U.S. Food and Drug Administration/ Office of Women's Health: Impact of Gender Analysis and Pharmacogenomics on Clinical Efficacy, Safety, and Pharmocokinetics of Drugs Used for the Treatment of Alzheimer's Disease

The objectives of this project were to examine the representation of women in Alzheimer's disease trials and to identify whether gender and ApoE genotype are predictive factors of the response to Alzheimer's disease drugs.

Lead Agency:

U.S. Department of Health and Human Services(HHS), U.S. Food and Drug Administration (FDA), Office of Women's Health (OWH)

Agency Mission:

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

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Partner Agencies:

Center for Drug Evaluation and Research (CDER)
Office of Clinical Pharmacology (OCP)
Division of Neurology Products (DNP)
Office of Drug Evaluation I (ODEI)
Office of New Drugs (OND)
Office of Pharmacoepidemiology and Statistical Science (OPASS)
Office of Biostatistics (OB)
Divison of Biometrics I(DBI)

General Description:

Impact of Gender Analysis and Pharmacogenomics on Clinical Efficacy, Safety, and Pharmacokinetics of Drugs Used for the Treatment of Alzheimer's Disease
Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Risk factors for AD include one form of the apolipoprotein E (ApoE) genotype and gender: females and ApoE4 carriers are at higher risk for AD. Several literature reports showed that certain patients respond better to the treatment than others. Thus, it will be very helpful to identify whether gender and ApoE genotype are predictive factors of the response to AD.

The medications approved at the time of the study are cholinesterase inhibitors and drugs regulating glutamate.

This project examined the clinical trials associated with AD for gender-based analysis. Historically females have been underrepresented in clinical research and thus have examined these clinical trials determine if the number of women enrolled is adequate. Further, since AD affects 1.5 to 3 times as many women as men and because there are studies that suggest gender is likely to be a more powerful determinant of outcome of cholinesterase inhibitor treatment than ApoE status in the short term, it was of increased importance that we track the inclusion of women and investigate the roles that gender may play.

Large strides have been made to ensure that women were not underrepresented in these clinical trials. Issues of insufficient enrollment are no longer significant in AD clinical trials. Available genomic data show that AD patients with homozygous ApoE4 responded more positively to treatment of these two drugs on the cognitive function than ApoE4 negative and heterozygous ApoE4 patients. This work shows that pharmacogenomic information in FDA submissions is useful for examining efficacy in important AD disease subgroups. To better understand the impact of ApoE on clinical efficacy, collection of pharmacogenomic information in the IND and NDA submission is recommended.

Excellence: What makes this project exceptional?

Alzheimer's disease (AD) is characterized by progressive impairment in memory, language, visual-spatial perceptions, and judgment. Risk factors for AD include one form of the apolipoprotein E (APOE) genotype and gender. Females are at higher risk for AD. Although AD affects both men and women, studies show that 1.5 to 3 times as many women suffer from AD as do their male counterparts. The results from the study showed that the ratios of women to men ranged from as low as 1.3 to 2.1. This study also explored the relationship between ApoE biomarker and clinical outcome of AD patients when treated with approved drugs. Since there is no cure for AD, any progress that can be made in understanding the disease is a tremendous step forward.

Significance: How is this research relevant to older persons, populations and/or an aging society?

Alzheimer's Disease (AD), an age-related neurodegenerative disorder, is the most common cause of dementia in elderly people. There are two types of AD, early onset and late onset. In early onset AD, symptoms first appear before age 65. Early onset AD is much less common, accounting for only 5-10% of cases. Late-onset AD, the more common form, develops after age 65. Although AD affects both men and women, studies show that 1.5 to 3 times as many women suffer from AD as do their male counterparts. In 1992, researchers found that certain forms of the apolipoprotein E (ApoE) gene can influence AD risk. The *ApoE4* is the main known genetic risk factor for AD. The *ApoE4* alleles decrease and the *ApoE2* alleles increase age at onset of AD. It is estimated that the number of AD patients will reach 9 million by the year 2040 if there are no curative treatments developed.

Effectiveness: What is the impact and/or application of this research to older persons?

One of the objectives of this project was to determine whether enrollment of women in AD clinical trials is sufficient and fairly representative of the disease demographic. Based on the obtained results, it can be said that large strides have been made to ensure that women were not underrepresented in these clinical trials. The results of the study demonstrate the importance of collecting pharmacogenomic data in AD trials.

Innovativeness: Why is this research exciting and newsworthy?

Tracking inclusion of women in these clinical trials and identifying the gender and the genomic effects on the pharmacokinetic/ pharmacodynamic of drugs used to treat AD will help achieve the goal of personalized medicine.