



Sex Differences in Alzheimer's Disease Treatments



Amanda G. Smith, MD

Director Of Clinical Research

USF Health Byrd Alzheimer's Institute &
Professor

Department of Psychiatry and Behavioral Neurosciences
USF Health Morsani College of Medicine

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

Janice B. Schwartz, MD^{1,2}; Sandra Weintraub, PhD^{3,4}

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May 8, 2023

A Call to Action to Address Sex Differences in Alzheimer Disease Clinical Trials

Rachel F. Buckley, PhD^{1,2}; Jessica Gong, MSc^{3,4}; Mark Woodward, PhD^{3,4}

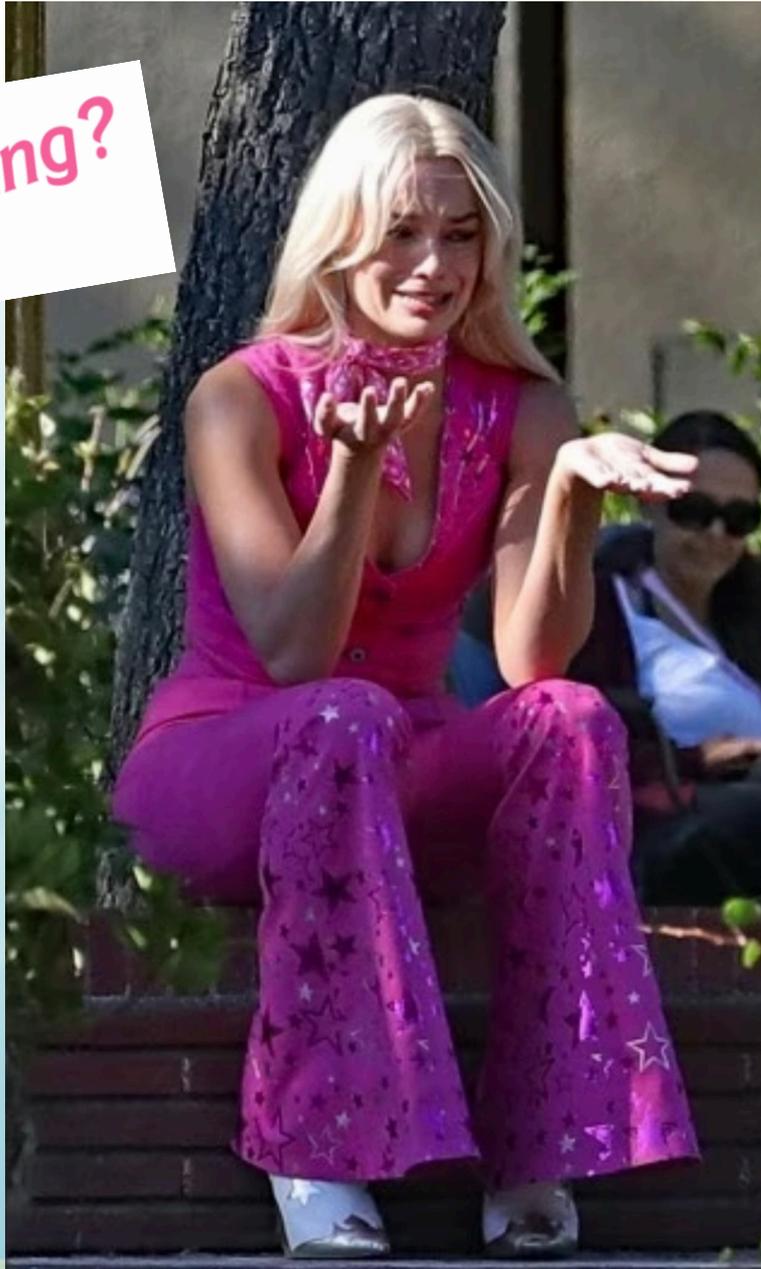
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Historically, scientific findings from male in vitro and in vivo models have formed the standard of medical knowledge. This approach, exacerbated by low female representation in medical research and a dearth of studies investigating sex differences, has led to substantial public health, clinical, and humanitarian implications, as well as economic consequences. A cardinal example from the field of cardiology was the discovery of critical sex-specific treatment effects through ad hoc observational analyses, years after the results of clinical trials had been published. There is a pressing need to study and report sex differences across the field of medicine but most crucially now in Alzheimer disease (AD).

