Does Antidepressant Therapy Improve Cognition in Elderly Depressed Patients?

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A growing body of research has found cognitive impairment to be a common clinical feature of late-life depression (1). Cognitive domains reported to be affected include short-term memory (2), executive functioning (3), information processing (4,5), and psychomotor speed (6). The cognitive impairment appears to be associated with both anatomical abnormalities such as white matter hyperintensities (3,7,8), as well as functional abnormalities in frontal and prefrontal regions (9,10). Alterations in serotonergic neurotransmission have also been implicated, both directly and through interaction with central cholinergic pathways, in cognitive function (11–15). There is also evidence suggesting that impaired cognitive status at pre-treatment baseline may delay or reduce the antidepressant response (16).

Treatment of depression in elderly people with tricyclic antidepressants (TCAs) has been found to be associated with either no change or a decrement in certain cognitive functions, although few of these studies selected for cognitively impaired subjects or studied long-term clinical significance of such changes (17–22). This is generally attributed to their anticholinergic effects. In contrast, treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants does not appear to worsen cognitive function, and some preliminary findings have suggested that they may improve some aspects of cognition (23–26). However, there are no long-term studies with cognition as a primary outcome that have actually tested of cognition (23–26). However, there are no long-term studies with cognition as a primary outcome that have actually tested of cognition (23–26). However, there are no long-term studies with cognition as a primary outcome that have actually tested

Acute improvement in depression is associated with cognitive improvement as measured by the SLT and DSST. Prospective studies are warranted to study the effects of potential differences among antidepressant therapies on long-term cognitive outcomes in geriatric depression.
baseline? We hypothesized, based on previous research (33), that this group would demonstrate the greatest benefit in terms of improved cognitive function, but that the cognitive function of this subgroup would not achieve normative levels. We further hypothesized that abnormal baseline cognitive functioning would predict either lower (or slower) antidepressant response rates.

**METHODS**

Patients in the current analysis consisted of 255 elderly women and 185 elderly men who participated in one of two multicenter, double-blind studies comparing the efficacy of sertraline to either fluoxetine (total, \( n = 236 \)) or nortriptyline (total, \( n = 208 \)) in the treatment of late-life depression. Details of study methodology are presented in previous publications (20,21).

Briefly, both studies had similar inclusion and exclusion criteria, which required outpatients 60 years of age or older to meet DSM-III-R criteria for major depressive disorder (single episode or recurrent, without psychotic features) and to have a 24-item Hamilton Depression Rating Scale (HAM-D) total score \( \geq 18 \) at baseline. Both studies were approved by Institutional Review Boards at each site, and written informed consent was obtained from all patients prior to study entry. Patients were excluded for any of the following: (a) any other current Axis I disorder; (b) MMSE \( < 24 \); (c) presence of any medical contraindications to antidepressant therapy; (d) any significant hematologic, endocrine, or cardiovascular conditions that might impair study drug absorption, metabolism, or excretion; (e) failure to respond to electroconvulsive therapy in a prior depressive episode or to adequate trials (6 weeks) of 2 or more antidepressants in daily doses equivalent to 150 mg amitriptyline administered for 3 weeks; and (f) concomitant use of all other psychotropic medications (except temazepam or chloral hydrate used sparingly for sleep).

**Study Procedures**

Patients entered a single-blind, placebo run-in phase followed by random assignment to 12 weeks of double-blind treatment with either sertraline 50 mg per day or (in study 1) fluoxetine 20 mg per day; or (study 2) 25 mg of nortriptyline. The studies differed somewhat in their dosing schedules. In study 1, doses of both sertraline and fluoxetine could be increased at week 4 to 100 mg/d for sertraline, or 40 mg/d for fluoxetine if, in the investigator’s opinion, an adequate clinical response had not been observed and no dose-limiting side effects had occurred. A patient’s daily dose could be reduced at any time down to 50 mg of sertraline or 20 mg of fluoxetine due to adverse events and/or if clinically indicated. In study 2, sertraline was titrated in increments of 50 mg every 3 weeks, based on tolerability and clinical response, to a maximal daily dose of 150 mg. Nortriptyline was initiated at a dose of 25 mg in the evening, and could be titrated in increments of 25 mg per week to a maximal daily dose of 100 mg. Doses of nortriptyline above 25 mg were given 3 times per day, while all sertraline doses were administered in the evening, with a double-dummy design employed to maintain the blind. Compliance with study treatment was monitored by pill counts, and patients who were less than 75% compliant for two subsequent visits were dropped from the study.

