Treating Depression in Alzheimer Disease

Efficacy and Safety of Sertraline Therapy, and the Benefits of Depression Reduction: The DIADS

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Context: Major depression affects about 25% of the patients who have Alzheimer disease and has serious adverse consequences for patients and caregivers. Results of prior antidepressant treatment studies have produced contradictory findings and have not fully assessed the benefits of depression reduction.

Objectives: To assess the efficacy and safety of sertraline hydrochloride for the treatment of major depression in Alzheimer disease, and to evaluate the effect of depression reduction on activities of daily living, cognition, and nonmood behavioral disturbance.

Design: Randomized, placebo-controlled, parallel, 12-week, flexible-dose clinical trial with a 1-week, single-blind placebo phase. The study was conducted between January 1, 1998, and July 19, 2001.

Setting: University outpatient clinic.

Participants: Forty-four outpatients who have probable Alzheimer disease and major depressive episodes.

Intervention: Sertraline hydrochloride, mean dosage of 95 mg/d, or identical placebo, randomly assigned.

Main Outcome Measures: Response rate, Cornell Scale for Depression in Dementia, Hamilton Depression Rating Scale, Mini-Mental State Examination, Psychogeriatric Depression Rating Scale–activities of daily living subscale, and Neuropsychiatric Inventory to quantify patient behavior disturbance and caregiver distress.

Results: In the sertraline-treated group 9 patients (38%) were full responders and 11 (46%) were partial responders compared with 3 (20%) and 4 (15%), respectively, in the placebo-treated group (P = .007). The sertraline-treated group had greater improvements in the scores for the Cornell Scale for Depression in Dementia (P = .002) and Hamilton Depression Rating Scale (P = .01), and a statistical trend toward less decline in activities of daily living on the Psychogeriatric Depression Rating Scale–activities of daily living subscale (P = .07). There was no difference between the treatment groups in Mini-Mental State Examination (P = .22) or Neuropsychiatric Inventory (P = .32) ratings over time. When full responders, partial responders, and nonresponders were compared, full responders only, or full and partial responders had significantly better ratings on activities of daily living (P = .04), behavioral disturbance (P = .01), and caregiver distress (P = .006), but not on the Mini-Mental State Examination (P = .76). Safety monitoring indicated few differences in adverse effects between the 2 treatment groups.

Conclusions: Sertraline is superior to placebo for the treatment of major depression in Alzheimer disease. Depression reduction is accompanied by lessened behavior disturbance and improved activities of daily living, but not improved cognition.

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ALZHEIMER DISEASE (AD) is a progressive disease with debilitating consequences for patients, their families, and the public welfare. While cognitive and functional decline is the hallmark of AD, neuropsychiatric disturbances afflict about 90% of the patients. The treatment of neuropsychiatric disturbances is an essential part of the treatment of AD. Despite this, the evidence supporting the use of interventions for these disturbances has been sparse. Depression is one of the most common neuropsychiatric disturbances in AD. Population studies estimate that 20% of the persons who have AD also have depression while clinical studies suggest that the prevalence of a major depression is 20% to 25%, with other depressive syndromes affecting an additional 20% to 30%. Studies from long-term care estimate the annual incidence of depression to be at least 6%, . The natural history of depression over the course of AD has not been fully studied. Depression may be the first
symptom of AD and may be more common in mild to moderate dementia and less prevalent in severe dementia. While depressive symptoms fluctuate over time, at least one study has reported that depression has a 30% to 40% probability of being persistent over at least 6 months.

Depression, a major cause of disability in AD, has been associated with excess impairment in the quality of life, greater disability in activities of daily living (ADL), greater likelihood of physical aggression, greater likelihood of being discharged from an assisted-living facility, earlier entry into a nursing home, and greater caregiver burden. In addition, depression in the presence of cognitive impairment may lead to an increase in mortality or suicide.