What is happening?



Where things stand...

- A substantial body of literature exists regarding the sex differences in the **risks** for and **course** of Alzheimer's disease
- Formal analysis of sex differences pertaining to ***treatment*** lags far behind
- Women are being enrolled in AD trials in adequate/equal numbers

- Analysis of studies with **cholinesterase inhibitors**
- Two studies suggested that there may be an interaction between apoE genotype, sex, and tacrine
- 7 clinical trials and 13 case studies produced little evidence of an association between treatment outcomes and sex
- In one study women with AD treated with donepezil had lower mortality rates than men
- One study produced weak evidence that women treated with ChEIs may experience more adverse effects than men

- Sex and ESR1 genotype may influence the response to treatment with **donepezil** and **rivastigmine** in patients with Alzheimer's disease
- Among the patients under treatment with either drug, the women responded more markedly than the men as measured by MMSE
- Concluded women seemed to be more sensitive to therapy and to have experienced less cognitive decline

Mean changes of mini mental state examination scores in patients on the whole and stratified by sex

	All patients				Male patients				Female patients			
	Mean	SD	N	p	Mean	SD	N	p	Mean	SD	N	p
Untreated	-2.4	2.2	27		-2.1	3.0	11		-2.6	1.5	16	
Treated (all)	-2.0	2.1	157	0.27	-2.7	2.4	39	0.22	-1.7	1.9	118	0.018
Donepezil	-1.8	1.8	96	0.20	-2.2	1.8	26	0.46	-1.7	1.8	70	0.018
Rivastigmine	-2.3	2.5	61	0.64	-3.9	3.1	13	0.05	-1.9	2.2	48	0.033

Mazure et al 2016

- Important comment piece in response to Lancet Neurology Commission's call to action for AD
- Suggested testing for effects of ApoE4 and other genes by sex rather than pooling data
- Suggested that variations in clinical presentations, behaviors, and localized brain changes among sexes may necessitate different management strategies
- “A focus on the effect of sex on Alzheimer's disease and other dementias is essential to ensure progress in understanding treatment and prevention of these disorders.”

Canevelli et al 2017

- Looked at all available randomized trials on cholinesterase inhibitors and memantine
- NONE of the studies reported data on efficacy, safety, and tolerability separately in male vs female subjects
- Looked at an additional 48 studies that did not meet their initial criteria
- Of those, only 2 took in to account the potential influence of sex and gender on treatment effects, reporting no significant difference