Clinical assessments were made at day 1 of washout, the end of washout (baseline), at weekly intervals for the first 4 weeks of double-blind treatment, and at 2-week intervals thereafter.

**Outcome Measures**

Primary investigator-rated efficacy measures included the 24-item HAM-D (34) and Clinical Global Impressions Severity and Improvement ratings (CGI-S and CGI-I) (35).

Cognitive assessments included a Shopping List Task (SLT), also known as the Buschke-Fuld Selective Reminding Test, which assesses storage, retention, and retrieval of spoken words with a verbal list learning task (36,37). It is a standardized test designed to quantify short-term and long-term memory storage and retrieval and includes the following scored factors: number of items recalled, number of items retrieved from long-term storage, and size of learned list. A 12-item list of words was read to the patient at a rate of 1 word every 2 seconds. Immediately following, the patient was asked to recall the entire list. Then, only those words not recalled on the first trial were read to the patient, and, immediately following, the patient was again asked to recall the entire list. This procedure was followed for 6 trials. Items recalled immediately after prompting were taken to be retrieved from short-term storage, and items recalled on 2 consecutive trials without reminding were taken to come from long-term storage.

Additional cognitive assessments included the Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale (38), and the MMSE (39). In the DSST, which measures visual tracking, motor performance, and coding, patients were presented with a sheet containing randomized digits (0–9) arranged in rows. In the space below each digit, they were required to insert the appropriate symbol indicated by a substitution code at the top of the page. Patients were given 90 seconds to complete as many substitutions as possible, and the number of correct substitutions was recorded.

A composite anticholinergic severity score was created by summing the maximum treatment-emergent severity scores for dry mouth and constipation (1 = mild, 2 = moderate, 3 = severe). While this is not a prospectively validated index of cholinergic effects, it is practical and clinically relevant. As such, it should be viewed as an exploratory variable. Drug-induced anticholinergic activity, acting centrally, has previously been associated with cognitive impairment in elderly persons (40).

**Statistical Analyses**

As stated previously, this was an analyses of pooled data from two prospective trials. Data analysis for efficacy included all patients who completed at least 4 weeks of study treatment; 4 weeks were required for titration to a full dose. For categorical variables, treatment groups were compared using Fisher’s exact tests. For the cognitive test scores, the treatment groups were compared with respect to the change from baseline to endpoint using an analysis of variance model. Post hoc comparisons between the treatment groups were...
performed using Tukey’s least significant difference. The relationship between baseline demographic variables and cognitive test scores were examined using a multiple regression analysis. Pearson correlation coefficients were computed to examine the association between clinical variables and endpoint improvement in composite cognitive score. Survival analysis was performed using a log rank test based on Kaplan-Meier estimates. All statistical tests were two-sided, with statistical significance set at a 0.05 alpha level. No adjustments for multiplicity were made and, hence, the post hoc comparisons are not to be viewed as conclusive statements of fact but as hypotheses-generating findings. Readers should interpret the results accordingly.

RESULTS
The efficacy evaluable sample for the current analysis consisted of 217 patients on sertraline pooled from the two studies (62% female; mean ± SD [standard deviation] age, 68.0 ± 5.7 years; 56% with a recurrent episode; baseline HAM-D, 24.9 ± 4.6); 119 patients on fluoxetine (51% female; mean ± SD age, 67.4 ± 5.9 years; 53% with a recurrent episode; baseline HAM-D, 25.0 ± 4.7); and 104 patients on nortriptyline (58% female; mean ± SD age, 67.9 ± 6.6 years; 53% with a recurrent episode; baseline HAM-D, 24.8 ± 5.2).

