Published in final edited form as:
Am J Geriatr Psychiatry. 2012 December ; 20(12): 1036–1044. doi:10.1097/JGP.0b013e31826ce4c5.

Cognitive Outcomes after Sertaline Treatment in Patients with Depression of Alzheimer's Disease

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Conflict of interest

These disclosures include any anticipated conflicts through 9/31/11, according to the DIADS-2 Conflict of Interest Policy (available upon request from the study PI).

- Barbara Martin is involved in another trial for which Pfizer donated a different drug.
- Paul Rosenberg has received research funds from Pfizer and Merck in amounts greater than $10,000.
- Jacobo Mintzer is a current grant recipient for Wyeth, Lilly and Pfizer.
- Daniel Weintraub has received research support from Boehringer Ingelheim; Dr. Weintraub also has been a paid consultant for Acadia Pharmaceuticals, Novartis Pharmaceuticals, Boehringer Ingelheim, Osmotica Pharmaceutical, BrainCells Inc., EMD Serono, and Sanofi Aventis, and has participated on a Speaker's Bureau for Pfizer.
- Anton Porsteinsson is involved in research sponsored by Pfizer to study donepezil and PF04494700, Eli Lilly to study atomoxetine, a gamma-secretase inhibitor and a beta amyloid antibody, Wyeth to study a beta amyloid antibody, GSK to study a PPAR inhibitor and Forest to study memantine and neramexane; Dr. Porsteinsson has been a paid consultant and participated on a Speaker's Bureau for Pfizer and Forest.
- Lon S. Schneider is involved in research sponsored by Pfizer, the manufacturer of sertraline and other drugs used to treat mood disorders; Dr. Schneider has been a paid consultant for Abbott, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Johnson and Johnson, Lundbeck, Merck, and Wyeth, manufacturers of antidepressants or drugs used to treat mood disorders.
- Constantine Frangakis has no conflict of interests.
- Lea Drye has no conflict of interests.
- Peter Rabins has participated on Speaker's Bureaus for Wyeth, Eli Lilly, and Pfizer more than two years previous. He has provided legal testimony for Janssen Pharmaceutica.
- Cynthia Munro has no conflict of interests.
- Curtis Meinert is involved in another trial for which Pfizer donated a different drug; Dr. Meinert owns shares of GSK stock.
- Constantine Lyketsos was involved in another trial for which Pfizer donated a different drug; he also was involved in research sponsored by Forest to study escitalopram and citalopram and Pfizer to study sertraline and donepezil; Dr. Lyketsos served as a consultant for Organon, Eisai, GSK, Lilly, Wyeth, and Pfizer.

Abstract

Objectives—While many depressed patients with Alzheimer's disease are treated with antidepressants, the effect of such treatment on cognitive performance in these patients is not known. The authors report cognitive outcomes in patients with depression of Alzheimer's disease (dAD) after a 24-week trial of sertraline or placebo.

Design—Placebo-controlled, randomized, double-blind trial.

Setting—Outpatient memory clinics at 5 academic medical centers in the United States.

Participants—131 patients with dAD (60 men) and Mini Mental State Exam (MMSE) scores of 10–26.

Intervention—Sertraline (n=67), target dose of 100mg daily, or matching placebo (n=64). Caregivers received standardized psychosocial intervention throughout the trial.

Measurements—MMSE, ADAS-Cog, letter fluency, backwards Digit Span, Symbol Digit Modalities Test, and Finger Tapping Test, administered at baseline, and 8, 16, and 24 weeks following baseline.

Results—A series of linear models indicated no effect of treatment or of depression remission on cognitive test performance at 24 weeks. Regardless of treatment condition, very little change in cognitive test performance was noted in general.

Conclusions—Treatment with sertraline in patients with dAD is not associated with greater improvement in cognition at week 24 as compared to treatment with placebo.

Objective

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive and functional decline. In addition to the primary effects of AD on cognition, other factors associated with AD can affect cognitive functioning. One such factor is depression, which affects up to 50% of patients with AD (1). Because depressive symptoms in non-demented older adults are associated with deficits in cognitive performance (particularly executive functioning; 2–4), it is possible that treatment of depression will be associated with improved cognitive performance. For that reason, we are interested in the cognitive effects of antidepressant treatment or depression reduction in AD patients with depression.

