Invited Commentary | Neurology

Treatment for Alzheimer Disease—Sex and Gender Effects Need to Be Explicitly Analyzed and Reported in Clinical Trials

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Martinkova et al\(^1\) have described the representation and analysis of sex-specific data from published randomized clinical trials of pharmacologic agents for all stages of Alzheimer disease (AD) that enrolled more than 100 adult participants. They addressed 3 issues: (1) the proportion of women enrolled, (2) the proportion of studies that reported sex-stratified data, and (3) temporal trends in enrollment or reporting by sex. The authors found that women represented 59% of study participants, that this percentage did not change significantly over the past decade, and that there was a lesser chance of enrollment of women in trials in North America compared with the rest of the world. They also report that whereas approximately half of the studies may have included sex in randomization schema, fewer than 15% of the publications described methods for analyzing results by sex or presented analyses of potential sex differences in responses.

What conclusions should be drawn from these analyses, and what does this study add to the literature? The work confirms a prior meta-analysis that found higher enrollment of women (63.8%) than men in trials of approved AD therapeutics.\(^2\) Women are estimated to represent, on average, 68.2% of patients with AD dementia in Europe and 62.1% of those in the US. There are no mandated inclusion metrics for proportions of women or men in clinical trials; however, a participant-to-prevalence ratio (ie, the ratio of the clinical trial participant population to the patient population with the disorder to be treated) of 0.8 to 1.2 is usually considered adequate. The report by Martinkova et al\(^1\) describes a participant-to-prevalence ratio between 0.87 and 0.95 for women. Enrollment of women into trials of pharmacologic agents for AD appears to be adequate.

The striking omission described by the authors is the absence of data to evaluate potential sex or gender differences in responses to the AD drugs studied, also emphasized in an earlier meta-analysis.\(^3\) A considerable body of literature describes sex and gender differences in risks and the course of AD.\(^3,4\) Data from the Framingham Heart Study reported greater risk of AD dementia in women at age 45 years (1 in 5) than in men at the same age (1 in 10) and an overall increased lifetime risk in women older than 85 years.\(^5\) The mechanisms for higher risk of AD dementia in women than in men are not entirely understood. Biologically plausible explanations include longer lifespans on average in women than in men; the effects of sex hormones, including protective effects of testosterone or protective or deleterious effects of estrogen; differential effects of \(APOE4\) gene alleles in men compared with women; age at menopause or duration of exposure to estrogens; and higher depression rates in women than in men. Sociologically plausible explanations include lower average educational attainment in women due to lack of opportunity and lower socioeconomic status in women compared with men. The interpretation of neuropsychological test results relies on corrections for such variables as level of education, sex, race, and age. However, many instruments lack appropriate, fully demographically corrected norms. Thus, it is reasonable to hypothesize that differences in responses to medication may exist between men and women with AD dementia as a result of factors that may be uncontrolled in study design.

Data that could identify or address underlying mechanisms for potential sex-related differences in responses to AD medications were collected during the trials identified and analyzed in the systematic review by Martinkova et al,\(^1\) but sex-specific analyses were reported in less than 15% of the AD dementia study results.\(^1\) The authors also point out the relative paucity of biomarker availability (in vivo or postmortem) in the studies but do not sufficiently emphasize its importance.
The dementia ascribed to AD may in fact only be caused by AD in 75% of cases; therefore, the absence of biomarkers in many studies does not provide a criterion standard for AD study enrollment but only for dementia, which can have many causes and mixed pathologies.

It is not accurate to say, however, that analyses of sex differences in response to AD medications are absent from the public domain. Analyses by the US Food and Drug Administration (FDA) on potential sex differences in responses to new medical entities approved for use in the US draw a very different conclusion than Martinkova et al. Specifically, these articles state that sex-specific analyses were performed for approved new drugs and biologic agents, with the results made publicly available via Drugs@FDA in 74% of new drug application and biologic reviews from 2007 through 2009, 92% of medical and statistical reviews from 2010 through 2012, and 93% of safety and efficacy reviews from 2013 through 2015. Since 2015, the FDA has provided Drug Trial Snapshots online at the FDA website that present the participation of patients in trials that supported the approval of the drug by age, sex, and race and highlight whether there was any difference in benefits or side effects among these subgroups.

We compared data in the Drugs@FDA database for the clinical trial report of 1 of the 9 approved AD drugs included in the meta-analysis by Martinkova et al that was coded as missing sex-specific information. Sex-specific information did not appear in that article, but analyses of sex differences for efficacy, safety, and adverse drug-related effects are presented in Drugs@FDA. Analyses by the FDA within the clinical and statistical reports concluded no statistically significant group by gender interaction for responses in test scores, but they noted that several adverse effects varied by sex. It is not our intent to repeat the analyses by Martinkova et al in other databases, but as sex-specific data also exist for donepezil in Drugs@FDA (stating differences in adverse effects), it is likely that sex-specific data exist for most if not all approved AD drugs. Although this information may require significant effort to find, the lack of reporting on inclusion and responses by sex and gender appears largely limited to reports in the scientific literature and investigations on drugs not approved for marketing.

There are, however, gaps in knowledge from AD clinical trials of pharmacologic agents about other clinical subgroups that are beyond the scope of this commentary. These gaps include inadequate data on potential differences in responses in the oldest patients with AD (ie, 80-85 years or older)—as trials appear to be skewed toward enrollment of relatively younger patients—and underrepresentation of racial minority groups in AD clinical trials despite reasonable expectations that these groups may have differing response profiles to AD medications.

In summary, for the evaluation of new pharmacologic treatments for AD, women are being enrolled in clinical trials in adequate numbers; however, data on potential differences in responses are not being reported in the scientific literature but do appear elsewhere in the public domain. Clinical trials are expensive, time-consuming, and difficult to complete, and the data from trials should be used and made accessible to the fullest extent. Potential group differences in responses to medications need to be more widely investigated, and available data needs to be made more user-friendly to facilitate incorporation into our knowledge base and clinical care. Finally, it is important to also close the gaps in our knowledge about subgroups of patients with AD beyond sex or gender.
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Additional Information: The authors note that they are of female sex and gender.

REFERENCES