For patients on sertraline, the mean endpoint daily dose was 83.8 ± 34.7 mg; for fluoxetine, 29.0 ± 10.0 mg; and for nortriptyline 70.8 ± 28.9 mg (79% of patients on nortriptyline had plasma levels ≥ 50 ng/ml).

Overall, responder status (defined as a CGI-I score of “much” or “very much” improved) at study endpoint was achieved by 75% of patients treated with sertraline, 66% of the patients treated with fluoxetine, and 70% of patients treated with nortriptyline (chi-square [χ²] = 2.65, 2 df, p = .265). The mean improvement in HAM-D total score among CGI-I responders was similar for all three responder subgroups, with a combined mean endpoint score of 8.3 ± 5.2, reflecting a mean change of 16.1 ± 6.0.

Older age and male gender and, to a lesser extent, higher systolic blood pressure and greater illness severity were the variables most consistently associated with baseline cognitive impairment on a linear regression analysis (Table 1).

Table 2 presents pre-treatment and post-treatment cognitive data, by treatment group, for the total group, and for two clinically relevant subgroups: CGI responders and CGI responders who showed relative cognitive impairment at baseline on at least 1 of the 3 tests of cognitive function. The relative cognitive impairment subgroup was operationally defined as any patient who had a score on 1 or more of the cognitive function tests that was at least one standard deviation below the mean for the total sample at pre-treatment baseline.

As can be seen in Table 2, for both the total group and the CGI responder subgroup, both sertraline and fluoxetine demonstrated significantly greater endpoint improvement compared to nortriptyline on the DSST as well as the SLT measures. On the DSST, CGI responders treated with sertraline also demonstrated significantly greater endpoint improvement than responders treated with fluoxetine. The magnitude of improvement was greatest for the subgroup of CGI responders with relative baseline cognitive impairment (Table 2 and Figure 1). Nonetheless, endpoint responders in this cognitively impaired subgroup still maintained their cognitive impairment relative to the total group and the CGI responder subgroup.

We performed a correlational analysis to identify clinical and demographic variables that might be associated with improvement in overall cognitive function, which was defined in terms of a composite score created by summing the baseline-to-endpoint change scores on 3 tests: the DSST, the SLT Recalled, and the SLT Retrieved (Table 3). The results found two variables to be significantly correlated with post-treatment improvement in cognitive function: higher post-treatment HAM-D change score and a lower treatment-emergent anticholinergic severity score. Gender (analyzed using a Kruskal-Wallis test) was not found to be correlated with endpoint cognitive improvement (p = .85). Improvement in the HAM-D score was significantly correlated with improvement in cognitive function for patients treated with both sertraline and nortriptyline (Table 3). In contrast, improvement in depression symptomatology and cognitive function were not found to be correlated in patients treated with fluoxetine. This finding is illustrated in Figure 2, which shows the degree of improvement in the cognitive composite score by post-treatment HAM-D change score status. For patients treated with sertraline, improvement in cognitive function is clearly proportional to improvement in depression severity, with the greatest improvement in cognitive function associated with a greater than 15-point endpoint improvement in HAM-D, which was the criteria for remission.