The origin and pathophysiological features of depression in patients who have AD is uncertain. Insight into having AD is not associated with depression nor is there a consistent association between disability and depression. Neuropathological features of AD are important; depression is associated with selective loss of noradrenergic cells in the locus coeruleus, and possibly the serotonergic raphe nuclei. These findings have implications for the treatment of depression, specifically, the manipulation of relevant neurotransmitter systems in treating AD-associated depression.

Data on the treatment of depression in AD have recently been reviewed and summarized in a table to which the reader is referred for greater detail.

Despite expert recommendations on treating depression, findings from controlled pharmacological trials are difficult to interpret. Each of these treatment studies has used different methods, with a lack of uniformity in the definition of cognitive impairment or the definition of depression. Sample sizes have generally been small and the outcome of interest has varied. Almost all studies have been short term. Few focused on patients who have AD and major depression. Most included patients with a range of cognitive disorders or depression. One reported that moclobemide, an antidepressant not marketed in the United States, is superior to placebo. Another reported that imipramine hydrochloride, a highly anticholinergic antidepressant, is not superior to placebo, although a substantial placebo response might have affected that finding. A nonpharmacological intervention study demonstrated the efficacy of 2 caregiver interventions in reducing patient and caregiver depression, relative to a wait-list control group. Conflicting results have also been reported about the secondary benefits of depression reduction. Depression reduction has been associated with improvements in cognition in some studies, but not in others. Two studies reported no improvement in ADL. Secondary benefits in other domains have not been assessed.

The aims of this study were (1) to evaluate the safety and efficacy of sertraline hydrochloride in the treatment of major depression in patients with AD and (2) to evaluate potential secondary benefits of depression reduction in a series of nonmood domains including ADL, cognition, nonmood behavior disturbance, and caregiver distress. In a previously published interim analysis, we reported that sertraline therapy had efficacy, when compared with placebo, in reducing depression.

**METHOD**

**DESIGN**

Randomized, placebo-controlled, parallel, 12-week, flexible-dose clinical trial after a 1-week, single-blind placebo phase.

**PARTICIPANTS**

Participants were recruited from outpatient clinics of The Johns Hopkins Neuropsychiatry Service, The Johns Hopkins Hospital, Baltimore, Md, or The Copper Ridge Institute, Sykesville, Md, between January 1, 1998, and July 19, 2001. All participants or legal representatives provided informed consent for participation under the human subjects oversight of a Johns Hopkins institutional review board. After providing consent, participants underwent a screening evaluation to determine if they met inclusion criteria. Figure 1 contains a schematic of participant flow across study visits. At the screening visit, 3 participants were excluded for not meeting enrollment criteria. The remainder met the following:

**INCLUSION CRITERIA**

1. Diagnosis of probable AD by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association.
2. Score of 10 or more on the Mini-Mental State Examination (MMSE).
3. Diagnosis of major depressive episode, using DSM-IV. To address potential overlap between symptoms of AD and major depression, if DSM-IV criterion 2 were to count toward the diagnosis of a major depressive episode, it had to be clearly because of loss of pleasure (anhedonia) and not due entirely to loss of interest. Also if DSM-IV criterion 8 were to count toward the diagnosis, it had to be because of indecisiveness and not entirely because of difficulty concentrating.
4. Current residence in a community setting (home or assisted living).
5. Caregiver willing to accompany the participant to study visits.
6. Stable medical history and general health. Patients were excluded if they had a current unstable medical condition (eg, symptomatic uncontrolled diabetes mellitus), if they had a medical condition that would preclude use of sertraline therapy (eg, severe headaches or liver disease), or if they had a condition that affected their ability to participate (eg, cancer requiring frequent medical visits for chemotherapy).

**EXCLUSION CRITERIA**

1. Use of sertraline therapy contraindicated in the opinion of the study psychiatrist.
2. A lifetime diagnosis of schizophrenia, bipolar disorder, or pre-AD anxiety disorder.
4. Acutely suicidal or requiring inpatient psychiatric hospitalization, as determined by the study psychiatrist.

