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Donepezil Treatment in Ethnically Diverse Patients with Alzheimer's Disease

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Abstract

Objective—To compare the outcome of donepezil treatment in ethnically diverse Alzheimer Disease (AD) patients to ethnically diverse AD patients who did not receive donepezil.

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Design—Patients meeting NINCDS-ADRA criteria for probable or possible AD from a consortium of California sites were systematically followed for at least one year in this prospective, observational study. Their treatment regimens, including prescription of donepezil, were determined by their individual physician according to his or her usual criteria. Patients self-identified their ethnicity.

Results—The 64 ethnically diverse AD patients who completed the study and received donepezil treatment had an average one year decline of 2.30 points (3.9 SD) on the 30-point MMSE compared with a 1.70 point (4.2 SD) decline in the 74 ethnically diverse completers who received no donepezil or other anti-AD drugs during the study period. This difference was not statistically significant. The overall Cohen effect size of this treatment-associated difference was estimated at – 0.15. After using propensity analyses and other techniques to assess factors that could bias prescribing decisions, the lack of benefits associated with donepezil treatment remained. The lack of donepezil benefits also remained when more traditional analyses were applied to these data.

Conclusion—California ethnically diverse AD patients in this study apparently did not benefit from one year of donepezil treatment. These unpromising results are in contrast to modest benefits of donepezil treatment measured in a directly comparable California study involving white non-Latino AD patients.

Keywords

Donepezil effectiveness; Alzheimer Disease; Ethnic diversity; Clinical practice; Observational studies; Propensity analyses

Objective

The objective of this prospective, observational study was to compare the outcome of donepezil treatment in ethnically diverse Alzheimer Disease (AD) patients to outcomes of ethnically diverse AD patients who did not receive donepezil. All subjects identified for this present study were part of a large scale, ongoing California investigation that included all ethnic groups. This present focus on ethnic minorities was to address the relative lack of systematic information on specific drug effects in ethnically diverse AD patients.

The methodology of this study was designed to produce information that is useful to practicing clinicians. The AD subjects included were those who would be treated in a typical community setting; subjects were not excluded for medical conditions, concomitant medications or other enrollment restrictions of traditional randomized clinical trials (RCTs) involving anti-Alzheimer's drugs. The overall intent was to provide guidance for what individual physicians can expect in his or her practice when donepezil treatment is prescribed for one year in ethnically diverse AD patients.

Methods

Study Design

This study was designed to collect systematic data from a prospective, longitudinal, multisite, observational study in California that would assess the effectiveness of donepezil

in ethnically diverse patients with AD. Patients were enrolled in the study between January 1, 1998 and June 30, 2004. The diagnosis of AD was made using the National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association criteria for probable or possible AD and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for AD (1, 2). Men and women AD patients between 40 and 90 years of age were included.

Patients had Mini-Mental State Exam (MMSE) scores of 10 and 26 (3), sufficient physical abilities to participate in the initial outpatient diagnostic process, and a reliable caregiver who agreed to participate in the research and either lived with or closely monitored the patient. No patients could be taking donepezil or any other anti-AD drug at their baseline assessment or during the prior 4 weeks. All patients in this study identified their ethnic status as Latino, African-American, Asian American, or otherwise ethnically diverse Americans.

After baseline assessment, each patient's physician determined treatment, including whether or not donepezil was prescribed according to his/her clinical judgment. All patients were expected to participate in a structured clinic re-assessment about 1 year after baseline. Donepezil treatment status over the preceding year was confirmed at this reassessment. Depending on their clinical status, some patients were seen more frequently during the study period. Patients who took any experimental drug, any other anti-AD drug such as any other cholinesterase-Inhibitors (ChE-Is), or memantine throughout the study period were excluded from the final analyses.

Study sites

The 10 study sites included eight California Alzheimer's Disease Centers of California (CADCs): Stanford/Palo Alto VA (the coordinating site), University of California Davis at Martinez, University of California Davis at Sacramento, University of California Irvine, University of California Los Angeles, University of California San Diego, University of California San Francisco, and University of Southern California at Rancho, as well as two VA Mental Illness Research and Education Centers (MIRECC) in Northern California: San Francisco and Palo Alto.

The CADC sites have been closely collaborating and using common research data collection protocols, for over 20 years (4, 5). Data were processed centrally through the Institute for Health and Aging (IHA) at the University of California in San Francisco. To increase inter-site reliability and accuracy, training and recalibration exercises are held with case reports, videos, and autopsy findings (4, 6). The VA - MIRECC sites are also directed by CADC consortium investigators and use the same protocols. Patients are typically drawn from the surrounding communities.