Previously, we reported secondary analyses of a prior randomized, placebo-controlled, 12-week trial of sertraline for the treatment of major depression in patients with AD (5). Whereas improved mood was not associated with better cognitive outcomes, a sex difference in response to treatment was observed. Specifically, women who took sertraline, regardless of mood response to treatment, had greater cognitive improvement over the trial, compared to women on placebo. In men, sertraline was not associated with a cognitive advantage compared to placebo.

Since our prior work, it has become increasingly recognized that the depression seen in AD can be differentiated from typical depression seen in elderly without dementia. Specifically, depression in AD can be distinguished by the presence of irritability and social isolation with less evidence of guilt, suicidal thoughts, or reports of low self-esteem (6, 7). This appreciation led to the proposal that the depression of AD (dAD) may represent a distinct syndrome, which may or may not respond to treatment with available antidepressants.

The Depression in Alzheimer's Disease Study – 2 (DIADS-2) was designed to study the efficacy and safety the antidepressant sertraline for dAD. We have previously reported no effect of sertraline treatment of dAD on mood outcomes or remission after 12 or 24 weeks

of follow-up (8, 9). Here we explored the cognitive effects of treatment at week 24. In light of our prior findings that sertraline may benefit cognitive test performance in female patients, we designed the cognitive test battery for DIADS-2 with the goal of increasing its sensitivity to detect cognitive changes associated with improved mood (depression reduction), and also in response to selective serotonin reuptake inhibitor (SSRI) treatment.

Based on our prior findings (5), we hypothesized that treatment with sertraline would be associated with better cognitive outcomes than treatment with placebo, and that benefits in cognition might occur several weeks after any benefits in mood. We further hypothesized that the cognitive benefit of sertraline would be greater in women than in men.

METHODS

Study population

The study design has been published previously (10). In brief, patients were recruited from five outpatient memory disorder clinics. They were diagnosed with AD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (11) criteria, with Mini Mental State Examination (MMSE, 12) scores of 10–26. They also met criteria for dAD, the details of which have been described previously (6). The study included patients who were being treated with cholinesterase inhibitors and/or memantine, but excluded those treated with antipsychotics, other antidepressants, or benzodiazepines. Anticonvulsant medications were permitted for treatment of a preexisting seizure disorder. Participants and their authorized representatives provided informed consent according to procedures established by each site and their institutional review boards. Informed consent was also obtained from caregivers for the collection of caregiver measures. The study protocol was reviewed and approved by Institutional Review Boards at the participating institutions, and was carried out under the oversight of a Data Safety Monitoring Board operated by the National Institute of Mental Health. A CONSORT chart of patient disposition in the study has been published previously (8, 9).

Study design

This was a 24-week, randomized, multicenter clinical trial with two parallel treatment groups. One group (n=67) received sertraline (target dose 100 mg/day), while the other group (n=64) received matching placebo. A primary caregiver accompanied patients to study visits to receive a standardized psychosocial intervention and to participate in study assessments.

In-person clinic study visits occurred at baseline, and at 2, 4, 8, 12, 16, 20, and 24 weeks after baseline. At week 12, the course of depression was assessed and patients whose mood symptoms were rated as having not improved on the Alzheimer's Disease Cooperative Study-clinical global impression of change (mADCS-CGIC; 13) were unblinded to treatment condition and had the option of tapering off study medication and pursuing open-label treatment prescribed by their physicians. For the remainder of the participants, randomized study treatment ended at week 24. All patients, regardless if or when they terminated treatment, followed the same schedule of study visits and assessments until week 24 to allow for the evaluation of other study outcomes, such as the cognitive outcomes. At week 24, patients still on blinded treatment were unmasked to treatment assignment.

Outcomes

Patients underwent cognitive testing 4 times: baseline, and at weeks 8, 16, and 24 after baseline. To maximize sensitivity in detecting cognitive changes associated with remission of symptoms of depression in dAD, the cognitive test battery for DIADS-2 was chosen to

include tests found to differentiate between AD patients with and without depression in cross-sectional studies. One study in particular (14) included AD patients with depression, rather than dysthymia, and found that tests assessing attention, free recall, and psychomotor and fine motor speed revealed an effect of mood in AD patients. We therefore included tests of these domains for this study.