Every effort was made to include patients who would be offered sertraline to treat their depression in day-to-day practice to promote the generalizability of study findings.

**PROCEDURES AND TREATMENT**

After meeting entry criteria, beginning at enrollment, all patients and caregivers received illness education, encouragement, and emotional support. This was continued at all study visits. Participants who met inclusionary and exclusionary cri-
criteria were rated on the Hamilton Depression Rating Scale (HDRS) to establish a baseline and then received a single placebo pill daily during a 1-week, single-blind phase. This was intended to exclude patients with transient depressive symptoms. At the end of the single-blind phase, patients were assessed for meeting entry criteria and were excluded if they had more than a 30% reduction in HDRS scores. Participants who dropped out of the study in this phase were excluded from the analyses. No participants were excluded because they no longer met entry criteria or because of reduction in HDRS score.

On completing the single-blind phase, participants were assigned randomly using a random numbers generating computer program, in blocks of 6, without stratification, to the selective serotonin reuptake inhibitor, sertraline, or to placebo in identical-appearing pills. The research pharmacist implemented random allocation and masked treatment assignment was communicated by telephone to study staff. The starting dosage was 25 mg/d. Patients, caregivers, and investigators (except the investigational pharmacist) were all masked as to the assignment. The dosage was increased to 50 mg/d a week later. Pill—sertraline or placebo—dosages were increased steadily after that by the study psychiatrists (C.G.L., M.S., and P.V.R.) about every week to a total maximum dosage of 150 mg/d or the highest tolerated dose. After week 6, only downward titration for adverse effects was allowed.

Clinical follow-up and outcome assessment occurred every 3 weeks. Brief telephone contact was made weekly for education, encouragement, and emotional support. Adverse effects and adverse events were recorded at each follow-up.

Figure 1. Profile of the Depression in Alzheimer’s Disease Study.

### MAIN OUTCOME MEASURES

#### Response to Treatment

The principal outcome measure was response to treatment rated by 2 psychiatrists (M.S. or P.V.R.) who reviewed scores on baseline and follow-up depression rating scales—but not other measures—after patients completed the study. These psychiatrists were masked to assignment and did not personally manage each patient’s case. They rated each participant on a 3-point global scale as nonresponder (NR), partial responder (PR), or full responder (FR). No algorithm was involved. Rather, they were asked to use their best clinical judgment in making the determination. This rating was designed to capture a clinically salient, global rating of depression reduction, summarizing the course of each patient across the study, uninfluenced by knowledge of treatment assignment or by ratings on nonmood measures.

#### Depression

The Cornell Scale for Depression in Dementia (CSDD) and the HDRS given at baseline (week 0) and at weeks 3, 6, 9, and 12 rated depressive symptoms. The CSDD uses a comprehensive approach to rate symptoms of depression with input from patients and their caregivers, which improves reliability. It has good reliability and exhibits a high concordance with the clinical diagnosis of major, minor, or absent depression. The HDRS is the most widely used measure in clinical trials for depression and has well-established validity and reliability. By using
2 outcome measures, we expected to improve sensitivity and validity in detecting changes in depression. On both scales higher scores indicate more severe depression.

ADL Impairment

The Psychogeriatric Dependency Rating Scale—ADL subscale\(^5\) was used to quantify performance of activities of daily living. The Psychogeriatric Dependency Rating Scale is rater-completed and incorporates information from the patient, caregiver, and medical record. It has good reliability and validity and addresses all major ADL well. Higher scores indicate more severe ADL impairment.