Table 1. Clinical and Demographic Variables Associated With Worse Baseline Cognitive Test Scores: Results of a Multivariate Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variables Associated With Worse Cognitive Function at Baseline</th>
<th>Estimate</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number recalled (SLT)</td>
<td>-0.94</td>
<td>±0.16</td>
<td>.0001</td>
</tr>
<tr>
<td>Older age</td>
<td>-0.09</td>
<td>±0.01</td>
<td>.0001</td>
</tr>
<tr>
<td>Number retrieved (SLT)</td>
<td>-1.43</td>
<td>±0.21</td>
<td>.0001</td>
</tr>
<tr>
<td>Older age</td>
<td>-0.11</td>
<td>±0.02</td>
<td>.0001</td>
</tr>
<tr>
<td>Size of learned list (SLT)</td>
<td>-1.36</td>
<td>±0.24</td>
<td>.0001</td>
</tr>
<tr>
<td>Older age</td>
<td>-0.12</td>
<td>±0.02</td>
<td>.0001</td>
</tr>
<tr>
<td>Digit Symbol Substitution Test</td>
<td>-2.97</td>
<td>±1.18</td>
<td>.0124</td>
</tr>
<tr>
<td>Older age</td>
<td>-0.75</td>
<td>±0.10</td>
<td>.0001</td>
</tr>
<tr>
<td>Higher systolic blood pressure</td>
<td>-0.80</td>
<td>±0.03</td>
<td>.0150</td>
</tr>
<tr>
<td>Mini-Mental Status Examination</td>
<td>-0.04</td>
<td>±0.01</td>
<td>.0001</td>
</tr>
<tr>
<td>Higher baseline illness severity (CGI)</td>
<td>-0.33</td>
<td>±0.14</td>
<td>.0168</td>
</tr>
</tbody>
</table>

Notes: *Multivariate stepwise regression models were run for each independent variable. Regression variables were age, sex, number of concomitant medications, baseline Hamilton Depression Rating Scale (HAM-D), interaction of change in HAM-D and treatment, somnolence score, anticholinergic score, baseline severity, baseline pulse rate, and baseline systolic blood pressure. SE = standard error; SLT = Shopping List Task; CGI = Clinical Global Impression scale.
Table 2. Antidepressant Effect on Cognitive Test Scores in Elderly Patients With Major Depressive Disorder

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Sertraline N</th>
<th>Fluoxetine N</th>
<th>Nortriptyline N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Group, N</td>
<td>N = 185</td>
<td>N = 105</td>
<td>N = 96</td>
</tr>
<tr>
<td>CGI Responder Group, N</td>
<td>N = 138</td>
<td>N = 67</td>
<td>N = 69</td>
</tr>
<tr>
<td>CGI Responders With Baseline Cognitive Impairment, N</td>
<td>N = 26</td>
<td>N = 7</td>
<td>N = 13</td>
</tr>
<tr>
<td>Number recalled (SLT)</td>
<td>Pre-Treatment</td>
<td>Post-Treatment</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>Total group</td>
<td>7.6 ± 1.7</td>
<td>8.1 ± 1.8*</td>
<td>7.3 ± 1.6</td>
</tr>
<tr>
<td>CGI responder group</td>
<td>7.6 ± 1.6</td>
<td>8.0 ± 1.8*</td>
<td>7.5 ± 1.5</td>
</tr>
<tr>
<td>CGI responders with baseline cognitive impairment</td>
<td>5.0 ± 0.7</td>
<td>6.1 ± 1.4</td>
<td>5.7 ± 1.0</td>
</tr>
<tr>
<td>Number retrieved (SLT)</td>
<td>Pre-Treatment</td>
<td>Post-Treatment</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>Total group</td>
<td>5.3 ± 2.6</td>
<td>6.1 ± 2.7*</td>
<td>4.9 ± 2.4</td>
</tr>
<tr>
<td>CGI responder group</td>
<td>5.3 ± 2.5</td>
<td>6.0 ± 2.8*</td>
<td>5.2 ± 2.4</td>
</tr>
<tr>
<td>CGI responders with baseline cognitive impairment</td>
<td>1.7 ± 1.2</td>
<td>3.4 ± 2.1</td>
<td>2.2 ± 1.4</td>
</tr>
<tr>
<td>Size of learned list (SLT)</td>
<td>Pre-Treatment</td>
<td>Post-Treatment</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>Total group</td>
<td>4.2 ± 2.5</td>
<td>5.1 ± 2.8*</td>
<td>3.7 ± 2.3</td>
</tr>
<tr>
<td>CGI responder group</td>
<td>4.2 ± 2.5</td>
<td>5.1 ± 2.8*</td>
<td>3.8 ± 2.3</td>
</tr>
<tr>
<td>CGI responders with baseline cognitive impairment</td>
<td>0.8 ± 1.0</td>
<td>2.4 ± 1.8</td>
<td>1.1 ± 0.8</td>
</tr>
<tr>
<td>Digit Symbol Substitution Test</td>
<td>Pre-Treatment</td>
<td>Post-Treatment</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>Total group</td>
<td>46.5 ± 11.9</td>
<td>53.4 ± 13.3*</td>
<td>47.4 ± 12.7</td>
</tr>
<tr>
<td>CGI responder group</td>
<td>46.2 ± 11.8</td>
<td>54.3 ± 13.5*</td>
<td>47.7 ± 12.1</td>
</tr>
<tr>
<td>CGI responders with baseline cognitive impairment</td>
<td>38.8 ± 14.9</td>
<td>48.3 ± 15.2</td>
<td>44.1 ± 13.8</td>
</tr>
<tr>
<td>Mini-Mental Status Examination</td>
<td>Pre-Treatment</td>
<td>Post-Treatment</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>Total group</td>
<td>28.6 ± 1.5</td>
<td>28.9 ± 1.4</td>
<td>28.9 ± 1.3</td>
</tr>
<tr>
<td>CGI responder group</td>
<td>28.6 ± 1.5</td>
<td>28.9 ± 1.4</td>
<td>28.9 ± 1.4</td>
</tr>
<tr>
<td>CGI responders with baseline cognitive impairment</td>
<td>27.9 ± 1.8</td>
<td>28.2 ± 1.6</td>
<td>28.3 ± 1.8</td>
</tr>
</tbody>
</table>