Analyses of data collected through DIADS-1 revealed a greater effect of sertraline than mood on cognitive change over time. Therefore, in addition to detecting the cognitive effects of depression, we were also interested in determining if sertraline, perhaps independent of mood, had an effect on cognitive functioning. Several studies found that word-learning and digit symbol tasks were among the most sensitive to the effects of sertraline, independent of mood (15–18). We thus included these measures in the battery for the current study. Outcome measures for this study of the cognitive outcomes were scores on the following tests:

Mini Mental State Exam (MMSE; 12)—This is a well-known global cognitive measure used for the detection of dementia and estimation of its severity. It has been widely used in clinical trials and the particular domains most often affected in AD (orientation, memory) are included in this instrument. Other items include those assessing working memory, naming, and the ability to follow verbal and written commands, spontaneously write a sentence, and copy two overlapping pentagons. Higher scores indicate better performance, with scores ranging from 0 – 30.

Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog; 19)—This scale was developed specifically to assess cognitive functioning in patients with Alzheimer's disease. It is widely used in clinical trials, and its sensitivity in detecting cognitive changes in patients with AD has been demonstrated in a number of studies (e.g., 20, 21). Scores are obtained for orientation, word-list recall and recognition, object naming, ability to follow simple requests, ideational and constructional praxis, and expressive language. Scores range from 0 – 70, with higher scores indicating worse performance.

Digit Span Subtest (Wechsler Memory Scale-III; 22)—In this measure of attention and working memory, the subject is asked to repeat sequences of single-digit numbers that are read aloud by the examiner. The length of the sequences increases progressively, with two trials of each sequence. The digits backward condition, whereby the digits must be repeated in reverse order, was used. One point is assigned for each correct response. Scores range from 0 to 14, with higher scores indicating better performance.

Letter Fluency (23)—For this task, the subject orally generates as many words as possible that begin with a specified letter, excluding proper names and different forms of the same word. Two trials, one constrained by the letter *s* and the other constrained by the letter *p* were used. The subject is allowed one minute to generate as many words as possible beginning with each letter. The sum of these two trials was used for analysis.

Digit Symbol Modalities Test (24)—In this timed visuo-perceptual decoding task subjects are required to associate single-digit numbers with unfamiliar symbols. A stimulus set of nine printed digit-symbol pairs is presented as a key. Below the key are rows of symbols with a blank box below each symbol. The examinee is instructed to write the correct number below each of the symbols using the digit-symbol key. The score is based on the number of substitutions completed within a 90-second time limit, with higher scores indicating better performance.

Finger Tapping Test (25)—This test of fine motor speed records the number of times the subject can tap a lever with the index finger of each hand, palm down and with fingers extended, in 10-second intervals. For the current protocol, 5 trials for each hand, dominant hand first, were recorded. The mean number of taps over the trials for each hand was used for analyses.

Data Analysis

The primary analyses were intention to treat, performed according to original treatment assignments (i.e., randomization to sertraline or placebo). Missing outcomes were imputed using the method of multiple imputation (26). Prediction models of missing data were estimated based on available baseline and follow-up data. These models were used to impute the missing outcomes five times. The results of five imputations were synthesized using simple combination rules (27) to yield estimates of treatment comparisons.

Because we hypothesized that any changes in cognition would occur later in time than changes in mood, the primary comparison of cognitive outcomes of the placebo and sertraline groups was focused on data ***at*** week 24. Linear regression models were used to compare treatment groups at 24 weeks on the MMSE, ADAS-Cog, Letter fluency, Digit Span backwards, Symbol Digit Substitution, and Finger Tapping Test. Transformations of the scores were used when needed (i.e., when the outcome was not normally distributed). Models controlled for participants' baseline scores on the particular cognitive test. To determine if the treatment effect on week 24 cognition differed in the subgroups defined by sex, ethnicity, or week 12 remission status, models were also estimated that allowed for treatment group by subgroup interactions.