Dementia-Associated Behavioral Disturbance

The Neuropsychiatric Inventory (NPI)\(^5\) is a valid and reliable measure widely used to quantify behavioral disturbance in patients who have dementia. Each of 12 domains is assessed on a different subscale: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep, and appetite. For each domain there are 2 separate scores. The first quantifies the severity of the behaviors incorporating frequency and intensity, and the second quantifies the distress that these behaviors cause to the caregiver. On both scales, higher scores indicate more severe disturbance or caregiver distress. The total NPI score is the sum of the subscales’ scores. To minimize the effect of the NPI mood symptoms on the total NPI score, we estimated a second NPI—the nonmood (NPI-NM) symptom score—and its parallel caregiver distress score—encompassing only the 7 nonmood domains: delusions, hallucinations, agitation/aggression, euphoria, apathy, disinhibition, and aberrant motor behavior. The 5 mood domains—depression, anxiety, irritability, sleep, and eating—were excluded as they were assessed on the CSDD and HDRS.

Cognition

The MMSE was used to quantify global cognitive functioning across study visits. The MMSE is highly reliable and is often used in clinical trials to track the progression of cognitive impairment associated with AD. The MMSE is capable of detecting changes of clinical significance.\(^3\) Lower scores indicate more severe dementia.

Adverse Effects

An adverse effects checklist, screening in part for adverse effects associated with sertraline therapy described in the Food and Drug Administration package insert, was completed at every visit. Information from patient interview, patient examination, and caregiver interview was used to make these ratings. Adverse events ascertained in this way were recorded at each visit and at each telephone contact. At each follow-up, participants were rated on the confusion assessment method\(^2\) to monitor for delirium.

ANALYSES

All analyses were performed using the intent-to-treat approach, with last observations carried forward, and included all 44 subjects who were randomized.

Efficacy and Safety Analyses

The placebo- and sertraline-treated groups were compared at baseline and at each of the follow-up visits. Table 1 lists baseline comparisons of the 2 groups on sociodemographics, dementia and depression histories, medical comorbidity, and standardized ratings. A proportional odds model was used to compare response rates between the 2 study groups. Repeated-measures analyses of covariance (ANCOVA) models, with baseline score as a covariate, were estimated to compare the 2 groups over time on all outcome variables. Adverse effects were compared in cross-tabulation.

Analysis of Effects of Depression Reduction on Nonmood Variables

The sample was divided according to the psychiatrists’ response ratings. The nonmood measures of the 3 groups were then compared using repeated-measures ANCOVA models, with the baseline score as a covariate.

RESULTS

BASELINE COMPARISONS OF THE SERTRALINE- AND PLACEBO-TREATED GROUPS

Table 1 compares treatment groups on baseline measures. The only significant finding was a greater proportion of women receiving sertraline therapy. Severity of medical comorbidity was assessed using the General Medical Health Rating. This is a 4-point global rating of severity of medical comorbidity developed for patients who have dementia. It considers the number of comorbid conditions, the number of medications for comorbidities, and general appearance. Higher scores indicate less severe or absent comorbidity. The 2 groups did not differ on the General Medical Health Rating, or any of the baseline outcome measures.

OUTCOME COMPARISONS OF THE SERTRALINE- AND PLACEBO-TREATED GROUPS

Table 2 contains a cross-tabulation of psychiatrists’ response ratings by study group. A worst-rank (the 2 subjects who dropped out after baseline were counted as full responders) proportional odds model showed a significant positive relationship; an exact P value of .006 was estimated using a permutation test. The mean percent reduction (95% confidence interval [CI]) for the 3 groups of responders (NR, PR, and FR) on the CSDD and HDRS were as follows. The results for the CSDD were NR, −1.4% (95% CI, −19% to 16%); PR, 38% (95% CI, 23%-53%); and FR, 66% (95% CI, 46%-86%). The results for the HDRS were NR, −0.7% (95% CI, −11% to 9%); PR, 46% (95% CI, 33%-58%); and FR, 67% (95% CI, 46%-87%).

