Safety and Efficacy of Donepezil in African Americans with Mild-to-Moderate Alzheimer's Disease

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Background: African Americans have a higher incidence and prevalence of Alzheimer's disease (AD) than whites but have been underrepresented in clinical trials, including studies of cholinesterase inhibitors.

Purpose: The purpose of this 12-week, open-label study was to evaluate the efficacy and safety of donepezil in African Americans with mild-to-moderate AD.

Methods: Efficacy was assessed via the Mini-Mental State Examination (MMSE), Clinician's Interview-Based Impression of Change-Plus interview with the patient and caregiver (CIBIC-Plus) and Fuld Object Memory Evaluation (FOME), a measure that has been validated for use with elderly African Americans.

Results: Significant improvements were observed in cognition (MMSE), global function (CIBIC-Plus) and memory (all four subscales of the FOME). Donepezil was well tolerated; 51% of patients experienced adverse events, most commonly diarrhea (5.6%), hypertension (5.6%) and urinary tract infection (4.8%).

Conclusions: These results suggest that donepezil is effective and safe in treating African Americans with mild-to-moderate AD, and support the value of FOME in assessing efficacy in AD trials in diverse populations.

Key words: Alzheimer's disease ■ donepezil ■ African Americans ■ pharmacotherapy ■ Fuld Object Memory Evaluation

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INTRODUCTION

The incidence and prevalence rates of Alzheimer's disease (AD) among African Americans have been reported to be more than twice as high as the rates in white (non-Hispanic) Americans.[1,2] Even after adjusting for education and other potentially confounding variables, African Americans have approximately a 2.5-fold higher risk than whites.[1] Although one study suggested that the relative risk rates may have been distorted by bias in classifying the disease in different races,[3] the above-mentioned reports offer compelling evidence that African Americans are more likely than whites to experience dementia; however, clinical data on the treatment of African Americans with AD are scarce.

Despite the prevalence of AD in the African-American community, there is often a delay in diagnosis and treatment. Separate studies by Hargrave et al.[4] and Shadlen et al.[5] demonstrated that African Americans with AD have, on average, more severe dementia at the time of initial diagnosis. Early recognition and treatment of AD are essential to maximize patient benefits and outcomes, including cognition and function.[6,7] It is therefore important to eliminate barriers to diagnosis and treatment.

There are several assessments used in clinical trials to assess cognitive status. The Mini-Mental State Examination (MMSE) is a widely used method for assessing cognitive status in clinical practice and research. Studies have shown that MMSE scores correlate significantly with education and inversely with age.[8-10] When corrected for possible confounding variables such as educational level, the MMSE score does correlate with other clinically relevant measures, such as activities of daily living, across a variety of populations.[8,10] However, the MMSE also has a strong, independent correlation with literacy level (measures of reading comprehension),[11] potentially underestimating the abilities of patients with low literacy. This effect likely explains the observation from a study in a hospital-based population that people falsely diagnosed with dementia or delirium using the MMSE all had <9 years of education.[12]

Another limitation of the MMSE is its reliance on spoken language, potentially biasing the measure in hearing-impaired elders.

The lack of culturally sensitive and educationally unbiased screening tools may be a barrier to diagnosis and treatment. Therefore, it is important to incorporate unbiased assessments in clinical trials. These instruments can be used to identify and diagnose AD in various patient populations across a variety of ethnic groups. The Fuld Object Memory Evaluation (FOME)[13] is an assessment that uses multiple sensory modalities and a selective reminding procedure to evaluate storage and retrieval of information. The validity of the FOME and its lack of relationship to education and literacy have been demonstrated in elderly African Americans and whites.[14,15] Unlike the MMSE, the FOME is a specific measure of memory. The FOME has been shown to be effective in detecting AD and in discriminating AD from other conditions such as Parkinson's disease or depression.[14-18] Mast et al.[16] reported a sensitivity of 98.3%, with good specificity, among African Americans. The FOME has been validated in multiethnic[14,15] and African-American[16] populations. Despite its utility as an unbiased tool for the detection of AD, to date, the FOME has not been used to assess efficacy in a clinical trial with the currently approved treatments for AD.