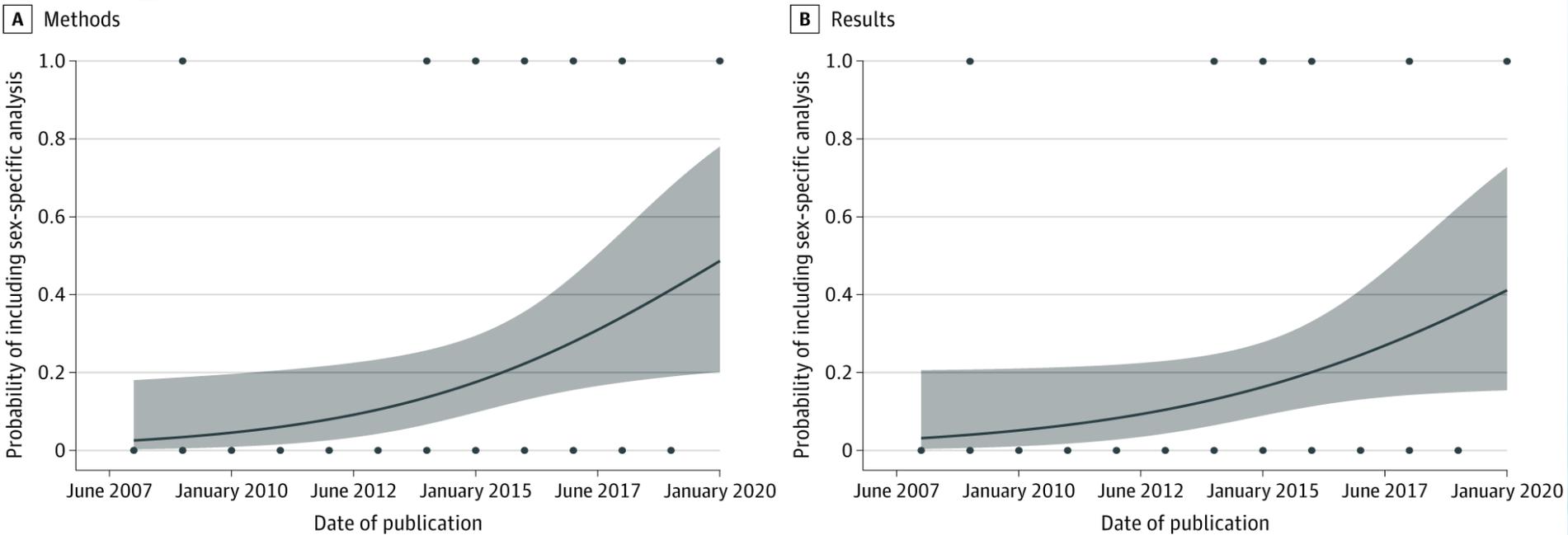
Main characteristics of the 48 studies

	Donepezil	Rivastigmine	Galantamine	Memantine	Total
Studies (n)	17	10	9	12	48
Participants (n)	5192	4908	6499	4089	20,688
Age (weighted mean \pm SD)	75.1 \pm 5.0	73.2 \pm 2.4	75.1 \pm 3.3	76.2 \pm 4.3	74.9 \pm 4.1
Sex (F, %)	64.5	63.3	64.4	63.9	63.8
Exploring sex differences (%)					
Efficacy	11.8	–	–	–	4.2
Tolerability	–	–	–	–	–
Exploring gender differences (%)					
Efficacy	11.8	–	–	–	4.2
Tolerability	–	–	–	–	–