Table 3 gives the means at baseline and each of the follow-up points and results of repeated-measures ANCOVA models for the outcome measures. For each outcome, effect sizes for week 12 relative to baseline are also shown, as are exact P values (in the table footnotes). Both CSDD and HDRS significantly differed between study groups. On the CSDD, the mean reduction fraction was 0.16 (95% confidence limits, 0.02, 0.30) for the placebo-treated group and 0.49 (95% confidence limits, 0.33, 0.65) for the sertraline-treated group. On the HDRS, the mean reduction fractions were 0.19 (95% confidence limits, 0.04, 0.34) and 0.41 (95% confidence limits, 0.22, 0.61), respectively. The 2 groups also showed a trend toward stabilization of ADL loss, as measured by the Psychogeriatric Dependency Rating Scale—ADL.
There were no significant drug-placebo differences between the 2 treatment groups on MMSE, total NPI, overall and caregiver distress, or NPI-NM, total and caregiver distress (the latter 2 are not given in Table 3). The mean reduction in total NPI scores was 3 times larger in the sertraline-treated group than the placebo-treated group (9.4 vs 3.1 points), although this did not reach the level of statistical significance. Reductions in NPI-NM domains were similar across the board with no pattern emerging of domain-specific reductions.

SAFETY AND TOLERABILITY

Figure 1 indicates that twice as many participants dropped out of the placebo-treated group (5/20 or 25%) compared with the sertraline-treated group (3/24 or 12.5%). Three of the 5 receiving placebo withdrew owing to lack of efficacy, while one third receiving sertraline therapy withdrew owing to adverse effects. Table 4 compares the 2 groups on adverse events. Delirium was assessed using the confusion assessment method. Overall rates were low at

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo-Treated Group (n = 20)</th>
<th>Sertraline Hydrochloride–Treated Group (n = 24)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>79.9 (5.2)</td>
<td>75.5 (9.5)</td>
<td>t2 = 1.84</td>
</tr>
<tr>
<td>Sex, No. (%) female</td>
<td>10 (50)</td>
<td>20 (83)</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Race, No. (%) black</td>
<td>3 (15)</td>
<td>8 (33)</td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>12.4 (3.5)</td>
<td>12 (4.4)</td>
<td>t2 = 0.29</td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td></td>
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<td>Fisher exact test</td>
</tr>
<tr>
<td>Currently married</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>8 (40)</td>
<td>11 (46)</td>
<td></td>
</tr>
<tr>
<td>Living situation, No. (%)</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>In relative’s home</td>
<td>5 (25)</td>
<td>5 (21)</td>
<td></td>
</tr>
<tr>
<td>In assisted living</td>
<td>2 (10)</td>
<td>5 (21)</td>
<td></td>
</tr>
<tr>
<td>Dementia history</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Duration, mean (SD), mo</td>
<td>39.3 (26.5)</td>
<td>34.6 (21.4)</td>
<td>t2 = 0.65</td>
</tr>
<tr>
<td>Family history, No. (%) positive</td>
<td>10 (50)</td>
<td>11 (46)</td>
<td></td>
</tr>
<tr>
<td>Depression history</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Duration, mean (SD), mo</td>
<td>18.6 (20.3)</td>
<td>17.3 (14.1)</td>
<td>t2 = 0.23</td>
</tr>
<tr>
<td>Family history, No. (%) positive</td>
<td>5 (25)</td>
<td>7 (29)</td>
<td></td>
</tr>
<tr>
<td>Personal history, No. (%) positive</td>
<td>3 (15)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Prior medications, mean (SD), No.</td>
<td>0.8 (1.5)</td>
<td>0.6 (1.0)</td>
<td>t2 = 0.42</td>
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<tr>
<td>Medical comorbidity</td>
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<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>GMHR, No. (%)</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Excellent</td>
<td>9 (45)</td>
<td>12 (50)</td>
<td>t = 0.44</td>
</tr>
<tr>
<td>Good</td>
<td>6 (30)</td>
<td>6 (25)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>4 (20)</td>
<td>6 (25)</td>
<td></td>
</tr>
<tr>
<td>Comorbid diagnoses, mean (SD), No.</td>
<td>2.9 (2.6)</td>
<td>2.0 (1.5)</td>
<td>t2 = 1.30</td>
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<tr>
<td>Concurrent medications, mean (SD), No.</td>
<td>3.4 (4.2)</td>
<td>2.4 (2.5)</td>
<td>t2 = 0.980</td>
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<td>Weight, mean (SD), kg</td>
<td>62.6 (14.5)</td>
<td>65.3 (14.0)</td>
<td>t2 = −0.024</td>
</tr>
<tr>
<td>Baseline standardized ratings (visit 2)</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>CSDD, mean (SD), score</td>
<td>18.1 (3.9)</td>
<td>20.2 (5.4)</td>
<td>t2 = −1.46</td>
</tr>
<tr>
<td>HDRS, mean (SD), score</td>
<td>21.8 (5.5)</td>
<td>23.7 (6.5)</td>
<td>t2 = −1.04</td>
</tr>
<tr>
<td>NPI, mean (SD), score</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Total</td>
<td>34.9 (14.8)</td>
<td>36.8 (22.1)</td>
<td>t2 = −0.31</td>
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<tr>
<td>Disruption</td>
<td>21.8 (12.9)</td>
<td>22.9 (20.0)</td>
<td>t2 = −0.21</td>
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<tr>
<td>PGDRS-ADL, mean (SD), score</td>
<td>7.2 (8.3)</td>
<td>6.8 (6.2)</td>
<td>t2 = 0.16</td>
</tr>
<tr>
<td>MMSE, mean (SD), score</td>
<td>16.3 (6.8)</td>
<td>17.5 (6.3)</td>
<td>t2 = −0.63</td>
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<tr>
<td>Treatment information</td>
<td></td>
<td></td>
<td>Fisher exact test</td>
</tr>
<tr>
<td>Completed 12 weeks, No. (%) completed</td>
<td>15 (0.83)</td>
<td>21 (0.88)</td>
<td></td>
</tr>
<tr>
<td>Peak dose, mean (SD), mg/d</td>
<td>113 (30)</td>
<td>108 (41)</td>
<td>t2 = 0.421</td>
</tr>
</tbody>
</table>