The sites strive to follow patients to autopsy and systematically determine correlations between premorbid clinical diagnoses and neuropathological findings. All sites are experienced in conducting NIH and industry sponsored collaborative trials of anti-AD medications. This study was part of ongoing multi-site CADC research collaborations (7, 8). These are carried out in accordance with all applicable Institutional Review Board requirements.

Outcome measures

The primary outcome measure was the 30-point MMSE (3), which has been used extensively in dementia and drug research. The MMSE provides a longitudinal “benchmark” that is utilized by clinicians in different countries and in different languages (9, 10); and has been evaluated psychometrically (11, 12). The 17-point Blessed-Roth Dementia Rating Scale (BRDRS) was used as a secondary functional outcome measure (13, 14). Higher scores on the BRDRS indicate greater functional impairment.

Statistical analysis

For both outcome measures, a *t* test was done to test for differences between the donepezil and no-donepezil groups in 1-year change. As discussed below, supplementary data analyses based on propensity methods (15) and other techniques were carried out to address the observational nature of this study in which assignment to treatment is non-random. We wanted to assure that no significant biases were created by each physician prescribing donepezil according to her/his criteria. To evaluate the possible sources of prescribing bias, we used a recursive partitioning method based on examination of the receiver operating characteristics (ROC), a signal detection technique (SDT) (16, 17). The ROC method used here was also used in our prior AD work in the community setting (18, 19). Recursive partitioning based on ROC/SDT produces a “decision tree”, in which significant predictors are combined with “and/or” rules to best predict a binary outcome, in this case the outcome of being prescribed Donepezil. The methodological rationale is described in greater detail elsewhere (20). The ROC analyses were done using publicly available software <http://www.stanford.edu/~yesavage/ROC.html>. We set the ROC decision tree methods at a *p* value of $< .01$ to identify predictors suggested by the literature that might explain whether or not sub groups of individuals were disproportionately prescribed donepezil. These 35 variables included both patient characteristics, such as baseline cognitive status (MMSE), age of disease onset, comorbid illnesses, concomitant medications, years of education, gender, marital status, relationship with caregiver, living arrangement, ethnicity, and veterans status, as well as non-patient characteristics, such as date of baseline assessment and study site (21, 22). All other data analyses were performed using SAS version 9.1.

Results

Patient Flow and “Study Completion” Rates

As summarized in Figure 1, 101 of the 229 ethnically diverse patients were prescribed donepezil by their physician according to his/her usual criteria and 128 were not. At the one-year follow-up period, 64 patients in the donepezil treatment group (63%) and 74 of the non-donepezil group (58%) had completed the study (Figure 1). To be a “study completer,” the patient needed to have an MMSE assessment 10 to 18 months after the baseline visit, and have no change in donepezil status.

To assess possible biases generated between AD patients who fulfilled criteria for “completers” and those who didn’t, we also used ROC analyses to investigate baseline characteristics in each group. Results indicated that study completion biases were primarily due to differences in study partners rather than clinical characteristics. Specifically, patients

were more likely to complete the study if their caregiver was a spouse or relative. Patients who entered the study with a friend, neighbor, paid caregiver, or other non-relative were less likely to complete the study. Given that there were no significant clinical differences between completers and non-completers, the remainder of the results will focus on the 138 study completers.

Treatment outcomes

Ethnically diverse AD patients who completed the study and received donepezil treatment had an average one year decline of 2.3 points (3.9 SD) on the 30-point MMSE compared with a 1.7 point (4.2 SD) decline in the ethnically diverse completers who received no donepezil or other anti-AD drugs during the study period.

The difference in 1-year cognitive decline between the donepezil treatment versus no-donepezil groups was not statistically significant ($t^{136} = .87, p = .38$). The overall Cohen effect size (23) was -0.15 . The ROC analyses indicated two Propensity subgroups related to study site: One subgroup consisted of patients enrolled at Palo Alto (PA) who were prescribed donepezil less frequently, and the other subgroup consisted of patients from the remaining sites who were prescribed donepezil more frequently.

