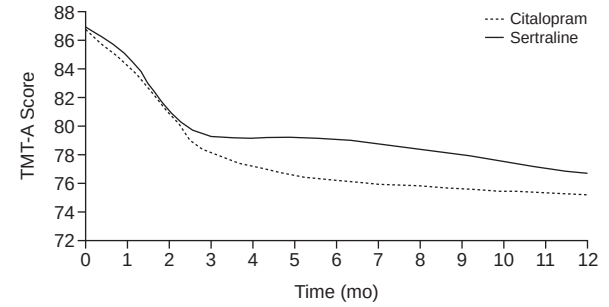
Figure 1. Changes in Hamilton Rating Scale for Depression (HAM-D) Scores Within the Study Period[a–d]



HAM-D	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	–2.2899	–1.6884	–1.2978	–0.6676	–0.3497
β_1 p Value	< .0001	< .0001	< .0001	< .0001	< .0001
β_2	–0.3144	–0.2109	–0.2008	–0.0715	0.0265
β_2 p Value	.4062	.5202	.5020	.7989	.9197

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 11.0262.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = –0.3497.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = 0.0265.

Figure 2. Changes in Trail Making Test-Part A (TMT-A) Scores Within the Study Period[a–d]

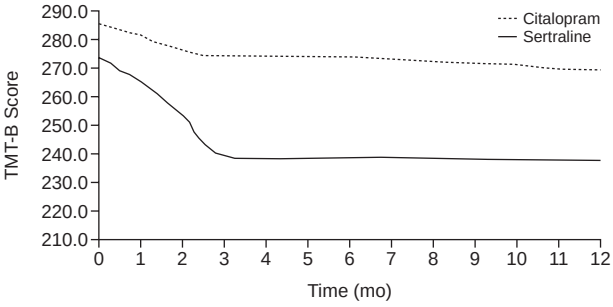


TMT-A	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	–2.2319	–2.9203	–2.7261	–1.4717	–0.7755
β_1 p Value	.1386	.0002	< .0001	< .0001	< .0001
β_2	0.4558	0.3704	0.5682	1.0293	1.0854
β_2 p Value	.7617	.7663	.6043	.3056	.2547

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 81.9358.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = –0.7755.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = 1.0854.

baseline in GAF scores were observed in both treatment groups. No statistically significant differences were found between the 2 treatments at each assessment for this variable. The mean GAF total scores at endpoint for both groups were greater than 71 (73.00 ± 4.39 for citalopram and 72.20 ± 4.76 for sertraline; $\beta_2 = –0.2957$, $p = .3839$), a score cutoff indicating no more than slight impairment in social or occupational functioning.

Figure 3. Changes in Trail Making Test-Part B (TMT-B) Scores Within the Study Period[a–d]



TMT-B	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	–6.1812	–7.3768	–7.8703	–4.0234	–1.9251
β_1 p Value	.6425	.2641	.0613	.0492	.0438
β_2	–13.8946	–16.8060	–21.2756	–23.9957	–25.3293
β_2 p Value	.2979	.1212	.0250	.0050	.0013

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 308.9500.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = –1.9251.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = –25.3293.

Significant within-group improvements were observed in all cognitive measures for the 2 study drugs during the trial. Changes from baseline for WMS were significant from month 1 forward, whereas a statistically significant improvement for TMT-A, VF, and MMSE was detected beginning with month 2 and for TMT-B from month 6 (Figures 2–6). Other than MMSE and TMT-B, no significant between-group differences in cognitive performances were found at each assessment. At the end of the follow-up, TMT-A, TMT-B, VF, and WMS scores for the 2 treatment groups were similar to archival normative data for the Italian general elderly population.

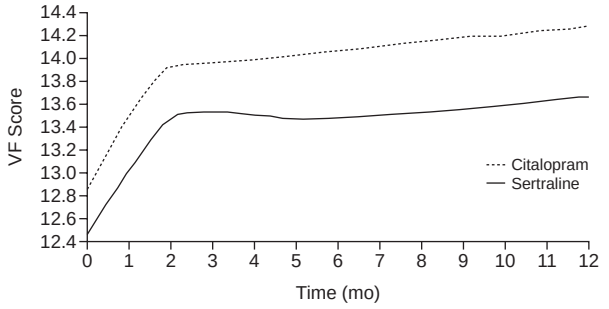
The most commonly reported and observed side effects related to medication are listed in Table 4. The proportion of patients experiencing at least 1 adverse event was similar for both groups. Concerning the prevalence of any specific side effect, no significant differences between groups were detected.

DISCUSSION

The present study was performed in elderly patients with minor depressive disorder and subsyndromal depressive symptomatology to assess the effects of 2 SSRI antidepressants for 1 year, including an evaluation of cognitive functions.