In addition to the comparison at week 24, mixed effects models compared the cognitive outcomes by treatment group ***over*** the 24 weeks. Because there was little change in the cognitive outcomes over the 24 weeks in either treatment group, only results for the week 24 comparison are shown here. Years of education differed by treatment group, so the results include adjustment for years of formal education. Models with and without adjustment for site were analyzed; the treatment effect estimates were virtually identical, so the results reported here are from the models without controlling for site.

Statistical analyses were performed using R version 2.7.1 (28). All p values are two sided. $P < 0.05$ was used as the threshold for statistical significance. No adjustments were made for multiple comparisons.

RESULTS

The final sample included 131 patients with median age of 79 (1^{st}, 3^{rd} quartiles: 73, 83). As shown in Table 1, only years of education, which was higher in the group treated with sertraline than it was in the group receiving placebo, differed between the groups. The median duration of dementia was 3 years (1^{st}, 3^{rd} quartiles: 2, 5). For most individuals in the study, depression did not predate cognitive decline.

Baseline cognitive test scores for the study groups are in Table 2. As is apparent, study participants performed below the range of normal healthy individuals, and the broad range of scores reflected the variable degree of cognitive impairment in the sample. The only difference between the treatment groups on cognitive test scores at baseline was on letter fluency; the sertraline group performed better than the placebo group on this measure.

For each test, four models were computed, all of which controlled for baseline test score and education. The first model tested the overall effect of treatment group, and did not suggest

any significant differences between the sertraline and placebo groups on cognitive test performance at week 24 (*p* values for each cognitive test ranged from .24 to .77). The second model, shown in Table 3, examined whether treatment effects were different in men compared to women; findings were again not significant for any cognitive test. Finger Tapping Test scores were modeled separately for the dominant and non-dominant hands, but because the results were not significant for either hand, only models for scores using the dominant hand are shown.

The third model included a term for remission status at week 12, to determine whether the effects of treatment differed in patients whose depression remitted by week 12 compared to those who did not respond to treatment by week 12. Results did not approach significance for any of the cognitive tests (data not shown). A model examining the effects of race was also conducted, but also did not reveal any significant differences (data not shown).

To examine whether we could identify any particular subgroup of participants whose memory improved over the trial, we examined the number of words recalled on the verbal memory test from the ADAS-Cog. The mean change in words not recalled from baseline to week 24 was close to zero (+0.26). Examination of individual test scores indicated that the maximum improvement in number of words recalled was approximately 2. Ten individuals (5 women) randomized to sertraline had 1 word or greater improvement in mean number of words not recalled. Eleven individuals (6 women) in the placebo group had 1 word or greater improvement in number of words not recalled. Thus, unlike in our prior study, none of our patients demonstrated any significant improvement on a test of verbal memory. Furthermore, none of the participants improved more than two points on any measure.

DISCUSSION

The current study of cognitive outcomes in patients with dAD after treatment with sertraline found no cognitive advantage of treatment over placebo, for either men or women. This difference from our previous findings might be because of several possibilities.

First, it is likely that the improvement we noted in our prior study was due to the additive effects of major depression and AD on cognition. The sample for our current study met criteria for dAD, rather than major depression, which may not respond in the same way to treatment as major depression in patients with AD. This alternative provides support for conceptualizing dAD as a separate disorder from major depression in patients with AD. It is the case, however, that 40% of our patients in the current study also met criteria for major depression. The fact that none of our subjects demonstrated any significant cognitive improvement with sertraline treatment suggests that this alternative cannot solely account for why the findings from our prior study were not replicated here. Second, it is possible that an initial cognitive advantage of sertraline over placebo in some patients is attenuated by 24 weeks. This does not appear likely from our data, as the 12-week cognitive data from the current study also suggest no cognitive advantage of drug over placebo.

Third, the cognitive battery used in this study was different than the battery used in the prior study. In our previous study, the tests on which sex-related cognitive advantages were most apparent were the Hopkins Verbal Learning Test (29) and the Block Design subtest of the Wechsler Intelligence Scale for Children-Revised Edition (30). In order to maintain consistency with other drug trials in patients with AD, we used the ADAS-Cog here. Because it has a word recall task, we did not want to burden subjects with an additional word-list-learning task. We also omitted the Block Design subtest in favor of tests that have been shown in prior studies to be more sensitive to the effects of sertraline (i.e., Symbol Digit Modalities Test, Finger Tapping Test).

