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A case for seeking sex-specific treatments in Alzheimer's disease

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There is no satisfactory explanation for the sex-related differences in the incidence of many diseases and this is also true of Alzheimer's disease (AD), where females have a higher lifetime risk of developing the disease and make up about two thirds of the AD patient population. The importance of understanding the cause(s) that account for this disproportionate distribution cannot be overestimated, and is likely to be a significant factor in the search for therapeutic strategies that will combat the disease and, furthermore, potentially point to a sex-targeted approach to treatment. This review considers the literature in the context of what is known about the impact of sex on processes targeted by drugs that are in clinical trial for AD, and existing knowledge on differing responses of males and females to these drugs. Current knowledge strongly supports the view that trials should make assessing sex-related difference in responses a priority with a focus on exploring the sex-stratified treatments.

KEYWORDS

Alzheimer's disease, sex, clinical trials, inflammation, amyloid

Background

Almost 65% of AD patients are women and the increased risk of AD in women is present even when their longer lifespan is taken into account (Viña and Lloret, 2010). A recent review concluded that, once a diagnosis is made, clinical symptoms occur more rapidly in females (Podcasy and Epperson, 2016) with greater tau pathology in females compared with males (Luchsinger et al., 2020; Edwards et al., 2021).

The evidence related to sex differences in Aβ deposition in AD is less clear but there is some evidence that there is a modest increase in Aβ pathology in females which may be age-related (Oveisgharan et al., 2018; Luchsinger et al., 2020). Dystrophic, iron-containing microglia develop and cluster around Aβ plaques (Meadowcroft et al., 2015) and are more prevalent in tissue from female compared with male AD patients (O'Neill et al., 2022). The advent of RNA sequencing (RNAseq) technology, and particularly single nucleus RNAseq, has permitted the comparison of differentially-expressed genes in postmortem samples from AD patients and evidence indicates that there is an upregulation of genes transcripts reflecting inflammatory/immune processes particularly in samples from female AD patients (Paranjpe et al., 2021; Guo et al., 2022), consistent with the knowledge that several genes involved in immune regulation are located on the X chromosome. One has to consider the importance of this given that about 20% of genes from the inactive X chromosome escape inactivation, including genes that play a role in inflammation and/or impact on AD risk (Youness et al., 2021; Song et al., 2024). However several genes associated with inflammation/the immune response were also upregulated in cortical samples from control postmenopausal, compared with premenopausal, women (Sárvári et al., 2012;

Coales et al., 2022), adding credence to the hypothesis that the triad of reduced ovarian function, inflammatory change and age amplifies AD risk and drives progression of disease in females (Mishra and Brinton, 2018).

The evidence that metabolism is also disrupted in AD is compelling (Demetrius et al., 2021) and several groups have reported decreased glucose utilization (Kapogiannis and Mattson, 2011; Butterfield and Halliwell, 2019; Wang et al., 2020) and mitochondrial dysfunction (Swerdlow, 2018; Wang et al., 2020; Misrani et al., 2021). Data from a longitudinal study over 2 years suggested that metabolic changes assessed by fluorodeoxyglucose-PET occurred to a greater extent in female AD patients compared with males (Park et al., 2023).

This review will consider that, at the very least, these sex-related differences in AD in pathology, immune function and metabolism point to the importance of interrogating the potential treatment regimes separately in males and females. It is important to point out that the majority of the studies cited here were carried out on western European and US populations; this is an acknowledged limitation that has been identified as a significant shortcoming in clinical trials (Reardon, 2023b).

Risk factors and AD: interaction with sex

Non-genetic risk factors in AD

The current estimate is that the risk of AD is reduced by about 40% if modifiable risk factors including cardiovascular disease, obesity and diabetes were eliminated (Livingston et al., 2020). Recent reviews (Mielke, 2018; Rahman et al., 2019) pinpoint a sex dimension in several risk factors (see **Table 1**) including level of education and social interaction, smoking, alcohol consumption and stress may also have a sex-related component (Podcasy and Epperson, 2016; Yan et al., 2018).

Exercise and diet are among the strategies that can have a far reaching impact on a number of modifiable AD risk factors. A study of 44,000 individuals with a 10 year follow-up period provided convincing evidence that disabling dementia in both men and women was inversely proportional to daily physical activity (Ihira et al., 2022) but both aerobic and resistance training appear to improve executive function to a greater extent in women (Barha et al., 2017). Moreover, the association between physical and cognitive ability and memory reserve is stronger in women than men and this is influenced by *APOE4* (Pa et al., 2022). While a scientific basis for this remains to be determined, evidence from animal studies suggests that sex-related differences in exercise-stimulated growth factors, brain architecture and/or cardiac or respiratory responses may play a role (Barha and Liu-Ambrose, 2018).

Adiposity is a confirmed risk factor for AD (Deng et al., 2022) and some evidence points to it driving inflammation to a greater extent in females compared with males (Khera et al., 2009) although gray matter volume decreases to a greater extent in obese males compared with females, suggesting that obese males may be at greater risk of later cognitive decline (Taki et al., 2008). Diet also appears to have sex-dependent effects with evidence that adherence to a Mediterranean diet exerts a greater benefit (Gregory et al., 2022), and greater protection against AD (Rahman et al., 2019), in women.