To date, more than a dozen randomized, controlled trials have demonstrated the efficacy of donepezil in AD. Whereas African Americans comprise 12% of the U.S. population,[19] they represent <5% of subjects in clinical trials of donepezil,[20-25] a cholinesterase inhibitor that has consistently demonstrated beneficial effects in function, behavior and cognition in randomized, controlled trials.[20-31] Although donepezil has been shown to be a safe and effective therapy for AD, it has not been specifically evaluated in African-American patients. The objective of this study was to evaluate the efficacy and safety of donepezil in African Americans with mild-to-moderate AD and to determine whether the FOME is a useful measure of outcome in patients with AD.

Table 1. Patient demographics, safety population (N=125)

Sex [n (%)]	
Male	33 (26.4)
Female	92 (73.6)
Age (Years)*	76.2 (9.5)
Education (Years)*	10.7 (3.5)

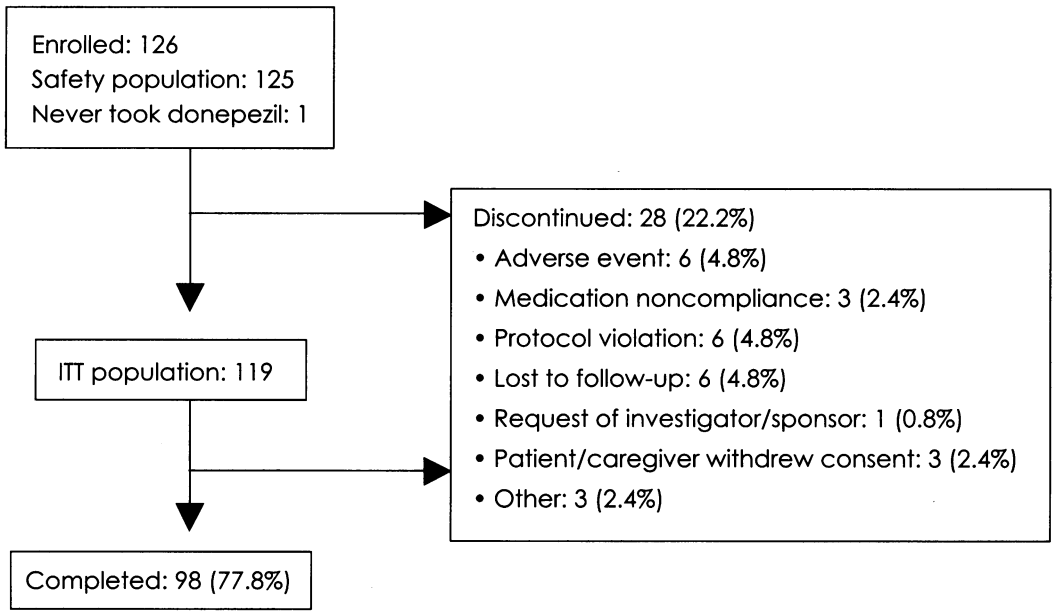
* Mean (standard deviation)

MATERIALS AND METHODS

Patients

Patients eligible for the study were African Americans aged ≥50 years with mild-to-moderate AD (MMSE score of 10–26) who had not received previous therapy with donepezil. All patients had to have a diagnosis of possible or probable AD prior to or during screening. Patients with AD and possible cerebrovascular disease (as evidenced by risk factors such as hypertension or diabetes) were eligible provided that the risk factors

Figure 1. Patient disposition



ITT: intent to treat; Percentages are based on the number of patients enrolled in the study

were controlled. Patients with vascular changes were included if they did not meet National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for probable vascular dementia.

