Challenging Assumptions About African American Participation in Alzheimer Disease Trials

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Objective: *The authors investigated potential effects of increased African American participation in Alzheimer disease (AD) and mild cognitive impairment (MCI) clinical trials by examining differences in comorbid conditions and treatment outcome affecting trial design.* **Methods:** *Using a meta-database of 18 studies from the Alzheimer's Disease Cooperative Study and the Alzheimer's Disease Neuroimaging Initiative, a cohort of 5,164 subjects were included for whom there were baseline demographic data and information on comorbid disorders, grouped by organ system. Meta-analysis was used to compare prevalence of comorbidities, dropouts, and rates of change on the cognitive subscale of the Alzheimer's Disease Assessment Scale by race. Clinical trial scenarios similar to recent therapeutic trials were simulated to determine effects of increased African American participation on statistical power.* **Results:** *Approximately 7% of AD, 4% of MCI, and 11% of normal participants were African American. African American subjects had higher prevalence of cardiovascular disorders (odds ratio: 2.10; 95% confidence interval [CI]: 1.71–2.57) and higher rate of dropouts (odds ratio: 1.60; 95% CI: 1.15–2.21) compared with whites but lower rates of other disorders. There were no significant differences in rate of progression (–0.862 points/year; 95% CI: −1.89 to 0.162) by race and little effect on power in simulated trials with sample sizes similar to current AD trial designs.* **Conclusion:** *Increasing African American participation in AD clinical trials will require adaptation of trial protocols to address comorbidities and dropouts. However, increased diversity is unlikely to negatively affect trial outcomes and should be encouraged to promote generalizability of trial results.* (Am J Geriatr Psychiatry 2017; ■■:■■–■■)

Key Words: Alzheimer disease, mild cognitive impairment, clinical trial design, racial differences, diversity

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INTRODUCTION

African Americans constitute approximately 9% of the elderly population in the United States, but the percentage of minority subjects in clinical trials of therapeutic agents for Alzheimer disease (AD) has consistently been less than 5%.[1] Investigators may view African American participants as sufficiently different from other participants that they impact the efficiency, outcomes, and validity of clinical trial enrollment. Such beliefs may be implicit in nature,[2] although this issue has not been specifically examined in the context of clinical trials. One example is the belief that African American subjects are more likely to have cardiac disease, hypertension, and other comorbidities that may affect trial validity.[3] Selection criteria based on these conditions, as well as demographic characteristics such as education, disproportionately exclude potential African American subjects.[4,5] Other examples are the belief that African American participants may be more likely to discontinue treatment or that relative lack of instruments with race- and education-adjusted normative data may lead to increased trial variability, making detection of therapeutic effects more difficult.[6,7]

Whether differences exist between African American and white participants in AD clinical trials cannot be tested retrospectively by examining individual trials because there are too few African American subjects in any one trial to perform post hoc model-based subanalyses. This study used meta-analysis of a meta-database of AD clinical trials and observational studies including over 5,100 subjects with approximately 350 African Americans to overcome limitations of individual studies, examining differences in medical comorbidity and dropout rate between African Americans and whites and their effect on outcomes in AD clinical trials.

METHODS

Study Overview and Subjects

Subjects were drawn from a meta-database[8] consisting of 18 studies from the Alzheimer's Disease Cooperative Study[9] and the Alzheimer's Disease Neuroimaging Initiative (ADNI),[10] representing both clinical trials and observational studies in AD, mild cognitive impairment (MCI), and normal participants (Supplemental Table S1). All diagnoses of AD were based on National Institute of Neurological and Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria,[11] with the additional requirement of minimal severity based on clinical ratings. Diagnosis of MCI required a Clinical Dementia Rating scale score of 0.5 with the memory box scored at 0.5 or greater and delayed recall from the Logical Memory II subscale of the Wechsler Memory Scale–Revised[12] to be ≤8 for 16 years of education, ≤4 for 8–15 years, or ≤2 for 0–7 years. Patients had to be largely intact with regard to general cognition and functional performance and could not qualify for a dementia diagnosis. Subjects with AD or MCI in most trials analyzed could continue using marketed antidementia drugs if they had been on stable doses before entry and were not excluded from simulations. Clinical assessments were done at 6-month intervals over the first 2 years.

Outcomes

Medical Comorbidities

Prevalence of comorbid medical disorders at baseline among trial subjects was determined from lists of conditions collected by the individual studies. Analyses were restricted to 17 of 18 studies in which African American subjects were enrolled. Comorbidities were mapped to 19 categories (psychiatric; neurologic [other than AD]; head, eyes, ears, nose, and throat; cardiovascular; respiratory; hepatic; dermatologic-connective tissue; musculoskeletal; endocrine-metabolic; gastrointestinal; hematopoietic-lymphatic; renal-genitourinary; allergies or drug sensitivities; alcohol abuse; drug abuse; smoking; malignancy; major surgical procedures; and other) currently in use by the ADNI and classified as present or absent.

Dropout Rates

Dropouts were defined as the number of subjects missing the final study visit, regardless of study duration, because studies being analyzed have different lengths. Most studies included in the analysis did not distinguish between death and dropout for other reasons. Analyses were restricted to 10 studies of AD or MCI with the cognitive subscale of the Alzheimer's