Paroxetine and Fluoxetine Effects On Mood and Cognitive Functions in Depressed Nondemented Elderly Patients

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Background: A large proportion of the elderly population complains of depressive symptoms. The ideal antidepressant for these patients, who often suffer from numerous concomitant diseases, should not worsen their cognitive functions and should be free of contraindications.

Method: To assess the effects of 2 selective serotonin reuptake inhibitors on cognitive functions in elderly depressed patients (ICD-10 criteria), we conducted a double-blind, randomized, parallel-group, multicenter study comparing paroxetine (20–40 mg daily) and fluoxetine (20–60 mg daily) treatment for 1 year. Cognitive performance was evaluated by means of the Buschke Selective Reminding Test, the Blessed Information and Memory Test, the Clifton Assessment Schedule, the Cancellation Task Test, and the Wechsler Paired Word Test; the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Anxiety Scale were administered to assess the course of depressive and anxiety symptoms, respectively.

Results: 242 patients were enrolled (mean ± SD age = 75.4 ± 6.6 years). During the study, no deterioration of cognition was observed; on the contrary, most of the tested cognitive functions improved. Good antidepressant efficacy was maintained for over 1 year with both drugs, based on the percentage of responders to treatment (patients achieving a HAM-D total score < 10; 60%). Both drugs showed a good tolerability and safety profile.

Conclusion: The 2 antidepressants proved to be suitable for the long-term treatment of depression in the elderly and to be devoid of detrimental effects on the tested cognitive functions.

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It is estimated that a large proportion of the elderly population (those aged over 65 years) complain of depressive symptoms,[1,2] with a prevalence of major depression ranging from 2% to 10%.[1,3] Depression in the elderly can be associated with behavioral symptoms, cognitive disturbance, and psychomotor abnormalities.

In the same population, the prevalence of dementia is reported to be about 5%, with 30% of demented patients complaining of depressive symptoms.[4] Mild reduction in some selective functions such as attention and learning; impairment of recall, long-term, and visual memory; and less accurate memory for spatial location information have been observed in depressed patients, while in patients with Alzheimer's disease, short-term memory declines more often.

In the elderly patient, subcortical vascular disease is often associated with depression and is characterized by psychomotor retardation, lack of insight, and impairment of executive function.[5] Cognitive impairment associated with depression is difficult to distinguish from cognitive impairment associated with subcortical vascular disease. Thus, the distinction between cognitive symptoms related to depression and cognitive decline in dementia plays an important role in therapeutic decisions.

In elderly depressed patients, antidepressant treatment should not worsen any concomitant cognitive impairment[6,7] or psychomotor retardation and should be devoid

of contraindications for concomitant somatic disease. Moreover, its onset of action should be rapid.

Tricyclic antidepressants (TCAs) have been the drugs of choice for depression for several years, although their interference with memory and cognitive functions, as well as their sedative effects, are widely recognized.[6,8] The introduction of selective serotonin reuptake inhibitor (SSRI) antidepressants, which have a more favorable side effect profile, seems to have overcome most of these problems.[6,9–11] Paroxetine and fluoxetine, which were among the first SSRIs to become available, have been widely studied in different depression subtypes.[11,12] Several short-term studies have reported that their overall efficacy and tolerability in geriatric depressed patients are satisfactory.[13–15] Compared with TCAs, paroxetine and fluoxetine have a better tolerability and safety profile, characterized by fewer anticholinergic and cardiovascular side effects.[12,15–18]

The aim of the present double-blind study was to evaluate the effect of paroxetine and fluoxetine on cognitive functions and depressive symptoms in nondemented depressed elderly patients in a long-term trial lasting 1 year. We also investigated the safety and the overall tolerability of both drugs.