The evidence is that menopause constitutes a risk of AD and it has been reported that the reduction in brain glucose metabolism that occurs with the menopause is linked with prodromal AD and, indeed, it has been proposed that early estrogen therapy may be a useful strategy in reducing the menopause-associated risk of AD (Mosconi and Brinton, 2018; Mosconi et al., 2018; Mishra et al., 2022).

Despite heterogeneity in evaluating educational achievement, a recent review concluded that the evidence linking poorer education and increased risk of AD was robust (Maccora et al., 2020). The fact that education was more limited for women than men in the past opened up the possibility that this contributed to the greater risk of AD in women (Bloomberg et al., 2021; Gong et al., 2023) and a recent analysis of 2 prospective studies has suggested that females may benefit more from education than men in terms of AD risk (Bloomberg et al., 2021).

Genetic risk factors in AD

APOE is the greatest genetic risk factor for sporadic AD and the ε4 allele confers the greatest risk (Corder et al., 1993; Strittmatter et al., 1993) although many additional susceptibility genes, particularly related to amyloid, tau, immunity, lipids and endocytosis, have been identified by Genome-wide association studies (GWAS) (Bellenguez et al., 2022). Genes that confer significant risk of AD include *TREM2*, *BIN1*, *PICALM*, *CLU* and *CR1*.

The interaction between sex and APOE

The risk of AD in *APOE4*-ε4 carriers has been reported to be greater in females (Riedel et al., 2016) but recent evidence indicated that having 1 copy of *APOE4*-ε4 was associated with similar risk of AD in men and women between the ages of 55 and 85 years, whereas a greater risk was observed in women aged 65–75 years (Neu et al., 2017). *APOE4* is associated with faster disease progression (Buckley et al., 2018), increased tau pathology (Deming et al., 2018) and more rapid decline in performance in memory tasks (Ungar et al., 2014) in female carriers (Neu et al., 2017). It is a predictor of transition from MCI to AD in males and females, but with a greater impact in females. In preclinical studies, memory impairment was observed at an earlier age in female *ApoE* 3xTg mice, and amyloid pathology and β-secretase expression were more pronounced in the hippocampus of female mice (Hou et al., 2015).

The impact of hormone replacement therapy on AD risk in postmenopausal women is inconsistent and may be related to *APOE4* since it was reported to improve episodic memory (Burkhardt et al., 2004) and reduced the risk of cognitive impairment (Yaffe et al., 2000) albeit only in *APOE-ε4* non-carriers.

Interactions between sex and other genes that confer risk

A number of studies have reported transcriptome-wide sex differences in AD including genes that suggested activation of the immune system which were increased in male and female AD

TABLE 1 Modifiable risk factors that are impacted by sex.

Modifiable risk factor	The sex dimension
Education	Poor education is reported to present a greater risk of AD in women (Letenneur et al., 2000) and risk of AD is reduced with additional years of education (Nebel et al., 2018). A large prospective cohort study of individuals born between 1930 and 1955 indicated a positive effect of education in women on fluency but not memory (Bloomberg et al., 2021).
Hearing loss	A study of 655 individuals found that moderate/severe hearing loss was associated with poorer cognitive function in men (Huang et al., 2020) although the risk of dementia was greater in older women (> 65 years) with sudden hearing loss (Tai et al., 2021).
Head trauma	A study of >14,000 individuals with head injury revealed that the risk of dementia was greater in women with head injury compared with men (Schneider et al., 2021).
Cardiovascular disease	A population-based study of >500,000 individuals found that women with cardiovascular disease are more likely to have AD than men with cardiovascular disease (Dong et al., 2022).
Alcohol	A recent metanalysis of 7 studies that included sex as a risk factor for AD did not identify clearcut differences between men and women although AD cases in European countries that could be attributed to alcohol were greater in men than women (Kilian et al., 2023).
Obesity	Among 6,582 non-demented individuals, 7% developed dementia within a 15 year follow-up. Obesity increased risk of dementia and was significantly greater in obese women (Ma et al., 2020).
Smoking	The risk of dementia is greater in women who smoke/have smoked (Zhang et al., 2021).
Depression	Untreated depression in women is associated with the likelihood of developing AD and treatment reduces this risk (Norton et al., 2019).
Social Isolation	Many studies suggest that social isolation poses a greater risk of dementia in women but a recent comprehensive review indicates a lack of consensus (Ren et al., 2023)
Physical inactivity	Evidence suggesting a sex-related difference in risk arising from physical inactivity is mixed with no clear association (Sindi et al., 2021)
Diabetes	Two studies with >85,000 (Lee et al., 2021) or >3000 (Verhagen et al., 2022) participants with type 2 diabetes established that during a 6 year follow-up period development of AD or accelerated cognitive decline was greater in women.
Air pollution	The incidence of AD is increased in individuals exposed to higher $PM_{2.5}$ and NO_2 (Shi et al., 2021). Some evidence suggests that air pollution has a greater negative impact on cognition in females (Kim et al., 2019). In a rat model of AD, exposure to traffic-related air pollution induced earlier and more profound amyloid pathology in females compared with males (Patten et al., 2021)
Inflammation	Data from a longitudinal study with >38,000 individuals found that *APOE*-ε4 carriers and females with higher CSF TNF-α, IL-9, and IL-12p40 levels were at the highest risk of progression to MCI/AD (Contreras et al., 2022).