Table 2. Baseline patient characteristics, intent-to-treat population (N=119)

Characteristic	Mean (SD)
MMSE score	19.9 (4.6)
FOME storage score	29.2 (13.9)
FOME retrieval score	20.3 (12.0)
CIBIS score	3.3 (0.90)

MMSE: Mini-Mental State Examination; FOME: Fuld Object Memory Evaluation; CIBIS: Clinician's Interview-Based Impression of Severity with caregiver input

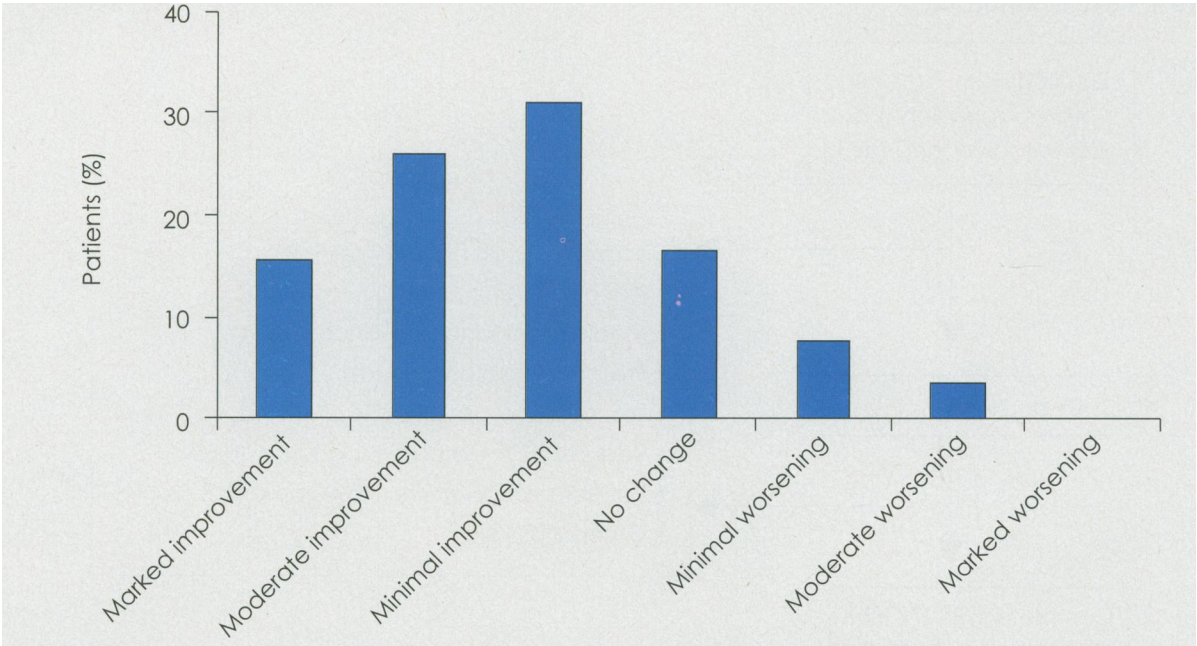
Table 3. Treatment-emergent adverse events occurring in >3% of patients

Adverse Event	n (%)
Any adverse event	64 (51.2)
Diarrhea	7 (5.6)
Hypertension	7 (5.6)
Urinary tract infection	6 (4.8)
Headache	5 (4.0)
Anorexia	5 (4.0)
Dizziness	5 (4.0)
Nausea	5 (4.0)

A further requirement was computed tomography or magnetic resonance imaging findings consistent with a diagnosis of AD within the 12 months prior to screening. Other eligibility criteria included community residence, clinical laboratory values within normal limits, ambulatory status or ambulatory aided (i.e., walker, cane or wheelchair) and vision and hearing sufficient for compliance with testing procedures. Exclusion criteria included: 1) any active or clinically significant condition affecting absorption, distribution or metabolism of the study medication; 2) a known hypersensitivity to piperidine derivatives or cholinesterase inhibitors; 3) any clinically significant obstructive pulmonary disease or asthma untreated for >3 months; 4) a recent hematologic/oncologic disorder; 5) a current diagnosis of major depressive disorder or any current primary psychiatric diagnosis other than AD; 6) dementia complicated by delirium; and 7) a known or suspected history of alcoholism or drug abuse.