There were no significant drug-placebo differences between the 2 treatment groups on MMSE, total NPI, overall and caregiver distress, or NPI-NM, total and caregiver distress (the latter 2 are not given in Table 3). The mean reduction in total NPI scores was 3 times larger in the sertraline-treated group than the placebo-treated group (9.4 vs 3.1 points), although this did not reach the level of statistical significance. Reductions in NPI-NM domains were similar across the board with no pattern emerging of domain-specific reductions.

Table 2. Comparison of Response Rates as Rated by Independent Psychiatrists Reviewing CSDD and HDRS Scores Over Timea

<table>
<thead>
<tr>
<th>Consensus Rating</th>
<th>Placebo–Treated Group (n = 20)</th>
<th>Sertraline Hydrochloride–Treated Group (n = 24)</th>
<th>Proportional Odds Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>No response</td>
<td>13 (65)</td>
<td>4 (17)</td>
<td>χ2 test = 7.29, P = .007†</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (15)</td>
<td>11 (46)</td>
<td></td>
</tr>
<tr>
<td>Full response</td>
<td>4 (20)</td>
<td>9 (38)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CSDD, Cornell Scale for Depression in Dementia; HDRS, Hamilton Depression Rating Scale.

*Data are given as number (percentage) of patients.
†Exact P value, .006.
all study visits. The most common adverse affects were dizziness and gastrointestinal symptoms. There was no difference in frequency of adverse events between the 2 study groups. These findings suggest that sertraline therapy was well tolerated in these doses.

### EFFECTS OF DEPRESSION REDUCTION

The effect of depression reduction on nonmood outcomes was assessed using a series of ANCOVA models, as above, comparing the 3 groups of responders. Figure 2A and B show the baseline-adjusted CSDD or HDRS means and SEs at each visit for the 3 groups. The 3 groups significantly differed on these measures, as expected, since the psychiatrists’ ratings were based on these measures. Depression scores were unchanged over time in the NR group, while being significantly lower in the PR and FR groups than in the NR group by week 3. The FRs and PR groups separated at week 9 and remained so in week 12. Improvement was evident in most PR patients by week 3 and was complete by week 6, while FRs continued to improve until week 12.

