Donepezil Treatment in Ethnically Diverse Patients with Alzheimer Disease

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Objective: *To compare the outcome of donepezil treatment in ethnically diverse Alzheimer disease (AD) patients with ethnically diverse AD patients who did not receive donepezil.* **Methods:** *Patients meeting NINCDS-ADRA criteria for probable or possible AD from a consortium of California sites were systematically followed for at least 1 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 1-year decline of 2.30 points (standard deviation: 3.9) on the 30-point Mini-Mental State Exam compared with a 1.70-point (standard deviation: 4.2) 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:** *Ethnically diverse AD patients in this study apparently did not benefit from 1 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.* (Am J Geriatr Psychiatry 2015; 23:384–390)

Key Words: Donepezil effectiveness, Alzheimer disease, ethnic diversity, clinical practice, observational studies, propensity analyses

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INTRODUCTION

In this prospective, observational study, we compared the outcome of donepezil treatment in ethnically diverse Alzheimer disease (AD) patients with 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. We focused on ethnic minorities here 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 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 drugs. The overall intent was to provide guidance for what individual physicians can expect in their practices when donepezil treatment is prescribed for 1 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 with AD between 40 and 90 years of age were included.

Patients had Mini-Mental State Exam (MMSE) scores of at least 10 and no more than 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 American.

After baseline assessment, each patient's physician determined treatment, including whether or not donepezil was prescribed according to his or her clinical judgment. All patients were expected to participate in a structured clinic reassessment 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, or meantime throughout the study period were excluded from the final analyses.

Study Sites

The 10 study sites included 8 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) and 2 VA Mental Illness Research and Education Centers 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 at the University of California in San Francisco. To increase intersite reliability and accuracy, training and recalibration exercises are held with case reports, videos, and autopsy findings.[4,6] The VA Mental Illness Research and Education Center 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 neuropathologic findings. All sites are experienced in conducting National Institutes of Health and industry-sponsored collaborative trials of anti-AD medications. This study was

TABLE 1. Baseline Patient Characteristics

	Donepezil Treatment		No Donepezil Treatment	
	Completers (N = 64)	Non-Completers (N = 37)	Completers (N = 74)	Non-Completers (N = 54)
mean ± SD				
Age, years	74.5 ± 9.4	77.7 ± 7.8	76.6 ± 8.4	76.5 ± 8.0
Age at symptom onset, years	69.6 ± 10.8	73.2 ± 8.1	72.0 ± 8.6	72.3 ± 8.2
Years of education	11.1 ± 4.5	10.9 ± 5.5	11.4 ± 4.5	8.6 ± 5.2
MMSE score	19.0 ± 4.3	17.1 ± 4.4	18.5 ± 4.3	16.9 ± 4.5
BRDRS score	4.2 ± 2.5	4.5 ± 3.0	5.1 ± 2.6	5.2 ± 3.3
N (%)				
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 no. of concomitant meds	2	2	3	3
Median no. of comorbid illnesses	1	1	2	1

part of ongoing multisite CADC research collaborations[7,8] carried out in accordance with all applicable Institutional Review Board requirements.

Outcome Measures

The primary outcome measure was the 30-point MMSE,[3] used extensively in dementia and drug research. The MMSE provides a longitudinal "benchmark" used 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 performed to assess differences between the donepezil and no-donepezil groups in a 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 nonrandom. We wanted to ensure that no significant biases were created by each physician prescribing donepezil according to her or his criteria.

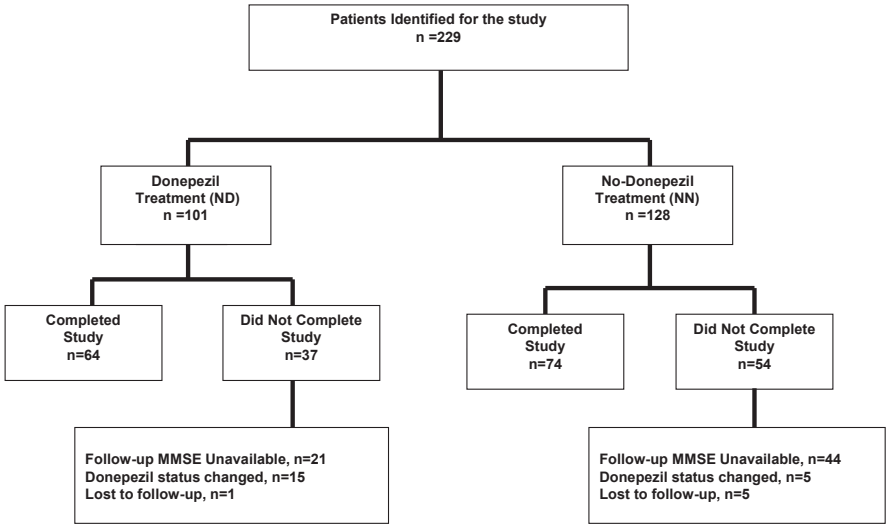
To evaluate the possible sources of prescribing bias, we used a recursive partitioning method based on examination of the receiver operating characteristic (ROC), a signal detection technique.[16,17] The ROC method used here was also used in our prior AD work in the community setting.[18,19] Recursive partitioning based on ROC/signal detection technique 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 methodologic 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 $p < 0.01$ to identify predictors suggested by the literature that might explain whether or not subgroups of individuals were disproportionally prescribed donepezil. These 35 variables included both patient characteristics, such as baseline cognitive status (MMSE), age at disease onset, comorbid illnesses, concomitant medications, years of education, gender, marital status, relationship with caregiver, living arrangement, ethnicity, and veterans status, as well as nonpatient characteristics, such as date of baseline assessment and study site.[21,22] All other data analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Flow and Study Completion Rates

One hundred one of the 229 ethnically diverse patients were prescribed donepezil by their physician

FIGURE 1. AD Patient Flow in the ethnically diverse sample in the California study.



according to his or her usual criteria and 128 were not (Table 1). At the 1-year follow-up period, 64 patients in the donepezil treatment group (63%) and 74 in the no-donepezil treatment group (58%) had completed the study (Fig. 1). To be a study completer, the patient needed to have an MMSE assessment 10−18 months after the baseline visit and have no change in donepezil status.