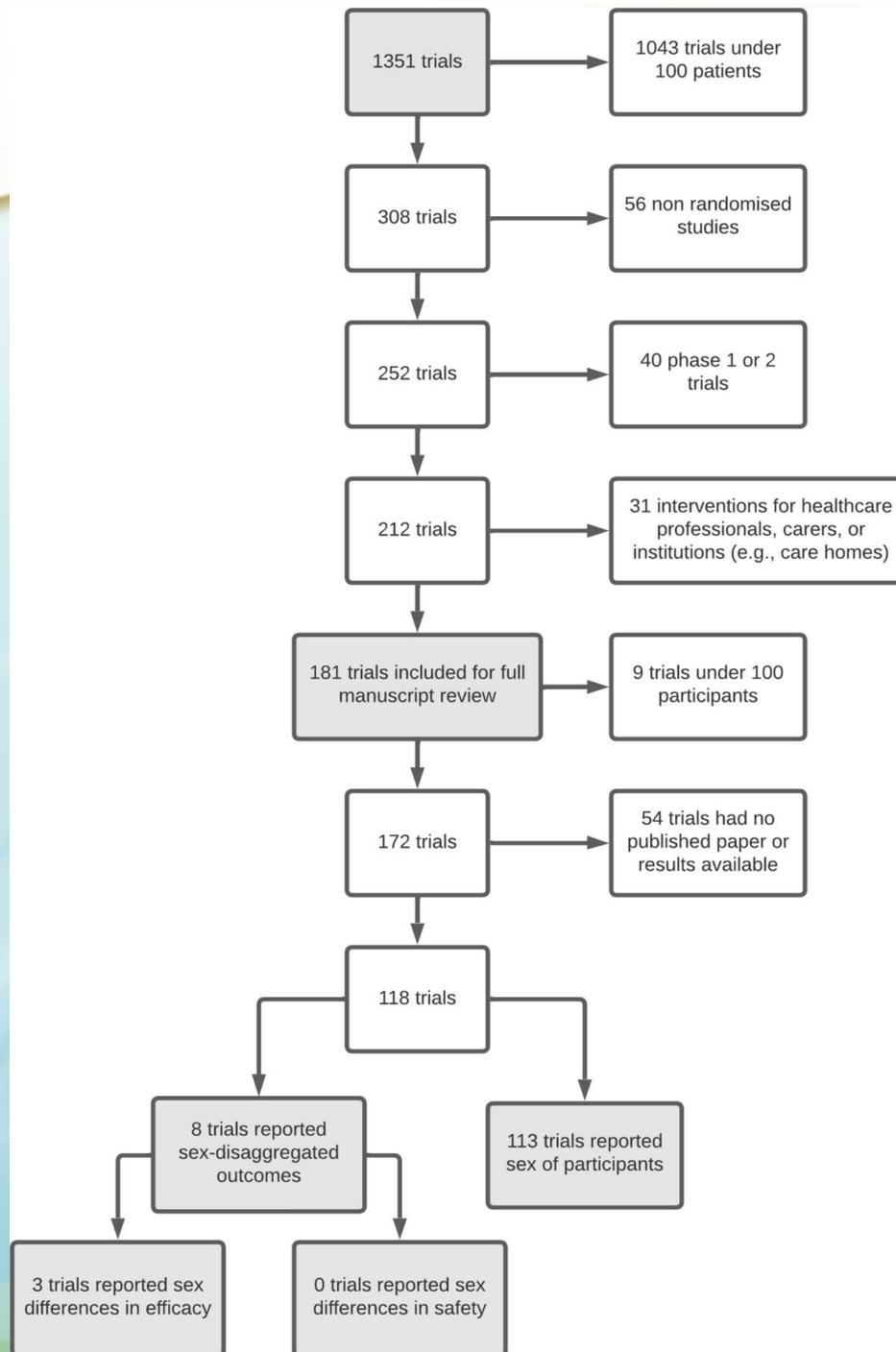
- Distribution of neuropsychiatric symptoms in dementia varies by sex
- Females have higher total scores on the NPI and also on scales of *depression* and *anxiety*
- Males have higher rates of *agitation*
- Better characterization of the underlying causes of these differences may help identify better treatment targets

- Meta-analysis of 56 randomized clinical trials for AD with 39,575 total participants
- The proportion of women in RCTs of experimental drugs (57.9%) was lower than the proportion of women in the general population with AD in the US (62.1%) and Europe (68.2%)
- Only 7 articles (12.5%) reported sex-stratified results, though the proportion seemed to increase over time

Probability of including a sex-specific analysis increased only slightly over a 13-year period