The results of this study seem to indicate that sertraline and citalopram at low doses are equivalent in reducing depressive symptomatology in a sample of elderly outpatients with minor depressive disorder and subsyndromal depressive symptomatology. Consistent and clini-

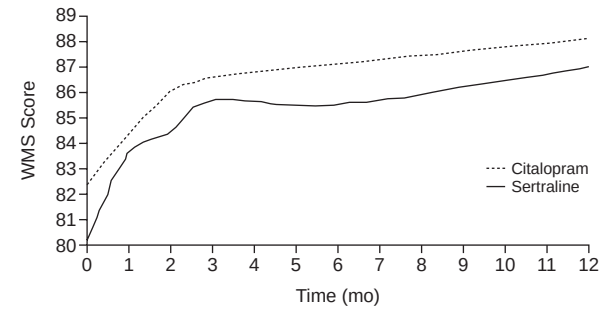
Figure 4. Changes in Verbal Fluency Test (VF) Scores Within the Study Period[a–d]



VF	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	0.5841	0.5040	0.3613	0.1570	0.0775
β_1 p Value	.1704	.0203	.0092	.0204	.0135
β_2	–0.4255	–0.4337	–0.4281	–0.4565	–0.4817
β_2 p Value	.3176	.2213	.1684	.1032	.0593

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 13.9355.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = 0.0775.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = –0.4817.

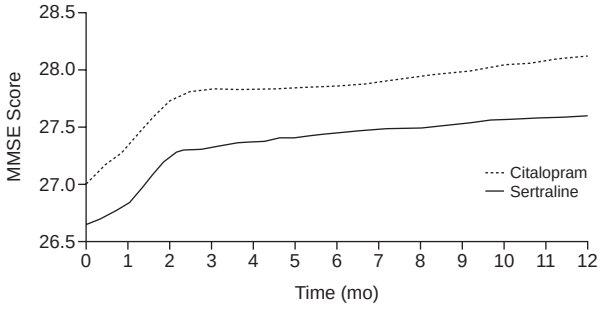
Figure 5. Changes in Wechsler Memory Scale (WMS) Scores Within the Study Period[a–d]



WMS	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	2.6812	1.9638	1.5855	0.7406	0.4018
β_1 p Value	.0420	.0025	< .0001	.0002	< .0001
β_2	–1.4280	–1.4790	–1.3362	–1.3927	–1.3466
β_2 p Value	.2767	.1614	.1397	.0859	.0711

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 85.4540.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = 0.4018.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = –1.3466.

Figure 6. Changes in Mini-Mental State Examination (MMSE) Scores Within the Study Period[a–d]



MMSE	Baseline vs. 1st mo	Baseline vs. 2nd mo	Baseline vs. 3rd mo	Baseline vs. 6th mo	Baseline vs. 12th mo
β_1	0.2638	0.3232	0.2557	0.1277	0.0698
β_1 p Value	.3632	.0157	.0015	.0007	< .0001
β_2	–0.4374	–0.4513	–0.4644	–0.4562	–0.4677
β_2 p Value	.1330	.0398	.0106	.0037	.0008

[a]Mixed linear regression for repeated measures, modeled as parameter = time drug.
[b]α (estimate of the intercept) = 27.8285.
[c]β_1 (estimate of the time-factor effect–angular coefficient) = 0.0698.
[d]β_2 (estimate of the drug-factor effect–angular coefficient) = –0.4677.

Table 4. Most Frequent Adverse Events in Patients Treated With Citalopram or Sertraline

	Citalopram (N = 66)		Sertraline (N = 72)			
Adverse Event	N	%	N	%	Statistic[a]	p Value
Nausea	16	24.2	13	18.1	0.7941	.373
Headache	7	10.6	7	9.7	0.0295	.864
Dizziness	10	15.2	7	9.7	0.9397	.332
Dyspepsia	8	12.1	8	11.1	0.0343	.853
Asthenia	3	4.5	4	5.6	0.2906	1.000
Sexual dysfunction	5	7.6	6	8.3	0.0269	.870
Other	4	6.1	8	11.1	1.1063	.293
At least 1 adverse event	35	53.0	35	48.6	0.2691	.604

[a]For asthenia, the statistic is the Fisher exact test. For all other adverse events, the statistic is the χ^2 test with df = 1.

cally significant improvements were noted for the 2 treatment groups on both interviewer-rated and patient-rated depression scales. It should be noted that nearly half of the subjects in the 2 therapeutic arms achieved HAM-D remitter status at study endpoint.

The fact that patients in both treatment groups continued to show improvement in their depressive symptoms throughout the 12 months of the study suggests that patience is warranted in the treatment of these older individuals. Results of major depression treatment studies in the elderly suggest that full clinical response may take longer than with younger patients.[21,32] Our data seem to suggest that, as in major depression, a switch of treatment after a relatively short period could be inadequate for the elderly patient suffering from minor depression.