METHOD

Selection Criteria

Male and female outpatients, aged over 65 years, meeting ICD-10 criteria for depression (paragraphs F32, F32.1, and F32.2), were admitted to the study after written informed consent had been obtained. Patients were eligible if their Mini-Mental State Examination (MMSE)[19,20] score was at least 22, their Hamilton Rating Scale for Depression (HAM-D)[21] score was higher than 18, and their Raskin Severity of Depression Scale[22] score was higher than their Covi Anxiety Scale[23] score. Patients with concomitant uncontrolled systemic diseases, high suicidal risk, or bipolar disorder, dementia, schizophrenia, or history of alcohol or drug addiction were excluded, as well as patients treated with depot neuroleptics during the last 6 months before baseline or with oral neuroleptics in the last 2 weeks; nootropics, electroconvulsive therapy, or continuous benzodiazepine therapy during the last 8 weeks; SSRIs during the last 4 weeks; monoamine oxidase inhibitors during the last 3 weeks; tricyclic or tetracyclic antidepressants during the last week; or experimental drugs during the last 3 months.

Study Design

The study was a double-blind, parallel-group multicenter clinical trial conducted in 38 centers. Patients were randomly assigned to either paroxetine or fluoxetine treatment for 1 year.

After a placebo run-in period of 3 to 7 days (the shorter period for patients not taking any psychoactive drug at the screening visit), patients were randomly assigned to study compound at dose level 1 (paroxetine, 20 mg daily, or fluoxetine, 20 mg daily). On day 21, investigators could increase the daily dosages up to dose level 2 (paroxetine, 30 mg daily, or fluoxetine, 40 mg daily), depending on response and tolerance; 3 weeks later (on day 42), doses could be increased further to level 3 (paroxetine, 40 mg daily, or fluoxetine, 60 mg daily). The dosage could be adjusted according to clinical response within a dose range of 20 to 40 mg for paroxetine and 20 to 60 mg for fluoxetine during the remaining study period.

During the 1-year study period, after the screening assessment, patients underwent 9 additional visits: on day 0 (first dispensing of study drug) and at weeks 3, 6, 12 (end of the acute phase), 20, 28, 36 (end of the medium-term phase), 44, and 52. Investigators were trained to administer the psychometric test battery according to common standards.

Stabilized treatments for concomitant systemic diseases, temazepam for occasional treatment of insomnia, and short or intermediate half-life benzodiazepines for management of anxiety symptoms on a p.r.n. basis—but in agreement with the exclusion criteria—were allowed in both groups.

The study was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice.

Efficacy Parameters

Cognitive functions were assessed by means of the Buschke Selective Reminding Test (BSRT)[24] (7 words; 6+1 repetitions) for short- and long-term memory, the Blessed Information and Memory Test (BIMT)[25] for cognitive evaluation, the Clifton Assessment Schedule (CLAS)[26] for writing, reading, calculation, and memory function, the Cancellation Task Test (CTT)[27] for attention skills, and the Wechsler Paired Word Test (WPW)[28,29] for word learning. The MMSE was also used to evaluate global cognitive performance. The HAM-D[21] and the Clinical Anxiety Scale (CAS)[30] were used to assess depressive and anxiety symptoms. Responders for depression were defined as patients with a HAM-D score less than 10[31] at the end of treatment. Similarly, responders for anxiety were defined as patients with a CAS score less than 8 at the end of treatment. The Clinical Global Impressions scale (CGI)[32] was also administered.

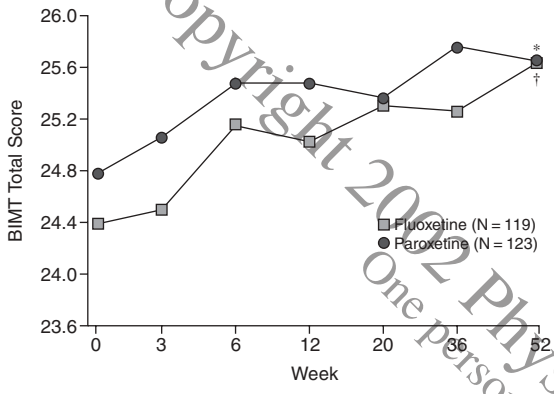
Statistical Analysis

Statistical evaluation was performed on the basis of an endpoint analysis, and all data were analyzed on an observed-case basis. One-way analysis of variance (ANOVA; treatment was the only defined factor) was based on a comparison between groups. The Kaplan-Meier method was used to compare the "time to reach a HAM-D score < 10" variable and "time to reach a CAS score < 8" variable between groups.