Strengths of this study include the double-blind, randomized treatment assignment, with a placebo control. Although our results did not support our hypotheses, they do indicate that sertraline did not impair cognition. In concert with findings from other studies indicating that psychotropic medication is not associated with functional decline (31, 32), the current results indicate that the use of sertraline is also safe cognitively. Another strength is that the sample is likely to be broadly representative of patients with dAD seen in similar settings, due to the relatively few exclusions that were based on medical conditions or concomitant medication use. Furthermore, a high rate of adherence to participation was achieved, with more than 90% of study participants remaining over the initial 12 weeks. Another strength of this trial was the use of a comprehensive cognitive test battery, designed specifically to maximize the likelihood of detecting effects of sertraline and to respond to changes in depression among AD patients. Furthermore, a consensus definition of dAD was used, which minimized the likelihood of between-site differences in study inclusion. The use of a structured psychosocial intervention, with centralized training, and monitoring to adherence of the protocol is also a strength of the study.

Several limitations are notable. First, whereas the study sample may be representative of typical patients with dAD seen in medical centers, the findings might not generalize to other settings, such as primary care. Second, it is possible that some aspects of cognitive functioning, not detected with the test battery, did improve with treatment. If this is the case, it is likely that these would have few functional effects. That is, the battery used in this study was comprehensive enough to detect cognitive changes typically associated with everyday functioning. Nevertheless, apparently very sensitive cognitive tasks (e.g., critical flicker fusion tasks), might have been more sensitive to treatment effects thus providing information regarding the pathophysiology of dAD, despite their lack of functional correlates.

In sum, 24 weeks of sertraline treatment for dAD was not associated with cognitive improvement or less cognitive deterioration than treatment with placebo. These results did not reproduce prior results of a smaller trial of sertraline in AD patients with major depressive episode and do not support the notion of a cognitive benefit for SSRI treatment in patients with dAD.

Acknowledgments

Sources of support

Grant funding:

National Institute of Mental Health, 1U01MH066136, 1U01MH068014, 1U01MH066174, 1U01MH066175, 1U01MH066176, 1U01MH066177; NIMH scientific collaborators participated on the trial's Steering Committee

Drug:

Sertraline and matching placebo provided by Pfizer, Inc.; Pfizer did not participate in the design or conduct of the trial; Manisha Hong, PharmD at Johns Hopkins Hospital Investigational Drug Service packaged and shipped drug

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REFERENCES

1. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: heterogeneity and related issues. Biol Psychiatry. 2003; 54(3):353–362. [PubMed: 12893110]
2. Alexopoulos GS, Kiosses DN, Klimstra S, et al. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. Am J Geriatr Psychiatry. 2002; 10(1):98–106. [PubMed: 11790640]
3. Cui X, Lyness JM, Tu X, et al. Does depression precede or follow executive dysfunction? Outcomes in older primary care patients. Am J Psychiatry. 2007; 164(8):1221–1228. [PubMed: 17671285]
4. Elderkin-Thompson V, Kumar A, Bilker WB, et al. Neuropsychological deficits among patients with late-onset minor and major depression. Arch Clin Neuropsychol. 2003; 18:529–549. [PubMed: 14591448]

5. Munro CA, Brandt J, Sheppard JM, et al. Cognitive response to pharmacological treatment for depression in Alzheimer disease: secondary outcomes from the depression in Alzheimer's disease study (DIADS). Am J Geriatr Psychiatry. 2004; 12(5):491–498. [PubMed: 15353387]

6. Olin JT, Schneider LS, Katz IR, et al. Provisional diagnostic criteria for depression of Alzheimer disease. Am J Geriatr Psychiatry. 2002; 10(2):125–128. [PubMed: 11925273]

7. Rosenberg PB, Onyike CU, Katz IR, et al. Depression of Alzheimer's Disease Study. Clinical application of operationalized criteria for 'Depression of Alzheimer's Disease'. Int J Geriatr Psychiatry. 2005; 20(2):119–127. [PubMed: 15660424]