Notes: *p < .05 for sertraline versus nortriptyline and for fluoxetine versus nortriptyline.
1Cognitive impairment is defined as a baseline score ≥1 standard deviation below the mean on one or more of the cognitive tests.
2p < .05 for sertraline versus fluoxetine.
CGI = Clinical Global Impressions Scale; SLT = Shopping List Task.

A multiple regression analysis confirmed that the two variables identified by correlational analysis were significant predictors of endpoint improvement in the cognitive function composite score: the HAM-D change score was found to be a significant positive predictor (p < .0001), and the anticholinergic severity score was found to be a significant negative predictor (p < .005). The amount of the variance in endpoint cognitive improvement accounted for by these two predictors, though, was small (R² = 9%; F, 20.88; df, 2, 422; p = .0001).

The effect of relative baseline cognitive impairment (as previously defined) on both the probability of achieving a CGI-I response and the time to response were analyzed. The estimated probability of endpoint response was 56.2% (95% CI [confidence interval]: 45.9–66.5) for patients with relative baseline cognitive impairment, compared with 63.3% (95% CI: 57.8–68.8) for patients without cognitive impairment (Fisher’s exact test, p = .263). The log-rank test found a median time to response for the relative cognitive impairment subgroup of 12 weeks compared with 10 weeks in the group without baseline cognitive impairment (log-rank χ² = 0.691; df = 1, p = .406).

**Discussion**

To our knowledge, this is one of the largest studies comparing the cognitive effects of 3 different antidepressants. The prospective sampling of patients, rigorous selection criteria, careful exclusion of patients with other cognitive disorders, and multicenter setting are strengths of this study and add credence to our findings. Several findings emerged from this study. Memory and DSST scores in these patients are in the range of scores that would generally be viewed as mild-to-moderate impairment. Cognitive impairment (those functions measured by the SLT and the DSST) was correlated with higher baseline depression severity and older age, although the correlation with severity was weaker than anticipated. The correlation between baseline cognitive impairment and higher systolic blood pressure is consistent with links between hypertension and memory loss in nondepressed samples. Our findings are also of interest given the emerging links between late-life depression and cardiovascular illness (10,41), as well as a recent randomized trial demonstrating safety and efficacy of sertraline for treating recurrent major depression in patients with acute myocardial infarction or unstable angina (34). In view of prior studies showing that depression and hypertension are independent risk factors for dementia, our findings raise the possibility that patients with both conditions are the ones at greatest risk for adverse outcomes. Prospective studies are needed to test this hypothesis. The selection of an antidepressant agent that is unlikely to adversely impact underlying cardiovascular disease and optimally improves cognition will be important in such studies.