A general linear model (GLM) analysis was done using the two subgroups as a stratification factor. There were no statistically significant differences in 1-yr decline between subgroups ($F(1,134) = .07, p = .79$). There were no significant differences in 1-yr decline between donepezil vs. no-donepezil groups ($F(1,134) = 1.96, p = .16$ for the main effect of Treatment; $F(1,134) = 3.02, p = .08$ for the Treatment x Site subgroup interaction). Thus, the analyses indicated that inclusion of the site factor and interaction did not bias overall results. There were no significant prescribing biases based on patient characteristics. Ethnically diverse patients who received donepezil had an average one-year increase (decline) of .8 (1.8 SD) points on the BRDRS compared to an increase (decline) of 1.4 (2.0 SD) points in the no-donepezil treatment group. The difference in functional decline between the two groups was not statistically significant ($t^{120} = -1.71, p = .09$). The overall Cohen effect size (23) was 0.31.

Conclusions

In this prospective observational study, the annualized MMSE changes in ethnically diverse AD patients were not significantly different between those who received donepezil treatment during the one-year study period and those who did not receive donepezil or other anti-AD medications. We had initially hypothesized that there would be some benefit from donepezil treatment. The lack of benefit was an unexpected finding and suggests decreased effectiveness of donepezil in minority populations. Had we used multiple imputation with intention to treat, the differences would have remained not statistically significant.

By contrast, in our first California study, which included only white – non Latino patients but was otherwise methodologically identical, there was a modest positive response to donepezil treatment (18). The reasons for these differences are unclear, but additional research is now underway that may add clarity. For example, the lack of treatment

effectiveness in the ethnically diverse observational study might be explained by poorer adherence, which has reportedly been more common among ethnically diverse patients (24). Figure 3 shows that the slopes of both the ethnically diverse and non-Latino white patient groups are similar overall, suggesting that the 1-yr cognitive declines are clinically comparable regardless of treatment status.

We were fortuitous in the timing of the data collection in these two prospective observational studies. In both, the sample collection began on January 1, 1998, just after donepezil received FDA approval in 1997. At that time, donepezil was not widely prescribed in California. Sample collection continued to June 30, 2004 when donepezil prescription for AD patients had become standard of practice for many clinicians. These temporal changes in the frequency of donepezil prescribing were not so large that they were identified as a significant source of prescribing bias by the ROC propensity analyses. Yet, temporal patterns might have contributed to the roughly equal sizes of the AD groups receiving donepezil or not receiving it, providing optimal power to detect differences in 1-yr cognitive declines. If there had been an extremely disproportionate prescription of donepezil, then the power of the main analysis and the propensity analyses would have been diminished (25).

There are a number of caveats in considering these two California studies. They include: small sample sizes, particularly with regard to individual ethnic groups; high rates of missing outcome data, and medication adherence concerns (26). However, a key strength of these studies is that the findings can be easily understood by clinicians throughout the world. The MMSE, our primary outcome measure, is a widely used mental status assessment tool worldwide. Both the MMSE and a telephone version of the measure (27) have been translated into numerous languages including Persian, Hindi, Cantonese, Spanish, and Brazilian Portuguese (28–33).

While underscoring the methodological concerns, it should be emphasized that the ethnically diverse data presented in this paper represent one of largest systematic minority AD drug studies to date. This is important because minority AD patients have been under-represented in drug development efforts, including the “pivotal” FDA trials that are essential for U.S. marketing approval. Our findings reinforce the need for further larger scale studies focused on specific ethnic groups. Our findings do not support the conclusion that donepezil should not be prescribed to ethnically diverse patients, but do suggest that physicians might consider lowering their expectations for one-year donepezil benefits.

These California observational findings can be compared to the landmark one year Nordic randomized clinical trial (RCT) of AD treatment with donepezil versus placebo (10). Of note is that the donepezil-treated California study group that was ethnically most like the Nordic patients—white, non-Latino Caucasians, also had one year changes quite similar to the RCT Nordic findings (18). Although there were some instances of statistical significance in these one year changes, they are of questionable clinical importance because of relatively small effect size. As noted before, the degree of benefit derived from donepezil and other cholinesterase inhibitors (ChE-Is), particularly in relation to their financial and medical costs, is controversial (34, 35). In other words, the *efficacy* of ChE-Is seen in some randomized clinical trials (RCTs) may not translate to *effectiveness* in real-world settings.

One advantage of the California observational studies is that results should generalize into clinical practice more directly than results from randomized clinical trials such as the Nordic study. The AD subjects included in the California studies were those who would be treated in a typical community setting; subjects were not excluded for medical conditions, concomitant medications or other enrollment restrictions of traditional randomized clinical trials involving anti-Alzheimer's drugs. Therefore, the more representative patient samples that are possible in observational studies can help provide useful guidance on what the individual physician can expect in his or her practice when donepezil treatment is prescribed for one year.