Table 1. Characteristics of the Patient Population

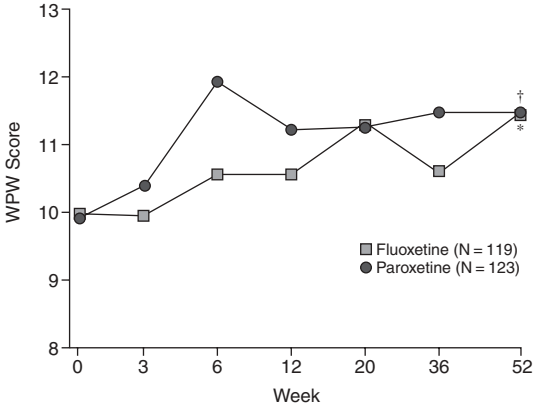
Characteristic	Paroxetine	Fluoxetine
Enrolled patients, N	123	119
Men/women, N	48/75	59/60
Age, mean ± SD, y	75.61 ± 6.99	74.85 ± 6.67
Education, mean ± SD, y	5.51 ± 2.71	6.15 ± 2.97
History of major depression, %	19.67	23.08
History of depressive symptoms, %	52.03	55.08
Benzodiazepine prn use, % of patients	16	12

Figure 1. Mean Blessed Information and Memory Test (BIMT) Total Score Changes in Elderly Nondemented Depressed Patients Treated With Paroxetine or Fluoxetine



*p < .004, end of study vs. baseline.
†p < .0001, end of study vs. baseline.

Figure 2. Mean Wechsler Paired Word Test (WPW) Score Changes in Elderly Nondemented Depressed Patients Treated With Paroxetine or Fluoxetine



*p < .003, end of study vs. baseline.
†p < .0008, end of study vs. baseline.

Categorical variables were compared by means of the Pearson chi-square test for independent evaluations between groups. Within each group, all variables were analyzed versus baseline, using the paired t test (specific hypothesis value for the mean = 0) and the nonparametric Wilcoxon signed rank test. All tests were 2-sided; $p \leq .05$ was regarded as the statistically significant level.

In order to evaluate any treatment center effects, a 2-way ANOVA was performed. A covariance analysis was applied to investigate the possible effect of depression severity (HAM-D total score) on the change over time of each cognitive parameter. A correlation analysis was performed between HAM-D item 8 (psychomotor retardation) and the main cognitive parameters, both in each treatment group and in the global population. Safety evaluation was performed in all randomized patients who received at least 1 dose of study drug.

RESULTS

Patient Population

A total of 242 patients of the 247 screened were enrolled: 123 were randomly assigned to receive paroxetine and 119, to receive fluoxetine. The characteristics of the patient population are summarized in Table 1. The duration of the present depressive episode was less than 6 months in 60% of patients and more than 1 year in nearly 25%. Forty percent of the patients had already been treated for the present episode.

No difference was observed between the 2 groups with regard to demographic data, past psychiatric history, present depressive episode, and benzodiazepine use on a p.r.n. basis (see Table 1). Likewise, no difference in cognition and depression parameters was observed at baseline in both treatment groups, after adjustment for the geographical distribution of clinical centers.

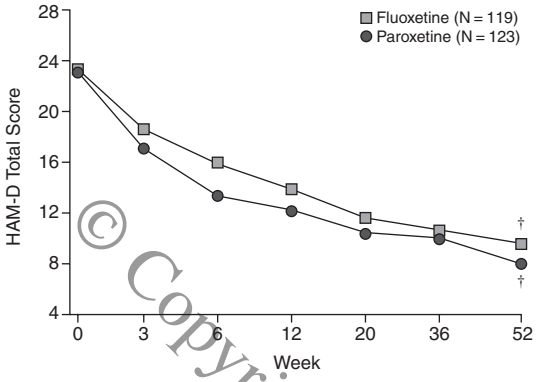
Therapeutic Effects

Cognitive performance. Total MMSE score during the 1-year study period showed no significant difference between groups. Both drugs were effective in improving cognitive function parameters, such as reading, writing, calculation, and memory function (assessed by means of the CLAS), starting from week 6 ($p < .05$ for fluoxetine, $p < .01$ for paroxetine); no differences were observed between groups. An increase in the MMSE total score was observed in both the paroxetine (12.4%) and fluoxetine (7.6%) groups at the end of treatment.