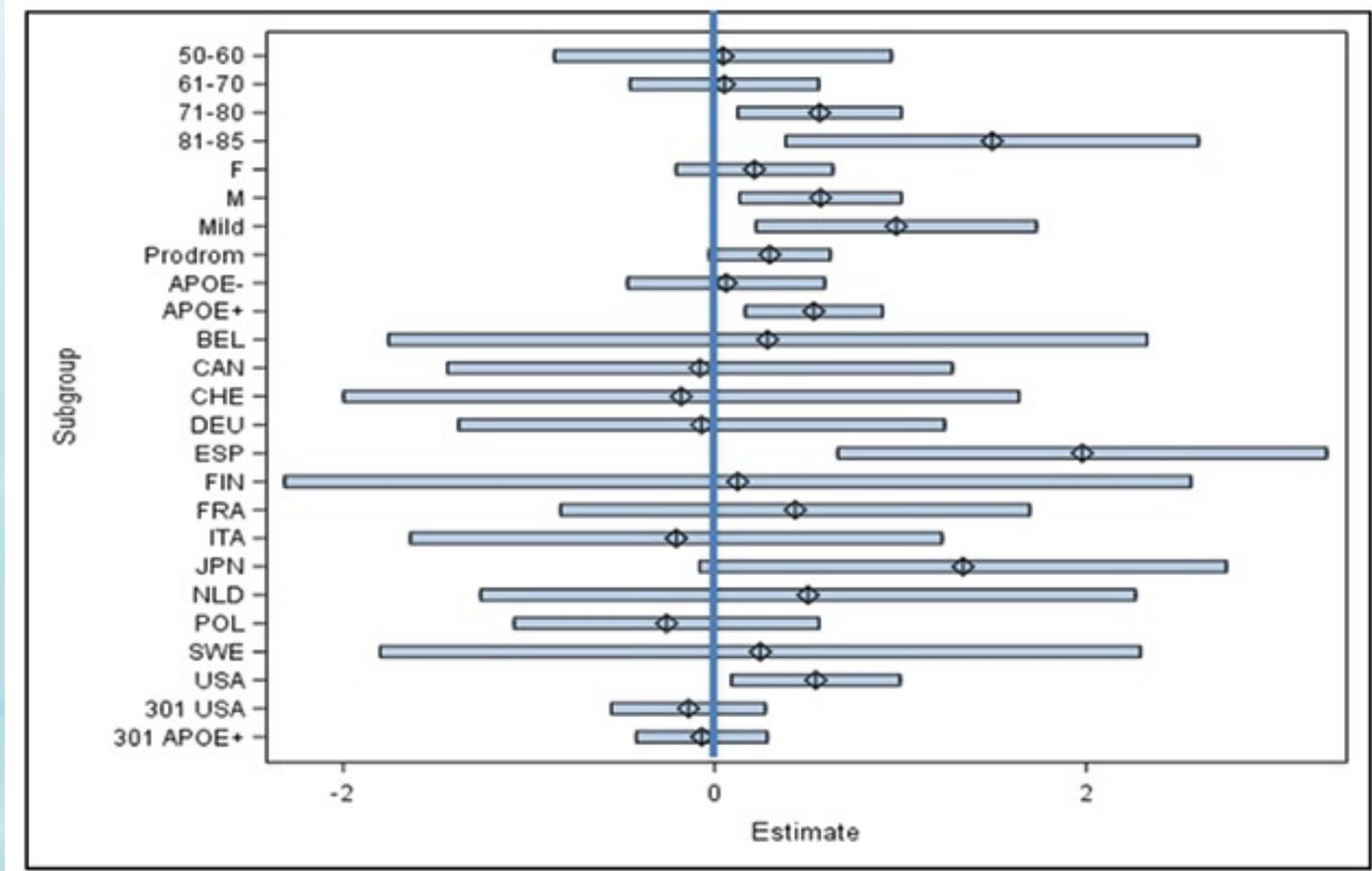


- Looked at 118 dementia trials between 2010 and 2021
- Only 8 (6.7%) reported outcomes by sex
- None reported screen failures or adverse events stratified by sex
- Women comprised 58% of the 110,469 total participants, which was lower than their estimated representation in the global dementia population (64%)