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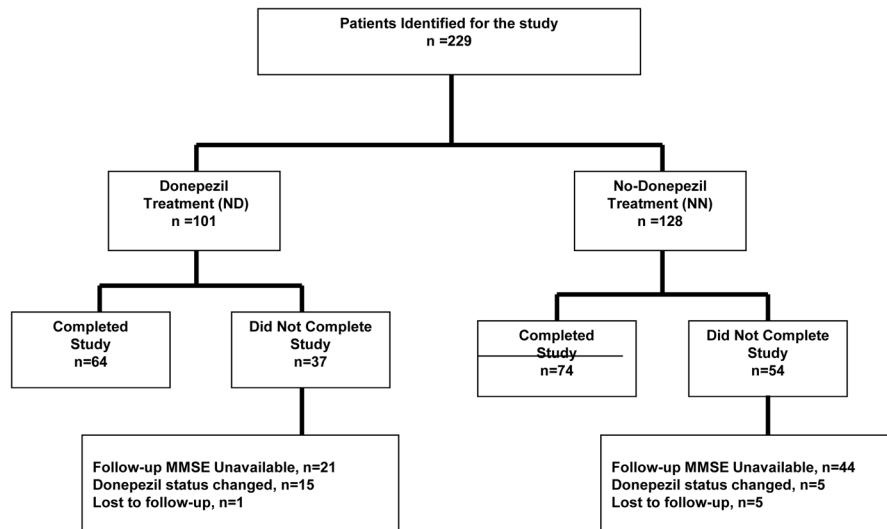


Figure 1.
California AD Patient Flow (Ethnically diverse)

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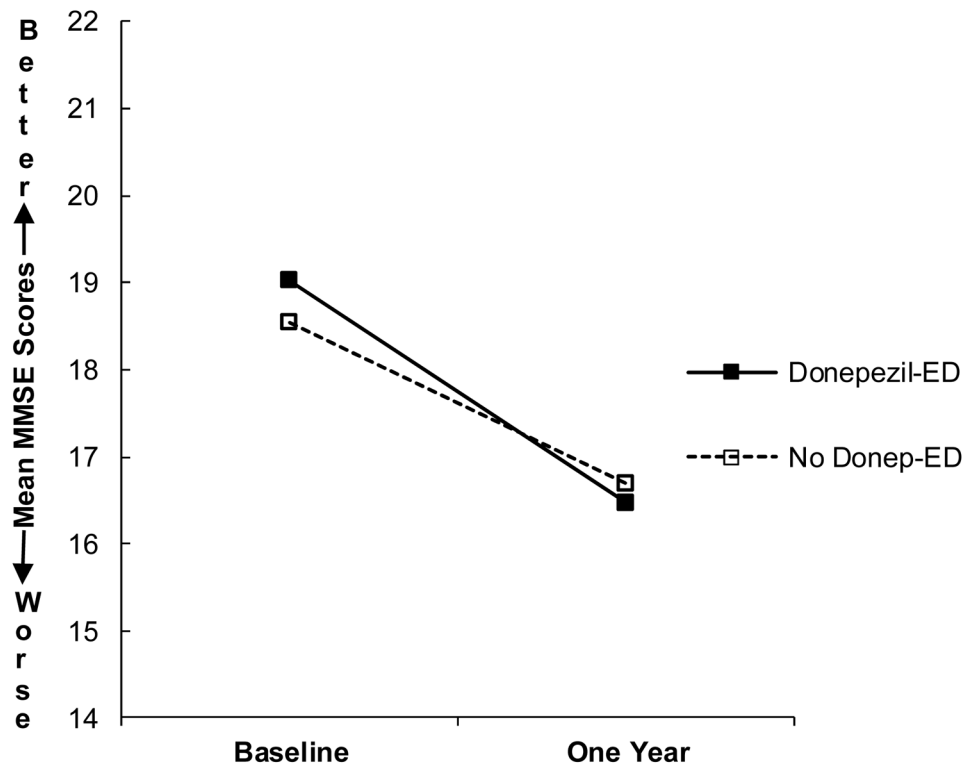


Figure 2.
 Mean Mini-Mental State Exam Scores at Baseline and One Year for Ethnically Diverse AD Patients Prescribed vs. Not Prescribed Donepezil
Notes: Donepezil-ED = Ethnically diverse AD patients prescribed donepezil, study completers (n=64)
 No Donepezil-ED = Ethnically diverse AD patients not prescribed donepezil, study completers (n=74)