Patients were required to be naïve to donepezil treatment. Patients who had previously used cholinesterase inhibitors (rivastigmine, galantamine, tacrine, metrifonate or physostigmine) or memantine were allowed if they had discontinued the medication ≥3 months prior to screening. This is considered to be an adequate washout period based on previous studies of these drugs. Medications that were allowed included analgesics, antihypertensives, diuretics and anticonvulsants (carbamazepine, phenytoin and valproate). Disallowed medications included anticholinergic agents (i.e.,

Figure 2. End point (ITT-LOCF) CIBIC-Plus scores



CIBIC-Plus: Clinician's Interview-Based Impression of Change-Plus Interview With Patient and Caregiver; ITT-LOCF: intent to treat-last observation carried forward

diphenhydramine), tricyclic and tetracyclic antidepressants, clonazepam, primidone, anxiolytics (i.e., alprazolam), antiparkinsonian agents (i.e., bromocriptine), stimulants (i.e., amphetamine) and phenothiazine antipsychotics. Putative cognitive enhancers such as ginkgo or high-dose vitamin E were discouraged but not excluded.

Prior to screening, the nature and purpose of the study were explained to each potential subject and his or her caregiver. Patients and caregivers were informed that they were completely free to refuse to enter the study or to withdraw from the study at any time. The study was conducted in compliance with the U.S. Food and Drug Administration Code of Federal Regulations (Title 21 Parts 50 and 56), Good Clinical Practice and the Declaration of Helsinki as amended. The protocol and informed consent form were reviewed and approved by the institutional review board at each site.

Study Design

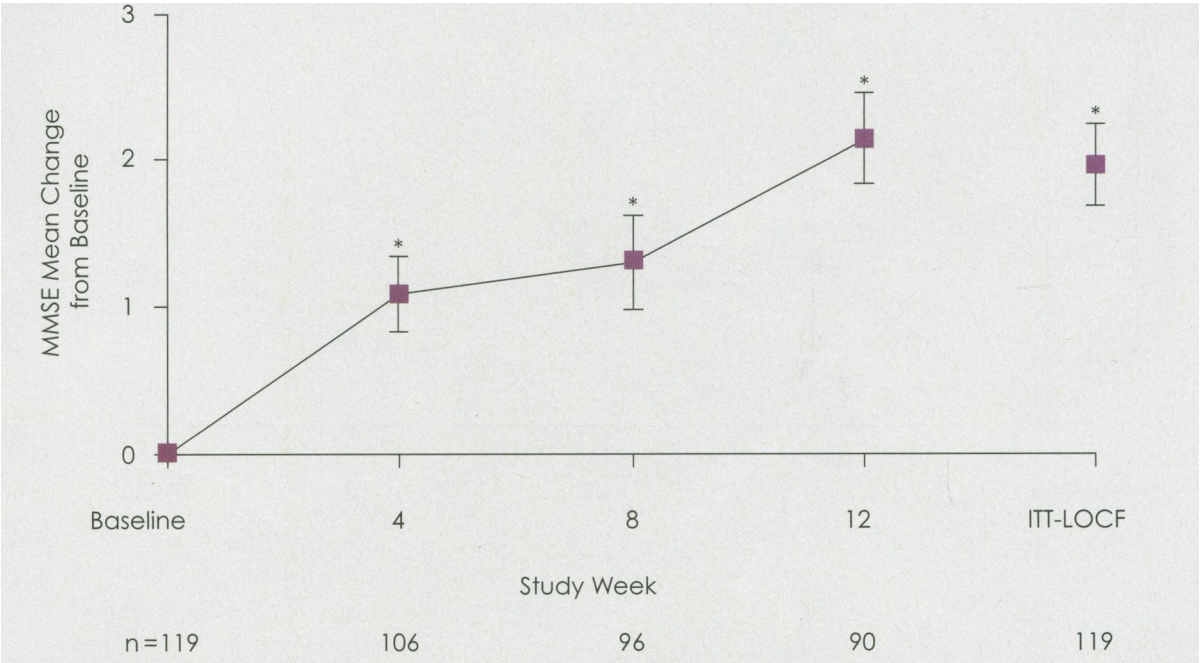
This was a multicenter, open-label 12-week trial. After written informed consent was obtained, patients entered a screening period that lasted up to four weeks and included assessment of medical history, complete physical and neurologic examination, a 12-lead electrocardiogram and clinical laboratory testing. Following these evaluations, medication was given at a dose of 5 mg/d (one 5-mg tablet) for the first four weeks of the study, after which the dosage was increased to 10 mg/d (two 5-mg tablets) based on the clinician's judgment. Following dose escalation, if the patient could not tolerate 10 mg of donepezil, the dosage was reduced temporarily to 5 mg. The patient was rechallenged with 10 mg of donepezil 7–10 days later. If the patient could not tolerate the higher dose after rechallenge, he or she was allowed to remain in the study, maintained on the 5-mg dose. Patients returned to the clinic at weeks 4, 8 and 12 for assessment of efficacy and safety.