Both drugs were significantly effective in improving BIMT total score ($p < .01$) (Figure 1) and BIMT nonpersonal memory score ($p < .02$). In the BIMT nonpersonal memory score, improvement at the end of treatment versus baseline was 20.22% and 17.63% with paroxetine and fluoxetine, respectively. Starting from week 6 up to the last visit, a significant improvement in the WPW total score was reported in both groups ($p < .001$ for paroxetine and $p < .003$ for fluoxetine, vs. baseline) (Figure 2).

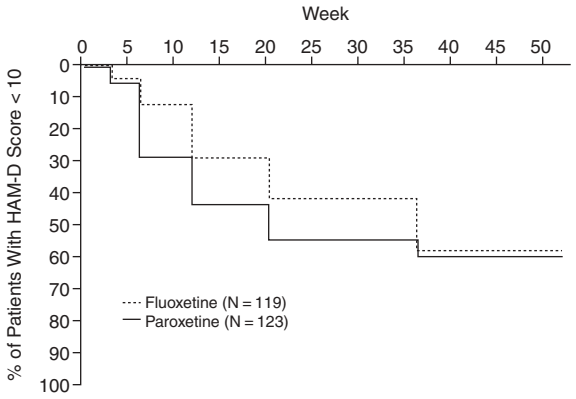
CTT correct answers results showed no significant differences between groups, although both treatments

Figure 3. Mean Hamilton Rating Scale for Depression (HAM-D) Total Score Changes in Elderly Nondemented Depressed Patients Treated With Paroxetine or Fluoxetine



†p < .0001, percentage change, end of study vs. baseline.

Figure 4. Survival Analysis Comparing the Time Needed for Each Patient to Reach a Total Hamilton Rating Scale for Depression (HAM-D) Score < 10 in the 2 Treatment Groups[a]



[a]p < .03, paroxetine vs. fluoxetine.

produced an improvement of the sum of 2- plus 3-digit matrix scores[27] at the end of the study versus baseline.

Both paroxetine and fluoxetine produced no detrimental effect on memory function as demonstrated by comparing baseline and end-of-study values of the various BSRT scores. Nevertheless, patients treated with paroxetine showed a significantly greater improvement in scores on a number of Buschke tests compared with those treated with fluoxetine at week 3: total recall (score = 28.7 vs. 25.9, respectively; p = .01), long-term storage (score = 27.5 vs. 24.9, p = .04), long-term recall total (score = 25.6 vs. 22.2, p = .02), and long-term recall consistent (score = 21.0 vs. 16.9, p = .02). At week 6, the same was true for long-term storage (score = 27.2 vs. 24.1, p = .04) and long-term recall random (score = 4.6 vs. 3.3, p = .04). At week 6, fluoxetine-treated patients reported a higher Buschke short-term recall score (4.0 vs. 5.3, p = .04).

Depressive symptoms. Paroxetine and fluoxetine significantly reduced the HAM-D total score (Figure 3; p < .0001 in both groups vs. baseline). Starting from week 3, both drugs induced a significant percentage decrease in HAM-D score versus baseline (p < .005). A significant difference between the 2 treatment groups was observed during the first 6 weeks of the study (week 3: –25.3% in the paroxetine group vs. –20% in the fluoxetine group, p < .05; week 6: –42.4% vs. –31.4%, p < .002).