Figure 2C-F displays baseline-adjusted mean Psychogeriatric Dependency Rating Scale–ADL, MMSE, and NPI–NM (total and caregiver distress) scores and their SEs. Regarding the time course of ADL change (Figure 2C) the 3 groups were comparable through week 6, with the lines crossing later on. This was mostly was because of sustained ADL worsening in the NR group. There was no difference by treatment response on MMSE scores (Figure 2D). The FRs had lower baseline scores on the NPI-NM symptom and caregiver distress scales (Figure 2E and F). At week 3 the 3 groups converged in their scores. At week 6 nonmood behavioral symptoms and their associated caregiver distress, as rated by the caregivers, were significantly improved in the FR group, relative to the PR and the NR groups.

### COMMENT

The findings from this 12-week randomized, placebo-controlled trial demonstrate that sertraline is effective for the treatment of major depression in patients who have
probable AD, at a mean dosage of 95 mg/d. The difference in FR rate between the 2 groups was 17% (effect size, 0.85), and the difference in any response rate was 49% (effect size, 1.4), both substantial effect sizes. Sertraline-treated patients also had a trend toward less ADL decline than their placebo-treated counterparts. While ADL scores of the sertraline-treated group remained stable, ADL scores of the placebo-treated group worsened substantially from a mean of about 5 (home-based level of care) to a mean near 10 (assisted-living level of care).20

### Table 4. Adverse Events, by Study Visit and Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Up to Week 3</th>
<th>Up to Week 6</th>
<th>Up to Week 9</th>
<th>Up to Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo-Treated Group (n = 20)</td>
<td>Sertraline-Hydrochloride-Treated Group (n = 24)</td>
<td>Placebo-Treated Group (n = 18)</td>
<td>Sertraline-Treated Group (n = 24)</td>
</tr>
<tr>
<td>Autonomic</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness/lightheadedness, syncope</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fall</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
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<td>4</td>
<td>5</td>
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</table>

*Data are given as the number of patients.

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While this may have been a chance finding, the ADL decline in the placebo-treated group might be attributed to the effects of sustained depression in combination with AD. Alternatively, it might be related to changed caregiver expectations, the primary source of information for ADL ratings. Or, perhaps this phenomenon represented regression toward the mean since the NRs had better ADL function at baseline and declined more over time (Figure 2C). Sertraline treatment was well tolerated, with few increases in adverse effects relative to placebo.

Depression reduction was also associated with benefits to nonmood outcomes of importance to patients who had AD and their caregivers. The most striking benefit involved ADLs, with stabilization, and perhaps some reversal of ADL decline, relative to NRs. In addition, nonmood behavior disturbance and its associated caregiver distress lessened with depression reduction with FRs exhibiting minimal behavior disturbance by the end of the study. This in part was owing to the fact that behavioral disturbance at baseline was associated with less likelihood of a full depressive response (Figure 2E). The latter reduction of caregiver distress with depression reduction bears special emphasis given the importance that caregivers play in the lives of patients with dementia.

The ADL and nonmood behavior benefits in the PR and FR groups were delayed relative to the time course of depression reduction. This is consistent with the hypothesis that depression reduction, and not sertraline treatment per se, was critical to improvements in these other domains. It is further supported by the fact that the effect on nonmood variables was most prominent in the comparison by response type as opposed to the comparison by treatment type. Of course it is impossible to be sure that depression reduction was the cause of the changes in the secondary variables since several mechanisms might have accounted for the effects on ADL, cognition, and behavioral end points.