Efficacy Parameters

Efficacy was assessed by the following:

1. The Clinician's Interview-Based Impression of Change-Plus interview with the patient and caregiver (CIBIC-Plus)[32] is a seven-point rating scale ranging from 1–7, with a higher score indicating greater deterioration in the patient's condition. A score of 1 on the CIBIC-Plus represents a marked improvement, 4 no change and 7 a markedly worse condition. The CIBIC-Plus is based on assessment of patient function in four domains: general, mental/cognitive, behavior and activities of daily living. The clinician administers the test by conducting an interview with the subject and the caregiver together at the baseline visit that serves as a reference for future ratings [Clinician's Interview-Based Impression of Severity with caregiver input (CIBIS)]. The subject and caregiver are then interviewed separately at

Figure 3. MMSE mean change from baseline



Positive numbers represent clinical improvement; ITT-LOCF: intent to treat-last observation carried forward; MMSE: Mini-Mental State Examination; * P≤0.0001 vs. baseline

each subsequent visit. Following both interviews, the clinician alone must make the decision as to whether the subject's condition has improved, worsened or remained unchanged.

2. The MMSE[33] is an evaluation of orientation, immediate recall, attention, delayed recall, concentration, naming, repetition, comprehension, language and praxis. One point on the MMSE is given for each correct item; total scores range from 0–30. A higher score represents better cognitive performance. Cognitively normal elders score in the range of 24–30 (mean 27.6, SD 1.7).[33]
3. The FOME is a brief test of explicit memory. The FOME is an evaluation of memory in which touch, sight and hearing are used to learn a list of common objects, which are recalled after a brief distracter task. The scoring components of the FOME are storage, retrieval, repeated retrieval (subcomponent of retrieval), ineffective reminders (subcomponent of storage) and rapid verbal retrieval. The storage score is the cumulative total of different items recalled across the five trials, and the retrieval score is the sum total of all items recalled across the five trials. Storage and retrieval scores range from 0–50.