The analysis of HAM-D cluster and factor scores[33,34] showed a similar profile for "psychomotor retardation" (factor V; p < .04, paroxetine vs. fluoxetine at week 3), "anxiety or somatization" (factor I; p < .02, paroxetine vs. fluoxetine at week 6), and the "core symptoms of depression" (Bech's cluster; p < .04, paroxetine vs. fluoxetine at week 6). To evaluate the percentage of responders, a survival analysis (Kaplan-Meier method), based on the time needed for each patient to reach a HAM-D total score less than 10, was performed, showing a good efficacy profile. A statistically significant difference in favor of paroxetine was observed with regard to the percentage of responders over time (p < .03) (Figure 4).

Relationship of cognition and mood. With regard to the possible relationship between depression and cognition, a significant correlation was found between the magnitude of antidepressant effect over time (HAM-D total score changes) and the improvement in scores on the CLAS (p < .05), BIMT (p < .002), and CTT (correct answers score) (p < .001) only at week 36 in both groups. Furthermore, the psychomotor retardation score (HAM-D item 8) negatively correlated with the CTT correct answers score only at week 36 in both groups (p < .05).

Anxiety symptoms. A significant percent reduction in CAS total score was observed in both groups (end of study vs. baseline scores: paroxetine, –45.8%; fluoxetine, –29.3%; p < .0001). These findings were confirmed by a survival analysis (Kaplan-Meier method) evaluating the time needed for each patient to reach a total CAS score less than 8. The proportion of patients reaching a CAS score < 8 at the end of the treatment was 77% for paroxetine and 67% for fluoxetine.

CGI scores. No significant differences were observed between paroxetine and fluoxetine groups in the percentage of patients rated as "improved" or "very much improved" (CGI-Improvement scale). Scores on the CGI-Severity of Illness scale improved in both treatment groups (p < .0001, end of treatment vs. baseline), paralleling the improvement of the efficacy index (expression of the tolerability vs. efficacy ratio at each visit).[35] A statistically significant difference in the efficacy index was observed between treatment groups at week 6 (2.62 for paroxetine vs. 2.24 for fluoxetine; p = .01).

Table 2. Percentage of Patients With Adverse Events

Category	Paroxetine (N = 123)	Fluoxetine (N = 119)
At least 1 adverse event	27.6	32.8
Adverse events involving		
Gastrointestinal system[a]	13.0	17.6
Central nervous system		
Neurologic[b]	8.1	8.4
Psychiatric[c]	4.1	10.1
Cardiovascular system[d]	6.5	7.5
Body as a whole[e]	11.4	7.5

[a]Mainly nausea, emesis, and gastralgia.
[b]Mainly headache and dizziness.
[c]Mainly anxiety, irritability, and agitation.
[d]Mainly hypertension and hypotension.
[e]Mainly fatigue and myalgia.

Adverse events. A total of 250 adverse events were reported in 84 of the 247 screened patients; 16 of these (7 in the paroxetine group and 9 in the fluoxetine group) were already present at baseline in 10 patients (5 in each group). Percentages of patients with adverse events related to gastrointestinal, central nervous, and cardiovascular systems are summarized in Table 2. A limited percentage of adverse events were classified as severe in both groups (12.8% in the fluoxetine group vs. 4.8% in the paroxetine group). Spontaneous recovery was reported in 56.7% of paroxetine-treated patients and in 29.9% of fluoxetine-treated patients.

Thirty-one of the 250 adverse events were classified as serious: 9 with paroxetine and 22 with fluoxetine ($p < .02$), related to 19 patients (7 and 12 patients, respectively). No patient complained of a switch to (hypo)manic state.

Premature withdrawal. The overall percentage of patients who prematurely discontinued treatment was 39.3% (95 of 242 enrolled patients), 40.6% and 37.8% for paroxetine and fluoxetine, respectively. Of the total withdrawals, 6.3% of patients stopped treatment because of marked improvement of depressive symptoms, 8.0% withdrew because of unsatisfactory therapeutic efficacy, and 15.0% withdrew because of side effects. There were 4 deaths (4.2%), 2 in each treatment group: 3 patients died during the study because of concomitant diseases and 1 patient in the fluoxetine group committed suicide. The remaining 66% of withdrawals were due to other reasons (noncompliance, protocol violations, administrative reasons, lost to follow-up).