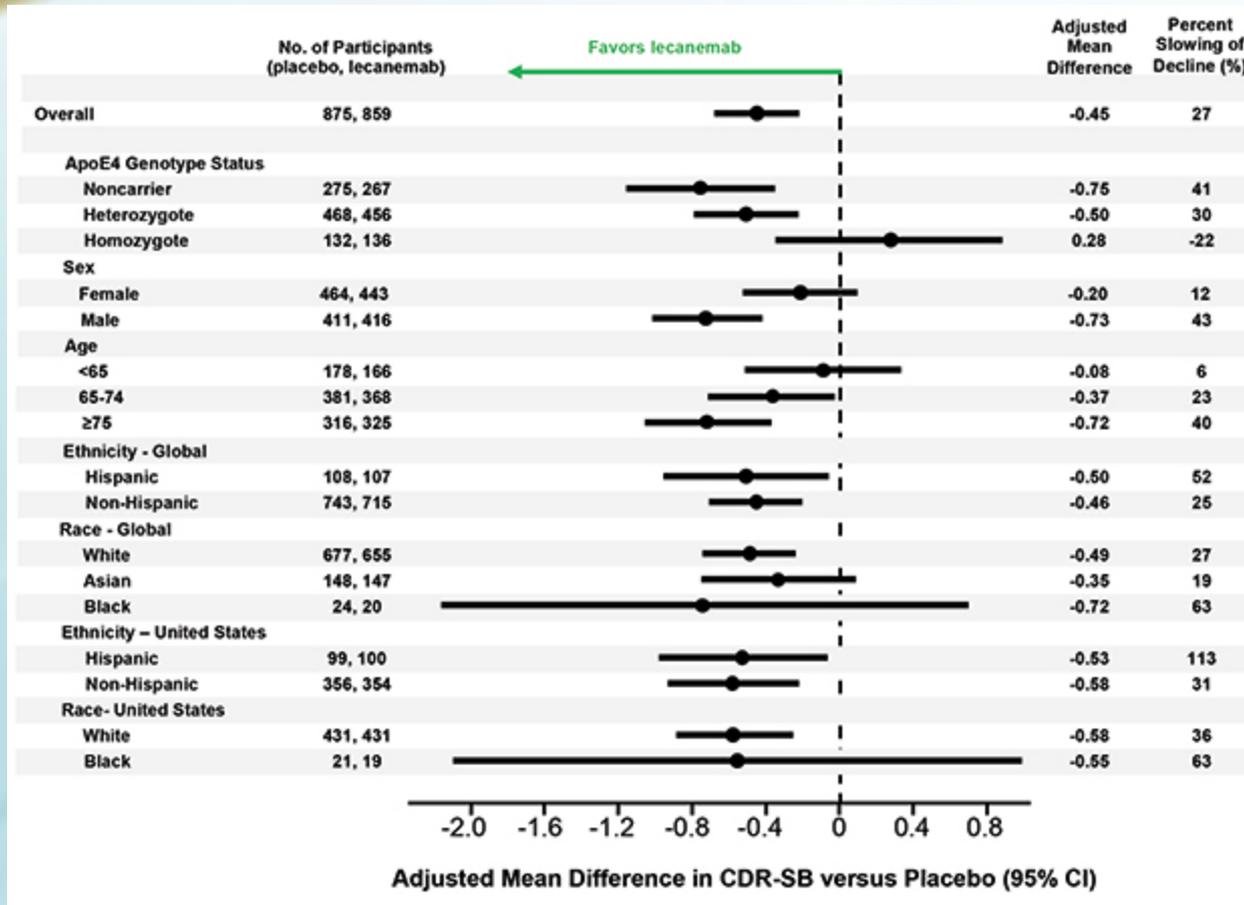
- Results for EMERGE & ENGAGE (aducanumab) and CLARITY-AD (lecanemab) did *not* include sex disaggregated results in the main trial reporting
- BUT subgroup analyses in the supplementary material revealed noteworthy sex differences
- Specifically, the cognitive benefits of these drugs as measured by both CDR-SB and ADAS-Cog were evident primarily in men