Our second finding was that 3 months of antidepressant treatment improved cognitive function. There were some differences among agents with both SSRIs showing greater...
Improvement in cognitive function at endpoint when compared to nortriptyline. This was also true for the subgroup of CGI responders. A reason for this may be nortriptyline’s anticholinergic effect, as suggested by the results of a correlational analysis, though the lack of established validity for the anticholinergic composite score suggests that these results need to be confirmed by further research. Improvement in depression, as defined using the CGI in our analyses, was most consistently related to cognitive improvement in those treated with sertraline. This correlation was weakest for fluoxetine and intermediate for nortriptyline. These findings lead us to speculate that there may be two potential mechanisms by which antidepressants affect cognition in depression—a direct effect caused by the pharmacologic actions of the drug on specific neurotransmitters as well as a secondary effect caused by improvement of depression (i.e., antidepressant efficacy). While there is evidence, including studies of SSRIs in normal volunteers (42–44), that a direct pharmacologic effect on serotonin neurotransmission might have an effect (12–15), a study design comparing the effect of SSRI versus cognitive–behavioral therapy on cognitive function in elderly depressed patients would help to clarify which mechanism is likely to be relevant.

Among treatment responders, the magnitude of cognitive improvement was larger in those patients who were most impaired at baseline (at least one standard deviation below the mean). At endpoint, though, cognitive function scores in this subgroup continued to be notably lower than the mean for the total patient sample. Sertraline treatment was consistently associated with a numerically greater degree of cognitive improvement among this impaired subgroup as well.

These findings are consistent with those reported in some earlier studies. Patients with poststroke depression have a greater severity of cognitive impairment than non-depressed patients, even when matched for size and location of stroke lesion (35). Poststroke depressed patients whose depression remitted following antidepressant treatment had significantly greater recovery of cognitive functions than those whose depression did not remit (35). Fann and colleagues conducted a pilot 8-week trial of sertraline for treating depression following mild traumatic brain injury (36). They reported improvements in psychomotor speed, recent verbal memory, recent visual memory, and general cognitive efficiency following successful depression treatment with sertraline in these patients. They speculated that the significant alleviation of cognitive impairments may not have been accounted for by natural recovery alone (36). These studies, in addition to those cited in the introduction, support the concept that treatment of depression may successfully improve certain cognitive functions.

Lower cognitive scores pre-treatment were also found to be associated with a modest and nonsignificantly lower endpoint improvement in depression (56.2% responders vs 63.3%). This may have been due to the somewhat longer time-to-response among the cognitively impaired subgroup (median of 12 weeks vs 10 weeks): given that the duration of the trial was 12 weeks, an additional 2–4 weeks of treatment may have yielded equivalent overall response rates in the cognitively impaired subgroup.

Finally, the results of a multiple regression analysis confirmed that improvement in depression severity predicted endpoint improvement in cognitive function. In addition, the regression analysis also identified a greater anticholinergic effect as being a significant (negative) predictor of endpoint cognitive improvement. This result suggests that a simple clinical assessment of peripheral anticholinergic side effects (dry mouth and constipation)
may serve as a proxy index of central anticholinergic activity, which, in turn, is correlated with negative cognitive effects. It should be noted, though, that only a modest 9% of the variance in endpoint cognitive improvement is accounted for by the combined antidepressant and anticholinergic effects.