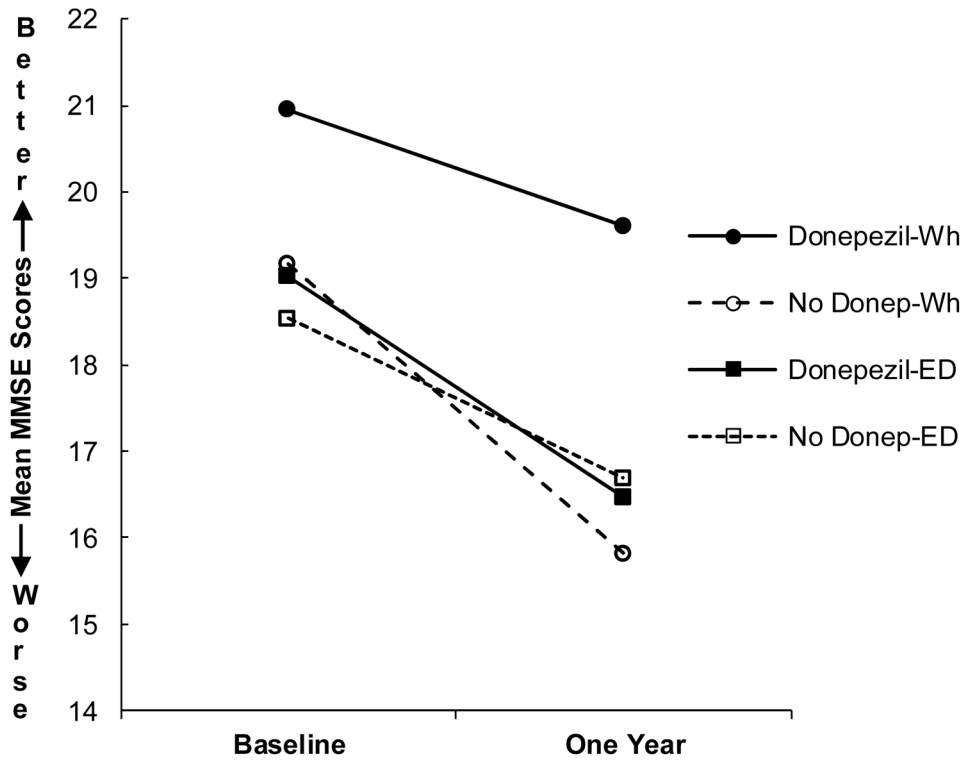


Figure 3.
 Donepezil treatment in ethnically diverse California AD patients compared with white non-Latino California AD patients
Notes: Donepezil-Wh = White non-Latino AD patients prescribed donepezil, study completers (n =148)
 No Donep-Wh = White non-Latino AD patients not prescribed donepezil, study completers (n =158)
 Donepezil-ED = Ethnically diverse AD patients prescribed donepezil, study completers (n=64)
 No Donep-ED = Ethnically diverse AD patients not prescribed donepezil, study completers (n=74)

Table 1

Baseline Patient Characteristics

	Donepezil Treatment		No Donepezil Treatment	
	Completers n=64	Non-Completers n=37	Completers n=74	Non-Completers n=54
Means \pm SD				
Age	74.5 \pm 9.4	77.7 \pm 7.8	76.6 \pm 8.4	76.5 \pm 8.0
Age at Symptom Onset	69.6 \pm 10.8	73.2 \pm 8.1	72.0 \pm 8.6	72.3 \pm 8.2
Years of Education	11.1 \pm 4.5	10.9 \pm 5.5	11.4 \pm 4.5	8.6 \pm 5.2
MMSE Score	19.0 \pm 4.3	17.1 \pm 4.4	18.5 \pm 4.3	16.9 \pm 4.5
BRDRS Score	4.2 \pm 2.5	4.5 \pm 3.0	5.1 \pm 2.6	5.2 \pm 3.3
Number (%)				
AD Probable	54 (84%)	33 (89%)	67 (91%)	40 (74%)
Women	48 (75%)	24 (65%)	54 (73%)	40 (74%)
Latinos	25 (39%)	15 (41%)	29 (39%)	30 (56%)
Asian Americans	18 (28%)	13 (35%)	30 (41%)	9 (17%)
African Americans	15 (23%)	4 (11%)	10 (14%)	9 (17%)
Other	6 (9%)	5 (14%)	5 (7%)	6 (11%)
Median # of concomitant meds	2	2	3	3
Median # of co-morbid illnesses	1	1	2	1

Notes: SD: Standard Deviation; MMSE: Mini Mental State Examination; BRDRS: Blessed Roth Dementia Rating Scale