Aducanumab subgroup effects - EMERGE



From FDA website

Lecanemab subgroup analysis



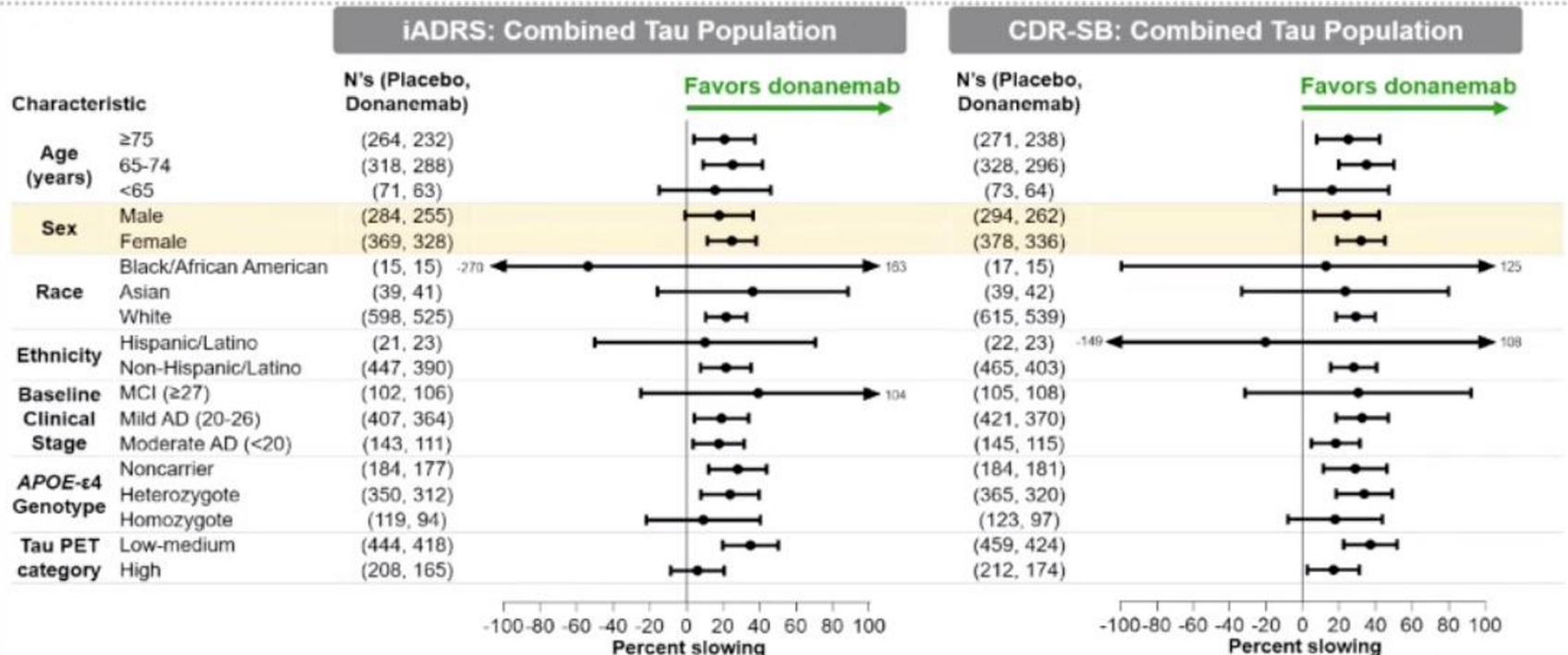
Presented at CTAD 2022, courtesy of Eisai, online at ALZFORUM

Finally.... some recent progress!