An important aim of this study was to evaluate the effects of each treatment on psychosocial functioning. Psychopharmacology studies traditionally focus on symptom reduction. Only a small minority have assessed psychosocial adjustment, often significantly disrupted in depressed subjects. Quality of improvement is an important consideration in the treatment of depression, and the possibility of a differential effect between treatments, even if only in the social functioning domain, needs

to be examined.[33] When evaluating the global benefits of any antidepressant, the extent to which it offers improvements in symptomatology, as opposed to a return to normal levels of social functioning, is an important consideration.[34] In our study, treatment with sertraline or citalopram was followed by statistically significant improvements in overall psychosocial functioning; the difference between the 2 drugs was not noteworthy. GAF total scores at endpoint were restored to a level that indicated no more than a slight impairment in social or occupational functioning.

The assessment of overall and specific cognitive functions by numerous appropriate and specific tests showed that, in our sample of patients with minor depressive disorder and subsyndromal depressive symptomatology, cognitive performances were mostly worse at baseline than archival normative data for the Italian elderly general population.[28,31] Treatment with sertraline or citalopram was not followed by drug-related detrimental effect. Conversely, statistically significant improvements of cognitive functions, namely attention, memory, and executive functioning, were observed with both treatments. Both antidepressants induced a progressive long-lasting improvement and/or stabilization of several mental functions, restoring cognitive performances to values similar to those of the Italian elderly general population. As regards the greater effects for sertraline on TMT-B and for citalopram on MMSE, we have to specify that it is difficult for us to make hypotheses on these results. Moreover, head-to-head comparisons between the effects of citalopram and sertraline on cognitive functions are lacking in the literature.

Although several antidepressants have demonstrated efficacy in the treatment of late-life major depression, far less research has been directed to examining the benefits of treatment on cognitive functions of these subjects.[19,21,35] Cognitive impairment can have a strong impact on everyday life activities. As a general rule, effective antidepressant pharmacotherapy devoid of important adverse effects on cognitive function is crucial in elderly depressed patients. Sertraline and citalopram are selective and potent SSRI antidepressants associated with a significant lower incidence of adverse events in comparison with tricyclic antidepressants.[36,37] Short-term double-blind studies in elderly patients with major depressive disorder demonstrate that sertraline and citalopram are devoid of negative effects on cognitive functions and psychomotor performances.[20,21,38–42] These studies, however, had a too short follow-up period (up to 12 weeks) to collect reliable data on the impact of long-term treatment with these drugs on cognitive functions. Today, it is widely accepted that late-life depression should be treated for long periods.[1,13,43,44] The evidence for the effectiveness of treatments for less severe depressive disorders, particularly in older patients, is limited, and, to our knowledge, this is the first study investigating the effects of antidepressants on cognitive functions in patients with minor depressive disorder and subsyndromal depressive symptomatology assessed with well-characterized standardized instruments.

Both sertraline and citalopram were well tolerated by the elderly patients during the whole study period. The duration of treatment may be considered long enough to reveal the effects of the 2 compounds. In general, adverse side effects were similar, both qualitatively and quantitatively, to those observed in other studies of SSRIs in elderly patients.[45] The safety profiles of the SSRIs make them a preferred drug class for treating depression in the elderly.

Some limitations to our study should be mentioned. The most important methodological weakness is the lack of a placebo control group, which makes it uncertain whether the benefits observed were due to the medications. One might conclude that most of the improvement in the 2 groups had more to do with the nonspecific benefits of being in a clinical trial. However, patients involved in our study were scheduled for 6 visits over 1 year, so the frequency of the assessments was similar to that usually employed in outpatient clinical practice. Apart from GDS and cognitive evaluations, during the trial, patients did not receive any specific psychological treatment or extra attention and were subjected only to clinical management. The fact that both treatment groups continued to show a progressive and long-lasting improvement in their depressive symptoms throughout the study (and even in the long term, after 6 or 12 months of treatment, when the benefits of being in a study can probably be reduced) is in contrast with the clinical effect of placebo, described by pattern analysis as characterized by an early response that is not sustained over time.[46] Moreover, the lack of a placebo arm is partly justified by ethical reasons due to the long duration of the study. Nonetheless, our results need to be interpreted with caution, as without a placebo group, the proportion of responses due solely to the effect of the medications remains unclear.