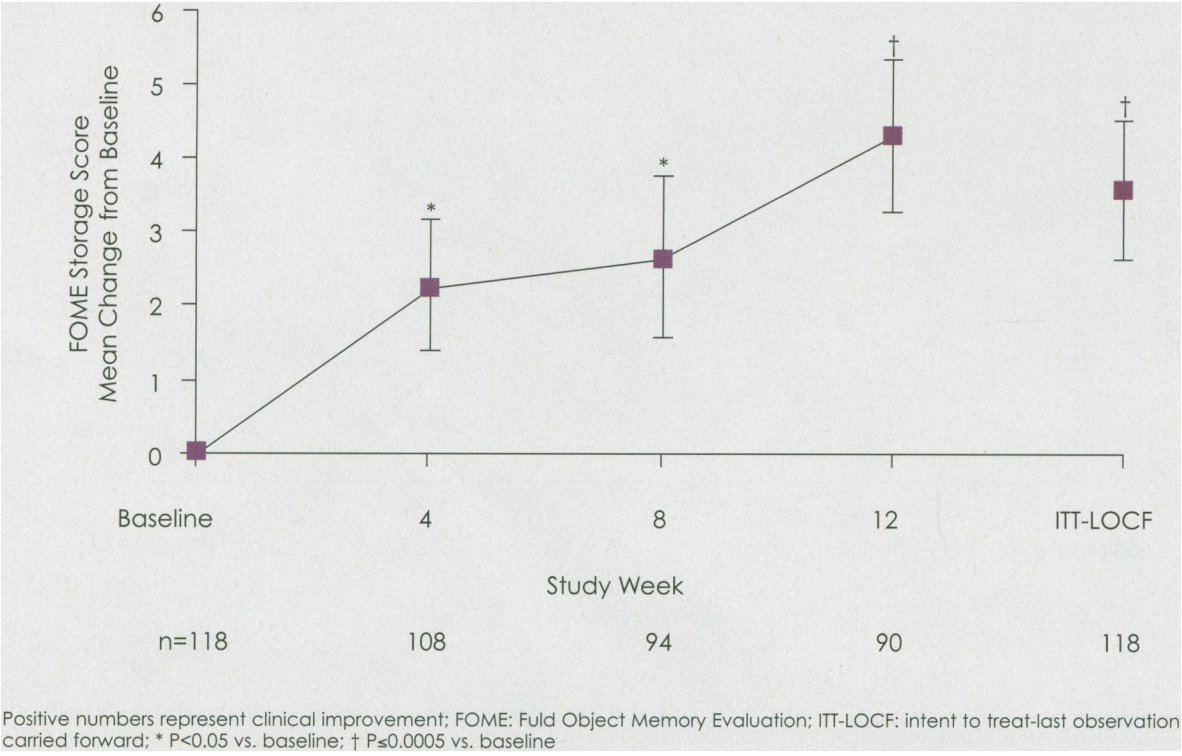
Efficacy parameters were evaluated at baseline, week 4, week 8 and week 12 (end of the study). Vital signs were also checked at these time points. Compliance with study medication was checked throughout the study period.

Statistical Analysis

The intent-to-treat (ITT) population consisted of all patients who were enrolled, received ≥1 dose of donepezil and had a baseline evaluation and ≥1 post-baseline evaluation. The last observation on open-label treatment was carried forward and used as the end point (LOCF). The observed-cases population for each visit included those patients in the ITT-LOCF population with a value at that visit. The fully evaluable population consisted of all patients included in the ITT-LOCF population who had total study medication compliance of ≥80%, ≥1 additional visit during the open-label treatment phase and no significant protocol violations. Efficacy analyses were conducted using the ITT and fully evaluable populations. The population included in the safety analysis consisted of all patients who were enrolled and took ≥1 dose of study medication.

Efficacy variables were analyzed by univariate Student's t test using SAS (SAS Institute Inc., Cary, NC). Significance was judged at the 0.05 level. Ninety-five percent confidence intervals were constructed on the mean change at end point for each variable. Additionally, the FOME score was analyzed by the following age groups: <65, 65–75 and >75.

Figure 4. FOME storage score mean change from baseline



Positive numbers represent clinical improvement; FOME: Fuld Object Memory Evaluation; ITT-LOCF: intent to treat-last observation carried forward; * P<0.05 vs. baseline; † P≤0.0005 vs. baseline

Safety Analysis

Adverse events were coded by preferred terms using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary. Adverse events were defined as any untoward medical occurrence and were reported by the patient in response to an open-ended question ("How are you doing?") or by the investigator in the event of abnormal laboratory values that resulted in intervention.

RESULTS

Patient Disposition

A total of 126 patients were enrolled in the study (Figure 1); one patient never took the study drug, resulting in a safety population of 125. The ITT population comprised 119 patients. Twenty-eight (22.2%) patients withdrew before the end of the 12-week study period. The most common reasons for discontinuation were adverse events, protocol violation and loss to follow-up. Patient demographics are presented in Table 1; scores on baseline evaluations are summarized in Table 2. Mean compliance was >90% at all scheduled visits. Eighty-eight percent of patients were taking 10-mg/d donepezil at the study end point.