8. Rosenberg PB, Drye LT, Martin BK, et al. Sertraline for the treatment of depression in Alzheimer Disease. Am J Geriatr Psychiatry. 2010; 18(2):136–145. [PubMed: 20087081]

9. Weintraub D, Rosenberg PB, Drye LT, et al. Sertraline for the treatment of depression in Alzheimer disease: week-24 outcomes. Am J Geriatr Psychiatry. 2010; 18(4):332–340. [PubMed: 20220589]

10. Martin BK, Frangakis CE, Rosenberg PB, et al. Design of Depression in Alzheimer's Disease Study-2. Am J Geriatr Psychiatry. 2006; 14(11):920–930. [PubMed: 17068314]

11. American Psychiatric Association (author). Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: 2000.

12. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

13. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-clinical global impression of change. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11(suppl 2):S22–S32. [PubMed: 9236949]

14. Wefel JS, Hoyt BD, Massma PJ. Neuropsychological functioning in depressed versus nondepressed participants with Alzheimer's disease. Clin Neuropsychol. 1999; 13(3):249–257. [PubMed: 10726596]

15. Finkel SI, Richter EM, Clary CM, et al. Comparative efficacy of sertraline vs. fluoxetine in patients age 70 or over with major depression. Am J Geriatr Psychiatry. 1999; 7(3):221–227. [PubMed: 10438693]

16. Furlan PM, Kallan MJ, Ten Have T, et al. Cognitive and psychomotor effects of paroxetine and sertraline on healthy elderly volunteers. Am J Geriatr Psychiatry. 2001; 9(4):429–438. [PubMed: 11739070]

17. Bondareff W, Murray A, Friedhoff A, et al. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry. 2000; 157:729–736. [PubMed: 10784465]

18. Newhouse PA, Krishnan RR, Doraiswamy PM, et al. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. Journal of Clinical Psychiatry. 2000; 61:559–568. [PubMed: 10982198]

19. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984; 141(11):1356–1364. [PubMed: 6496779]

20. Davis KL, Thal LJ, Gamzu ER, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. N Engl J Med. 1992; 327(18):1253–1259. [PubMed: 1406817]

21. Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: Measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry. 1994; 151(3):390–396. [PubMed: 8109647]

22. Wechsler, D. Manual for the Wechsler Memory Scale-Third Edition. San Antonio, TX: The Psychological Corporation; 1997.

23. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. Neuropsychologia. 1967; 5:135–140.

24. Smith, A. Symbol Digit Modalities Test. Los Angeles, CA: Western Psychological Services; 1982.

25. Reitan, RM. Manual for Administration of Neuropsychological Test Batteries for Adults and Children. Tucson, AZ: Reitan Neuropsychology Laboratories, Inc.; 1979.

26. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley; 1996.

27. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc. 1996; 91:473–489.
28. R. Development Core Team. A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2008.
29. Brandt, J.; Benedict, RHB. Hopkins Verbal Learning Test-Revised: Professional Manual. Odessa, FL: Psychological Assessment Resources; 2001.
30. Wechsler, D. Manual for the Wechsler Intelligence Scale for Children-Revised. San Antonio, TX: The Psychological Corporation; 1974.
31. Livingston G, Walker AE, Katona CL, Cooper C. Antipsychotics and cognitive decline in Alzheimer's disease: The LASER-Alzheimer's disease longitudinal study. J Neurol Neurosurg Psychiatry. 2007; 78:25–29. [PubMed: 16801350]
32. Lopez OL, Wisniewski SR, Becker JT, Boller F, DeKosky ST. Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. Arch Neurol. 1999; 56:1266–1272. [PubMed: 10520944]

Table 1

Demographic characteristics and clinical variables at baseline for dAD patients in the sertraline and placebo groups.