The current study has several limitations that are important to note and include the following:

- The post hoc exploratory nature of the analyses was not specifically powered to detect between drug differences in cognitive function and depression symptom measures.
- There was a lack of patients with significant baseline cognitive impairment.
- The limited number of cognitive tests performed may not have provided an adequate index of overall cognitive function. Some of the tests do not have age-appropriate norms available; furthermore, while some of the composite measures used in the analyses appear to have clinical and face validity, they have not been prospectively validated. This is true for both the anticholinergic composite and for the composite cognitive score. The latter may contain factors, such as the SLT recall and retrieval scores, that are highly correlated.
- The study treatment was of short duration and there was no placebo control.
- There was a potential lack of representativeness of the study sample (and uncertainty as to how well the results might generalize to depressed patients in the community); this is especially true because of study entry criteria requiring an MMSE score ≥ 24: In a community sample there would likely be a higher proportion of depressed patients with some degree of dementia.

**Conclusion**

The results of the current study are consistent with previous research that has identified cognitive impairment as one of the significant psychosocial consequences of late-life depression (1–5). The current study results indicate that treating depression successfully can have a demonstrable short-term impact on cognition. Our findings suggest that there may be detectable differences among antidepressants in terms of their SLT-related and DSST-related cognitive effects at the end of 12 weeks of acute therapy. Such findings

![Figure 2. Relationship between degree of endpoint improvement in Hamilton Depression Rating Scale (HAM-D) and improvement in cognitive functioning.](https://academic.oup.com/biomedgerontology/article-abstract/58/12/M1137/591650/1142)

*Multiple regression model included age, sex, baseline HAM-D, Interaction of change in HAM-D and treatment, anticholinergic score, somnolence score, change in supine heart rate, baseline CGIs, and number of medications.

Composite cognitive score = sum of baseline-to-endpoint change score of SLT Recalled + SLT retrieved from LT storage + DSST. Prior to summing, each component was expressed as "z score" (i.e., normalized) to ensure equal weight in the sum.

Composite Peripheral Anticholinergic Score = sum of maximum treatment-emergent severity of the two adverse events, constipation + dry mouth (regardless of treatment assignment) (Correlations are based on sample sizes that range from 370 to 385 patients).

LOCF = Last Observation Carried Forward; MMSE = Mini-Mental State Exam; HAM-D = Hamilton Depression Rating Scale; CG1-S = Clinical Global Impressions Severity rating; SLT = Shopping List Task; DSST = Digit Symbol Substitution Test.

Table 3. Summary of Multiple* Correlation Coefficients for Clinical Variables and LOCF–Endpoint Improvement in Composite Cognitive Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spearman Correlation</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.01</td>
<td>.60</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>-0.04</td>
<td>.53</td>
</tr>
<tr>
<td>Number of concomitant medications</td>
<td>-0.03</td>
<td>.08</td>
</tr>
<tr>
<td>Baseline HAM-D</td>
<td>0.00</td>
<td>.97</td>
</tr>
<tr>
<td>Change in HAM-D—Sertaline</td>
<td>-0.05</td>
<td>.0001</td>
</tr>
<tr>
<td>Change in HAM-D—Fluoxetine</td>
<td>-0.04</td>
<td>.01</td>
</tr>
<tr>
<td>Change in HAM-D—Nortriptyline</td>
<td>0.00</td>
<td>.82</td>
</tr>
<tr>
<td>Change in anticholinergic score3</td>
<td>-0.15</td>
<td>.10</td>
</tr>
<tr>
<td>Somnolence score</td>
<td>-0.05</td>
<td>.74</td>
</tr>
<tr>
<td>Change in supine heart rate</td>
<td>0.00</td>
<td>-.69</td>
</tr>
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</table>

*p Multiple regression model included age, sex, baseline HAM-D, Interaction of change in HAM-D and treatment, anticholinergic score, somnolence score, change in supine heart rate, baseline CGIs, and number of medications. **Composite peripheral anticholinergic score = sum of maximum treatment-emergent severity of the two adverse events, constipation + dry mouth (regardless of treatment assignment) (Correlations are based on sample sizes that range from 370 to 385 patients).
as well as future studies of this issue may help clinicians better select the most appropriate agents for treating depression in the elderly, particularly in those at risk for cognitive impairment due to concomitant vascular illness.

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