Trailblazer-2 topline results presented at AAIC 2023 (donanemab)

Subgroup Analyses: Combined Tau Population



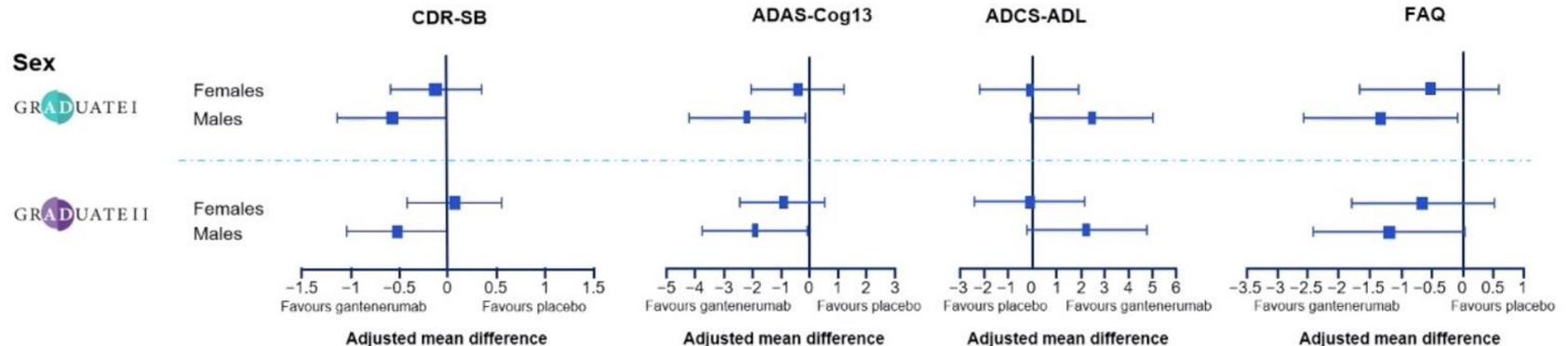
NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level and baseline acetylcholinesterase inhibitor/memantine use. Additional fixed terms include subgroup by treatment, subgroup by basis expansion, and subgroup by basis expansion by treatment interactions. Bars show the 95% confidence intervals, values are included for those that extend past the limits of the axis. Abbreviations: AD=Alzheimer's Disease, APOE=apolipoprotein E, CDR-SB=Clinical Dementia Rating Scale-Sum of Boxes, iADRS=Integrated Alzheimer's Disease Rating Scale, MCI=mild cognitive impairment, N=number of participants, NCS=natural cubic spline, PET=positron emission tomography.

Roche presented pooled data from Graduate I and II studies w/gantenerumab and looked at sex differences

- Consistent trends with better numerical outcomes in men across all endpoints and in both studies
- Looked at both biomarker and clinical outcomes

Clinical impact on CDR-SB, ADAS-Cog13, ADCS-ADL, and FAQ at Week 116 in male and female subgroups

Subgroup analysis showed consistent trends with better numerical outcomes in males across all endpoints and across both studies



CDR-SB subgroup analyses were prespecified. ADAS-Cog13, ADCS-ADL, and FAQ subgroup analyses were post hoc.
 ADAS-Cog13, Alzheimer's Disease Assessment Scale - Cognitive Subscale 13; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living; CDR-SB, Clinical Dementia Rating - Sum of Boxes; FAQ, Functional Activities Questionnaire.
 Bateman RJ, et al. Presented at AD/PD 2023, Gothenburg, Sweden.

Graduate data- biomarkers by sex

- Higher amyloid PET and tau burden at baseline in women
- Similar amyloid reduction at wk 116 in men and women
- Point estimates of treatment effects appear better in men but
- Numerically larger treatment effects in women on several CSF biomarkers (not Ab42 and NfL though)
- Numerically larger treatment effect on plasma Ab42 and 40 in women
- Less ventricular volume increase in men

What does this all mean?

- We don't know what we don't know!
- There may be key differences in treatment responses between men and women due to a variety of factors
- Identifying these differences may help us shape future studies and develop more personalized treatment for men vs. women
- Sex-disaggregated findings should be reported as part of the MAIN TRIAL RESULTS and not buried in later supplemental subgroup analyses

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QUESTIONS??

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WARNER BROS.