	Sertraline (N=67)	Placebo (n=64)
Age, mean (sd), years	76.5 (8.0)	78.2 (8.0)
Sex, % Female Male	59.7 40.3	48.4 51.6
Ethnic Group, % White, non-Hispanic African-American Hispanic / Latino Asian	73.1 17.9 7.5 1.5	60.9 25.0 14.1 0
Education, mean (sd), years	13.2 (3.6)	11.8 (3.8)
Duration of dementia, mean (sd), years	2.6 (2.1)	3.1 (2.3)
Depression episodes before cognitive symptoms, % No episodes One episode Two or more episodes Missing	77.6 13.4 6.0 3.0	70.3 20.3 9.4 0

Table 2

Medians (95% CI) for cognitive test performance for patients with dAD across study visits by treatment group (sertraline or placebo).

Test	Baseline		Week 8		Week 16		Week 24	
	Sertraline	**Placebo**	**Sertraline**	**Placebo**	**Sertraline**	**Placebo**	**Sertraline**	**Placebo**
MMSE	21.0 (19.5,22.5)	19.5 (17.5,22.0)	21.0 (19.0,23.0)	20.0 (17.5,22.0)	21.0 (18.5,23.5)	20.0 (17.5,22.5)	21.0 (19.0,23.0)	20.0 (17.5,22.5)
ADAS-Cog	21.0 (18.0,24.0)	24.5 (19.0,30.0)	23.0 (17.0,29.0)	24.5 (20.5,28.5)	21.0 (17.5,24.5)	23.0 (20.0,26.0)	21.0 (18.0,24.0)	22.5 (20.0,25.0)
Digit Span	4.0 (3.5,4.5)	4.0 (3.5,4.5)	4.0 (3.5,4.5)	5.0 (4.0,6.0)	4.0 (3.0,5.0)	4.0 (3.5,4.5)	4.0 (3.5,4.5)	4.0 (3.0,5.0)
Fluency	18.0 (15.0,21.0)	14.0 (11.5,16.5)	18.0 (15.0,21.0)	14.0 (10.5,17.5)	17.0 (13.5,20.5)	17.5 (14.0,21.0)	17.0 (14.0,20.0)	17.0 (14.5,19.5)
SDMT	16.0 (11.5,20.5)	11.0 (6.5,15,5)	15.0 (9.5,20.5)	9.0 (5.5,12.5)	12.0 (7.5,16.5)	10.5 (8.0,13.0)	13.0 (7.5,18.5)	9.0 (6.0,12.0)
FTT	33.0 (29.0,37.0)	30.5 (26.5,34,5)	32.0 (28.0,36.0)	32.0 (28.0,36.0)	32.0 (28.0,36.0)	33.0 (27.0,39.0)	34.0 (26.5,41.5)	33.5 (29.0,38.0)

Note. MMSE: Mini Mental State Examination; Digit Span: backwards digit span from the Wechsler Memory Scale-III; Fluency: letter fluency, sum of s and p; SDMT: Symbol Digit Modalities Test; FTT: Finger Tapping Test, dominant hand

Table 3

Estimates of the effect of treatment group, sex, and the interaction between treatment group and sex on cognitive test scores at week 24.*

Variable	Treatment Group (sertraline)		Sex		Treatment Group (sertraline) × Sex (women)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
MMSE	−1.11 (−2.88, 0.65)	0.22	0.58 (−1.08, 2.25)	0.50	1.03 (−1.39, 3.44)	0.40
ADAS-Cog	0.02 (−0.39, 0.43)	0.91	0.12 (−0.28, 0.51)	0.55	0.00 (−0.61, 0.61)	0.99
Digit Span	−0.05 (−0.31, 0.22)	0.74	−0.15 (−0.42, 0.12)	0.27	0.28 (−0.08, 0.65)	0.13
Fluency	−0.09 (−0.60, 0.43)	0.74	0.38 (−0.09, 0.85)	0.11	−0.19 (−0.85, 0.46)	0.55
SDMT	−0.38 (−1.03, 0.26)	0.24	−0.30 (−0.94, 0.34)	0.35	0.52 (−0.41, 1.44)	0.27
FTT	−1.57 (−7.55, 4.40)	0.61	0.93 (−5.60, 7.46)	0.78	0.35 (−8.10, 8.81)	0.93

*The model includes terms for baseline test score, MMSE, education, treatment group, sex and the treatment group by sex interaction.