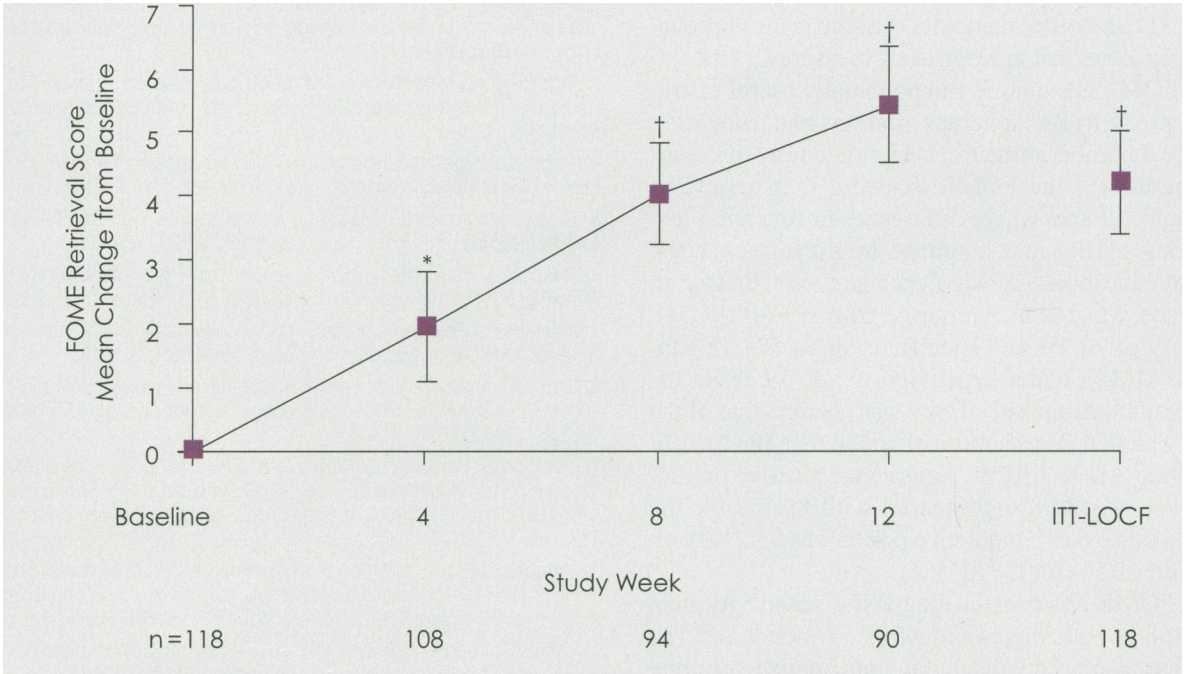
Efficacy

Analysis of CIBIC-Plus scores showed significant improvement in global function with donepezil treatment ($P<0.0001$, univariate Student's t test against no change) in the ITT-LOCF population. The majority of patients (72.4%) improved (markedly, moderately or minimally), while 11.2% were classified as having worsened (Figure 2).

Cognition as evaluated by mean MMSE score was significantly improved from baseline to the end of the study. In the ITT-LOCF population, the MMSE score [mean (standard deviation, SD)] increased from 19.9 (4.56) at baseline to 21.9 (4.81) at the end point ($P<0.0001$). Mean MMSE scores were significantly improved compared with baseline at each evaluation time point (Figure 3).