DISCUSSION

It is now recognized that depression in elderly patients is often clinically associated with some degree of memory and cognitive impairment, as well as psychomotor retardation.[6,7,13,36] The term *depressive pseudodementia* describes a substantial but reversible cognitive impairment, usually caused by an episode of major depression[4,36,37] and distinguishable from Alzheimer's disease, with the aid of well-established criteria, but not from vascular depression, which needs confirmation by brain imaging assessment.

Many widely prescribed antidepressant treatments (tricyclics and tetracyclics) have been shown to worsen cognition in elderly depressed patients,[6–8,38–41] and some evidence suggests that such worsened cognition should be predictable on the basis of their effects on specific neurotransmitter systems.[42] One common pathway of the TCA-induced adverse effects on cognition is related to central nervous system muscarinic receptor blockade.

Iatrogenic memory impairment can have a strong impact on everyday life activities.[43] As a general rule, effective antidepressant pharmacotherapy devoid of important adverse effects on cognitive function is crucial in elderly depressed patients. Paroxetine and fluoxetine are selective and potent SSRI antidepressants, associated with a significantly lower incidence of adverse events in comparison with TCAs.[15–17,44] Short-term double-blind studies in elderly patients demonstrate that paroxetine and fluoxetine are devoid of detrimental effects on cognitive functions and psychomotor performance.[13,14,43] These studies, however, were too short (6–12 weeks) to collect reliable data on the impact of long-term treatment on cognitive functions. Today, it is widely accepted that late-life depression should be treated for longer periods.

The present study was the first to be performed in depressed elderly patients to assess the effects of 2 SSRI antidepressants for 1 year, including an evaluation of cognitive functions. The main limitations of the present study are the absence of brain imaging to select a population of patients without evidence of subcortical and frontal vascular lesions and the lack of a placebo arm for ethical reasons due to the long duration of the study.

Both treatments were well tolerated during the whole study period. The duration of treatment may be considered long enough to reveal the effects of the 2 compounds. The assessment of overall and specific cognitive functions by numerous appropriate and specific tests disclosed no drug-related detrimental effect. Conversely, some statistically significant improvements of cognitive functions, namely attention, memory, and learning, were observed with both treatments. Both antidepressants induced a progressive long-lasting improvement and/or stabilization of several superior mental functions.

Both paroxetine and fluoxetine proved to be effective and prompt in relieving depressive symptoms, clinical response to treatment being noteworthy, too. Regarding the relationship between depression and cognition, we found a correlation between the magnitude of antidepressant effect and the improvement in CLAS, BIMT, and CTT scores at week 36 only. Since the observed correlation was temporally limited, its meaning is unclear and 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 some cognitive functions only during long-term treatment. Nevertheless, because of the lack of restrictive criteria excluding patients affected by vascular depression, it cannot be established whether depressive cognitive impairment or merely the deficit associated with incidental subcortical vascular disease responded to treatment.

Likewise, the negative correlation between the changes in psychomotor retardation and changes in CCT attention scores that was observed at week 36 might indicate that attention processes were affected by the improvement in psychomotor activity induced by long-term antidepressant treatment. Once again, further studies should be performed specifically investigating the relationship between psychomotor activity and attention in elderly patients.

Since anxiety notoriously interferes with cognitive processing by reducing the ability to pay attention and to concentrate, both HAM-D factor I and CAS scores were analyzed. Both drugs were effective in reducing anxiety and physical somatization symptoms. An early improvement in anxiety and somatization is of special value in the management of elderly patients, who are often affected by several concomitant somatic diseases and by somatic symptoms amplified by underlying depression. Regarding tolerability, both treatments showed a good safety profile, with a low overall percentage of patients with at least 1 adverse event.

In conclusion, paroxetine and fluoxetine were found to be effective, safe, and well tolerated in the long-term treatment of depression in elderly nondemented patients after individualized dosage titration. The 2 antidepressants had no detrimental effect on any of the assessed cognitive functions; conversely, some improvement over 1 year was observed in the majority of cognitive tests.

In view of their favorable safety and efficacy profile, paroxetine and fluoxetine 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.[45]

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil), temazepam (Restoril and others).

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