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

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The authors have nothing to disclose but note that they are of female sex and gender

Martinkova, et. al. have described the representation and analysis of sex-specific data from published randomized controlled clinical trials of pharmacologic agents for all stages of Alzheimer's Disease (AD) that enrolled more than 100 adult participants. [1] They addressed three 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. They found that women comprised 59% of study participants, that this percentage did not change significantly over the past decade, and detected a lesser chance of enrollment of women in trials in North America compared to the rest of the world. They also report that while about half of the studies may have included sex in randomization schema, fewer than 15% of the papers 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 comprise, on average, 68.2% of patients with Alzheimer's disease dementia in Europe and 62.1% of those in the U.S. There are no mandated inclusion metrics for proportions of women or men in clinical trials, however, a ratio of the clinical trial participant population to the patient population with the disorder to be treated or participant to prevalence ratio (PPR) of 0.8 to 1.2 is usually considered adequate. Martinkova, et.al. report [1] describes a PPR between 0.87-0.95 for women. Enrollment of women into AD trials of pharmacologic agents appears 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 the earlier meta-analysis. [2] A considerable body of literature describes sex and gender differences in risks for and the course of Alzheimer's disease. (see [3,4] for reviews.) Data from the Framingham Heart Study reported greater risk of AD dementia in women at age 45 years (1in 5) than in men at that age (1 in 10) and an overall increased life time risk in women over age 85 years. [5] The mechanisms for higher risk of AD dementia in women than men are not entirely elucidated. Biologically plausible explanations include longer lifespans on average in women than men, 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 to women, age at menopause or duration of exposure to estrogens, and higher depression

rates in women than men. Sociologically plausible explanations include lower average education in women than men due to lack of opportunity, and lower socioeconomic status in women compared to men The interpretation of neuropsychological test results relies on corrections for such variables as level of education, sex, race and age. [6] However, many instruments lack appropriate full demographically corrected norms. Thus, it is reasonable to hypothesize that differences in responses to medication may exist between men and women with Alzheimer's disease 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 AZ medications were collected during the trials identified and analyzed in the systematic review by Martinkova, et al but sex-specific analyses were reported in less than 15 per cent of the AD dementia study results.[1] The authors also point out the relative paucity of biomarker availability (*in vivo* or post mortem) in the studies but do not sufficiently emphasize its importance. Given that the dementia ascribed to AD may in fact only be "caused" by AD in 75% of cases, [7] the absence of biomarkers in many studies does not provide a "gold standard" for AD 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 AZ medications are absent from the public domain. Articles by the FDA on the analysis of potential sex differences in responses to new medical entities approved for use in the U.S. draw a very different conclusion than the authors. [8-10] Specifically, articles state sex-specific analyses were performed for approved new drugs and biologic agents and made publicly available (see Drugs@FDA) in 74% of new drug application and biologic reviews from 2007-2009, 92% of medical and statistical reviews from 2010-2012, and in safety and efficacy reviews in 93% from 2013-2015. [8-10] Since 2015, the FDA has also published Drug Trials Snapshots 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. (https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots)

We compared data in Drugs@FDA for the clinical trial paper of one of the 9 approved AZ drugs included in the meta-analysis by Martinkova, et.al. [1] that was coded as missing sex-specific information. (see Fig 2, for Grossberg, et al, 2013). Sex-specific information did not appear in the paper, but analyses of sex differences for efficacy, safety and adverse drug-related effects are presented in Drugs@FDA. FDA analyses within the

clinical and statistical reports concluded no statistically significant group by gender interaction for responses in test scores, but noted several adverse effects varied by sex. It is not our intent to repeat the analyses by Martinkova, et.al. [1] 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 exists for most if not all of approved AZ drugs. Although this information may require significant effort to find, the lack of reporting on inclusion and responses by sex/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 AZ clinical trials of pharmacologic agents about other clinical subgroups that are beyond the scope of this commentary. These include inadequate data on potential differences in responses in the oldest AZ patients (i.e., 80-85+ years) as trials appear to be skewed toward enrollment of younger old patients, and, under-representation of minority racial groups in AZ clinical trials despite reasonable expectations that these groups may have differing response profiles to AZ medications.

In summary, for the evaluation of new pharmacologic treatments for Alzheimer's disease, women are being enrolled in clinical trials in adequate numbers but data on potential differences in responses are not being reported in the scientific literature but 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. Lastly, it is important to also close the gaps in our knowledge about Alzheimer's disease patient subgroups beyond sex or gender.

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