Memory function as measured by the FOME was significantly improved. Significant improvements were observed between baseline and end point on all FOME subscales (mean FOME storage score, retrieval score, repeated retrieval score and ineffective reminder score) in the ITT-LOCF population. The FOME storage score [mean (SD)] improved from 29.2 (13.93) at baseline to 32.8 (13.06) at end point ($P=0.0003$). The retrieval score improved from 20.3 (12.03) at baseline to 24.5 (12.98) at end point ($P<0.0001$). The repeated retrieval score improved from 10.7 (8.39) at baseline to 14.4 (10.68) at end point ($P<0.0001$). The ineffective reminder score, in which a lower number indicates improvement, improved from 18.5 (11.6) at baseline to 15.1 (11.3) at end point ($P<0.0001$). Significant improvements compared with baseline were observed at each evaluation point in the

Figure 5. FOME retrieval score mean change from baseline



Positive numbers represent clinical improvement; FOME: Fuld Object Memory Evaluation; ITT-LOCF: intent to treat-last observation carried forward; * P=0.0045 vs. baseline; † P<0.0001 vs. baseline

FOME storage score (Figure 4) and the FOME retrieval score (Figure 5). Significant improvement in mean FOME scores (end point compared with baseline) were observed in all data analysis populations (ITT-LOCF, observed cases and fully evaluable with the exception of storage score at week 4) and in all age categories.

Safety

A total of 151 treatment-emergent adverse events occurred in 64 patients (51.2%, Table 3). The most common were diarrhea, hypertension and urinary tract infection. Headache, anorexia, dizziness and nausea were also reported. The adverse events were generally mild to moderate in intensity. Possible or probable drug-related adverse events occurred in 29 (23.2%) patients. No serious adverse events were judged by the investigator to be related to the study medication. Adverse events resulted in discontinuation from the study in six (4.8%) patients and to a reduction in dose in 10 (8.0%). No deaths occurred during the study, and laboratory findings were unremarkable.

DISCUSSION

This is the first study to evaluate an AD treatment in an exclusively African-American patient population. This is also the first study to include the FOME as an efficacy measure. The results of this 12-week, open-label study indicate that donepezil is safe and effective in African-American patients with AD. These results are of particular importance because this population has a high incidence and prevalence of AD and high rates of hypertension and hyperlipidemia,[34] which are risk factors for AD and other dementia.[35] Significant improvements were observed in all efficacy measures.

The FOME is a unique and potentially useful instrument for AD trials. Whereas literacy and education influence a number of neuropsychologic tests of cognitive function,[36,37] the FOME is useful in a variety of groups and cultures where differences in education level, hearing ability and language might influence the results of education-/literacy-dependent tests. In African Americans, Mast et al.[16] reported estimates of FOME sensitivity of 98.3% and specificity of 64.5%. In contrast, the MMSE had a sensitivity of only 79.3% in the same population, and specificity was equal to that of the FOME. The FOME was more effective than the MMSE at detecting AD in African Americans; positive predictive power was 83.8% compared with 80.7% for the MMSE, and negative predictive power was 95.2% compared with 62.5% for the MMSE.

The FOME has greater diagnostic sensitivity than the MMSE in both whites and African Americans.[16] The FOME has also been validated in non-English-speaking countries, including China and Japan.[15] A study in a biracial (African-American and white) sample of community-dwelling elders in rural Virginia with <10 years of education found that the recall score of the FOME was a significant predictor of social functioning.[38]

Although African Americans have a high risk of AD, they have been underrepresented in clinical trials. Ours was the first study of treatment of AD with a cholinesterase inhibitor specifically in African-American patients, and its findings support and extend those of previous studies: that donepezil is effective in improving or stabilizing cognition in AD patients. The major limitation of this study is its open-label design, as randomized, placebo-controlled trials allow more rigorous evaluation of treatment effect.

In the present study, donepezil was safe and well tolerated. Only five patients experienced serious adverse events; none were considered related to the study medication and none led to death. Six (4.8%) patients withdrew from the study as a result of adverse events typically considered related to study medication. Most of the adverse events reported in this study had been reported in previous studies of donepezil among AD patients. Clinical laboratory findings, electrocardiogram, vital signs and physical examination were not suggestive of any safety concerns in this population.

In conclusion, these results suggest that donepezil is effective and safe in treating African Americans with mild to moderate AD and support the value of FOME in assessing efficacy in AD trials in diverse populations.

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