Another limitation is the absence of rigorous criteria to detect patients with vascular disease, which may lead to a bias in sample selection. Various lines of evidence have led to the proposition that vascular brain disease is an important cause of late-onset depression, termed *vascular depression*.[47,48] Damage to end-arteries supplying subcortical striato-pallido-thalamo-cortical pathways may disrupt neurotransmitter circuitry involved in mood regulation, thus causing or predisposing one to depression. Vascular depression is defined by the presence of hyperintensities on MRI and appears to be associated not only to a late onset, but also to a greater cognitive impairment, especially involving executive dysfunction (depression-executive dysfunction syndrome of late life),[49,50] with a relative preservation of memory. Executive impairment

has been associated with relapse, recurrence, and chronicity of geriatric major depression and is a predictor of poor or delayed antidepressant response.[51] Unlike executive dysfunction, memory impairment does not seem to be related to relapse, recurrence, or fluctuations of depressive symptoms over time and does not appear to influence the response to antidepressant treatment.[49] However, a review of the literature examining cognitive deficits in depression and their brain correlates[52] suggested that both mnemonic deficits and executive impairment are widespread in depression, occurring independently of age, depression severity and subtype, task difficulty, motivation, and response bias. Moreover, some authors suggested that cognitive impairment in elderly depressed patients is mainly a state and not a trait phenomenon[53] and that cognitive function can improve after remission of depression.[54]

In our study, we did not use systematic MRI scans, but only a full neurologic examination to detect neurologic disease that could interfere with the interpretation of the results, so we could not definitely exclude from the trial those subjects whose depressive symptomatology was the sequela of vascular disease. However, some authors[55] observed that the presence of extrapyramidal signs, impaired motor sequencing, and grasp reflex was associated with both subcortical lesions and poor outcome, suggesting that neurologic impairment may be a good marker for the presence of white matter lesions seen on MRI.

In accordance with our exclusion criteria, patients involved in our study were not affected by cognitive decline or mild dementia, even if they were worse than historical controls for both executive functions and memory. One possible explanation to the significant, progressive, and long-lasting improvements in both memory and executive functioning with antidepressant treatment is that most patients were affected by nonvascular depression.

Other limitations are the lack of randomization and a possible indication bias. However, the study was carried out in a clinical setting that assigned alternatively those patients who accessed the outpatient service to 1 of 2 treatments; there were no reasons to modify the allocation to select a group with a different prognosis. The 2 medications were equivalent at the starting point for both clinicians and patients, because there was no a priori hypothesis and no commercial interests existed among researchers. As a result of the allocation phase, the baseline characteristics of the 2 groups were equivalent, allowing the definition of a quasirandomized study.

Another notable observation is that gender ratio in this study is skewed, as significantly more men than women were recruited. However, subjects involved in our study were 138 consecutive outpatients who had spontaneously come for a psychiatric evaluation. A similar gender ratio was observed in another sample of patients with minor depressive disorder and subsyndromal depressive symptomatology.[56] Furthermore, Angst and colleagues[57] observed that in minor depression the preponderance of females is smaller than in major depression, and Heun and colleagues[58] reported that prevalence rates for subthreshold depressive syndromes in the elderly are not significantly influenced by gender.

The possibility of learning effects as potential limitations in this repeated-measures design needs also to be taken into account. If an improvement of depressed patients within the time of treatment of depression is found, one must check a control group for a general test-training effect, but a control group is lacking for our study. A degree of anxiety during the testing might be relieved at the second testing because the person knows what is to be expected the second time. Furthermore, more efficient strategies to solve the tasks in the test can be applied in the second testing session. It could not be excluded that most of the apparent improvement in cognition observed between baseline and visit 1 is simply a learning effect, and the same can be said for assessments performed after 2 and 3 months of treatment. However, improvements of cognitive functions were observed even in the long term, after 6 and 12 months of treatment, when the benefit due to a learning effect could be partially attenuated. Finally, the use of a fixed-dose design could have yielded results more applicable to efficacy and safety issues, but maybe less relevant to clinical practice.

In conclusion, the results of the current study seem to suggest that sertraline and citalopram can induce a relief from depressive symptoms of minor depressive disorder and subsyndromal depressive symptomatology in elderly nondemented patients. The 2 antidepressants had no negative effect on any of the assessed cognitive functions; conversely, improvements over 1 year were observed in all cognitive tests. Regarding the relationship between depression and cognition, further studies are needed to clarify whether antidepressants might have a direct beneficial effect on cognition. It cannot be excluded either that the antidepressant effect on cognition is independent from the effects on mood or that the amelioration of mood influences improvement in cognitive functions. It is our intention to assess, by means of linear regression models, the relationship between depression, magnitude of antidepressant effect, and cognition in this sample of patients. In the view of their favorable safety and efficacy profile, sertraline and citalopram appear to be suitable antidepressants for elderly patients. Results of this study support the suggestion that long-term antidepressant treatment may be appropriate in the elderly depressed population.

Drug names: citalopram (Celexa), paroxetine (Paxil and others), sertraline (Zoloft).

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