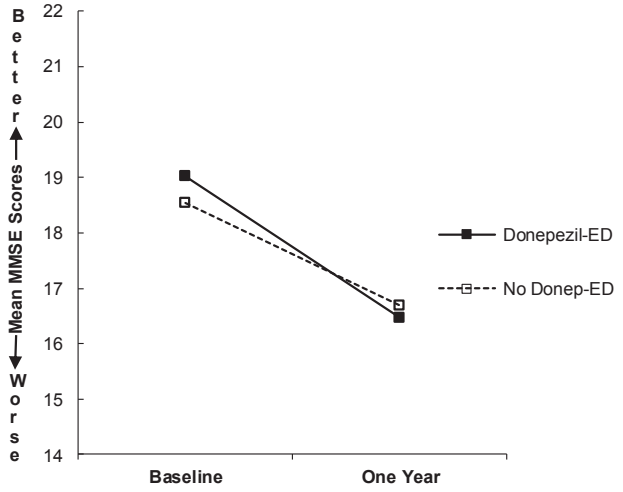
To assess possible biases generated between AD patients who fulfilled criteria for completers and those who did not, we also used ROC analyses to investigate baseline characteristics in each group. Results indicated that study completion biases were primarily due to differences in study partners rather 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 nonrelative were less likely to complete the study. Given that there were no significant clinical differences between completers and noncompleters, the remainder of the results focus on the 138 study completers.

Treatment Outcomes

Ethnically diverse AD patients who completed the study and received donepezil treatment had an average 1-year decline of 2.3 points (standard deviation [SD]: 3.9) on the 30-point MMSE compared with a 1.7-point (SD: 4.2) decline in the ethnically diverse completers who received no donepezil or other anti-AD drugs during the study period (Fig. 2). The difference in 1-year cognitive decline between the donepezil treatment versus no-donepezil groups was not statistically significant ($t^{136} = 0.87$, $p = 0.38$). 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 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 analysis was performed using the two subgroups as a stratification factor. There were no statistically significant differences in 1-year decline between subgroups ($F(1,134) = 0.07$, $p = 0.79$) and no significant differences in 1-year decline between the donepezil and no-donepezil groups ($F(1,134) = 1.96$, $p = 0.16$ for the main effect of treatment; $F(1,134) = 3.02$, $p = 0.08$ for the treatment × 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.

FIGURE 2. **Mean MMSE scores at baseline and at 1 year for ethnically diverse AD patients prescribed versus not prescribed donepezil. 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).**

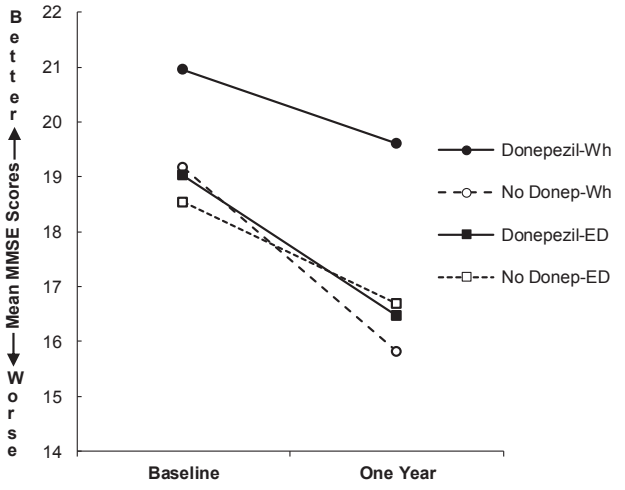


Ethnically diverse patients who received donepezil had an average 1-year increase (decline) of 0.8 points (SD: 1.8) on the BRDRS compared with an increase (decline) of 1.4 points (SD: 2.0) in the no-donepezil treatment group. The difference in functional decline between the two groups was not statistically significant ($t^{120} = -1.71$, $p = 0.09$). The overall Cohen effect size[23] was 0.31.

DISCUSSION

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 1-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.

FIGURE 3. **Donepezil treatment in ethnically diverse AD patients compared with white non-Latino AD patients from the California study. 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).**



In 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 compliance, which has reportedly been more common among ethnically diverse patients.[24] Figure 3 shows the slopes of both the ethnically diverse and non-Latino white patient groups are similar overall, suggesting the 1-year 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 U.S. Food and Drug Administration 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-year 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: small sample sizes, particularly with regard to individual ethnic groups; high rates of missing outcome data; and medication compliance 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]

Although underscoring methodologic concerns, it should be emphasized that the ethnically diverse data presented here 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 1-year donepezil benefits.

These observational findings from California can be compared with the landmark 1-year Nordic 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 and non- Latino, also had 1-year changes quite similar to the RCT Nordic findings.[18] Although there were some instances of statistical significance in these 1-year changes, they are of questionable clinical importance because of a relatively small effect size. As noted before, the degree of benefit derived from donepezil and other cholinesterase inhibitors, particularly in relation to their financial and medical costs, is controversial.[34,35] In other words, the *efficacy* of cholinesterase inhibitors seen in some 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 RCTs 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 RCTs involving anti-Alzheimer 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 1 year.

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