The efficacy findings here are similar to studies in which antidepressants were superior to placebo for the treatment of depression in patients with AD. However, 2 of these had small sample sizes, and the third used a medication, moclobemide, that is not approved for treatment of depression in the United States. The findings are in contrast to studies that reported a lack of efficacy of antidepressants vs placebo. Several of these also had methodological shortcomings. For example, in one study all patients had degenerative dementia, only about half had depression, and there was a substantial placebo response perhaps due to unintentional psychotherapy; in another most patients were not depressed at baseline; in another patients were included with minor depression, and all patients were women residents of a nursing home, with more severe dementia; and, in yet another about half the sample suffered from minor, not major depression. Thus, the existing evidence regarding the efficacy of pharmacological treatment for depression in patients with AD has been contradictory.

The effect size reported in this study is higher than has been reported before for treatment studies of depression in AD or for geriatric depression. This could be a chance finding. It might also be the result of the careful selection of patients included in the trial. We were careful to include participants who clearly met entry criteria with regard to probable AD with major depressive episode. This may further reflect the improved diagnostic reliability that comes from a single site study.

Previous efficacy studies have not fully addressed the question of the secondary benefits of depression reduction. Three placebo-controlled studies reported improvements in cognition with antidepressant therapy, and one other controlled study has reported improvements in cognition with improvements in depression. However, this was not borne out in 2 studies that reported either decline in or no benefits to cognition with treatment, findings that were likely due to the use of medications with significant anticholinergic activity. In this study there was no benefit to cognition as assessed by the MMSE even after 12 weeks, although there was no worsening of cognition with treatment.

Previous cross-sectional studies have found associations between depression and wandering or agitation, or physical aggression. In this study, behavioral improvement followed temporally and was commensurate with improvement in depression. This supports the hypothesis that depression in AD may lead to behavior disturbance since its treatment is followed by behavioral improvement. Responders in whom depression fully remitted experienced a reduction of behavioral disturbance into the minimally symptomatic range, PRs experienced on average a 50% reduction in behavioral disturbance, and NRs exhibited essentially no change in behavioral disturbance.

Limitations of this study were the recruitment of participants from specialty referral clinics and the requirement of meeting strict inclusion criteria for both AD and major depression. Thus, these findings might not apply to patients with other types of dementia or with milder mood disturbances. Similarly, these findings might not apply to patients with more severe dementia (MMSE score, <10). As well, the study sample size was small, and the global ratings of response were derived from physicians reviewing scale scores over time, and not from in-person examinations. Finally, the interim analysis may have biased the ratings of subsequent patients in the trial.

These findings support the validity of diagnosing depression in patients who have AD and should increase the confidence of clinicians regarding the detection and treatment of depression among patients who have AD. This is particularly true in the primary care setting in which AD itself is frequently undiagnosed, in part because clinicians feel that they do not have much in the form of treatment to offer. The detection and treatment of neuropsychiatric symptoms of AD, depression in particular, can be of benefit to patients.

These findings also guide the clinical management of depression in AD. A complete lack of improvement of depression after treatment for 6 weeks may suggest that the patient is an NR and that a different treatment should be tried. For patients who show at least a partial response after 6 weeks, waiting a few weeks longer with no dose adjustment might lead to further depression reduction. Activities of daily living and behavioral benefits may lag depression reduction. Maximizing depression reduction may maximize the behavioral benefit. In
some cases this might necessitate combination therapies with antidepressants, such as atypical antipsychotic agents if delusions or hallucinations are present, or anticonvulsants as agitation is prominent. Several questions about the management of depression in AD remain unanswered. The efficacy of antidepressants in milder depression is uncertain. The comparative efficacy of antidepressants from different classes has not been adequately explored, especially since there is an association between damage to the locus coeruleus and depression in AD suggesting that noradrenergic antidepressants may have better efficacy than pure serotonergic ones. The comparative efficacy of pharmacological and nonpharmacological therapies for depression in AD is unknown. Finally, little is known about how long treatment for depression in AD should be continued. The expert recommendation in geriatric depression is for continued treatment for as long as 1 year after remission, and perhaps longer for patients who have had more than 1 episode of depression. Future research should address these issues.

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