patients although the greater number of dysregulated genes, for example *CHI3L1* (Sanfilippo et al., 2019), was markedly increased in samples from females (Paranjpe et al., 2021). Evidence from the APP/PS1 mouse model also revealed female-specific upregulation of genes that modulate inflammatory mediators (Manji et al., 2019; Guillot-Sestier et al., 2021). Several other sex-related differences in genes have been identified and some are listed in **Table 2**.

Enrichment of genes reflecting upregulation of the PI3K-Akt signaling pathway was observed in brain samples from males and females but upregulation of genes related to the MAPK signaling pathway occurred in males only, which might translate into sex-specific responses to p38 MAPK inhibitors that are being assessed for efficacy in AD (Lee and Kim, 2017).

Is there evidence of sex-related differences in response to approved drugs for AD?

Drug efficacy is impacted by hormones (Kwon et al., 2017) and while the emphasis may have been on assessing interactions between contraceptive hormones or stress hormones and drugs, evidence points to other interactions with sex hormones, for example between hormones and antiepileptic drugs (Taubøll et al., 2021), hormones and pain medication (Athnaiel et al., 2023), hormones and antidepressants (Pavlidi et al., 2021). Further study is likely to uncover other hormone:drug interactions, perhaps relevant to AD. Here the emphasis is on assessing the impact of sex on drug action in AD.

Five drugs and two monoclonal antibodies have been approved for the treatment of AD (**Table 3**).

Is the response to FDA-approved drugs sex-dependent?

Sex-related differences in the responses of AD patients to cholinesterase inhibitors have been reported but data are limited with few studies explicitly analyzing the impact of sex on treatment outcomes as pointed out in recent reviews (Canevelli et al., 2017; Mehta et al., 2017). Mehta et al. (2017) evaluated 33 studies in which sex was considered as a demographic variable, sex-stratified data were reported in only 1 study where no difference was identified. Canevelli et al. (2017) reported that only 2 out of the 48 randomly-controlled trials specifically assessed sex differences and these reported no sex-related differences in cognition in response to donepezil, corroborating the findings of an earlier review which concluded that sex exerted a minimal impact on the effects of cholinesterase inhibitor efficacy in spite of evidence from animal studies (Haywood and Mukaetova-Ladinska, 2006).

The studies that analyzed the effect of sex are mostly small in scale and date back >10 years. One of the more

TABLE 2 Sex-related differences in some genes that confer AD risk.

Gene	Link to AD	References
CXCR4	Female-specific increase in AD	Brooks and Mias, 2019
SERPINB1, SERPINB6, SERPINB9	Correlation with amyloidosis in females	Deming et al., 2018
OSTN, CLDN16	Correlation with tau pathology in females	Deming et al., 2018
NCL,KIF2A	Associated with tau phosphorylation in females	Cáceres and González, 2020
BIN1, MS4A6A, DNAJA2, FERMT2	Contribute to AD progression more in females than males. May confer a higher risk in females.	Fan et al., 2020
ACE	An association between ACE genotype and AD reported in females	Crawford et al., 2000
BDNF	Female-specific polymorphism (rs6265) is associated with susceptibility to AD	Li et al., 2017
ZBTB7C	A variant (rs1944572) conferred an increase in AD risk in females and a decreased risk in males	Prokopenko et al., 2020
RELN	Polymorphisms (rs528528 and rs607755) are associated with AD risk in males	Fehér et al., 2015
GRN	Genetic variability is associated with AD risk in males	Viswanathan et al., 2009

TABLE 3 Drugs approved for the treatment of AD.

Drug and date approved	Target	Notes	The sex dimension
Donepezil (Aricept) 1996	Reversibly inhibits AChE; increases ACh availability enhancing cholinergic transmission	Does not modify the underlying pathophysiology of AD. Delays the progressive worsening of cognitive symptoms of AD. Modest effect. >250 clinical trials.	Variable data on sex-related changes in cognition including reports of no sex-related differences of donepezil (Canevelli et al., 2017), better effects in male AD patients (Davis and Barrett, 2009) and better effects in women AD patients (Scacchi et al., 2014)
Galantamine 2000	Weakly inhibits AChE and potentiates nicotinic and muscarinic receptors.	Benefits in global clinical function, behavioral symptoms, and activities of daily living.	Assessment of the impact of donepezil, rivastigmine and galantamine reported a more beneficial effect of cholinesterase inhibitors on cognition in males but the impact of the individual drugs was not reported (Wattmo et al., 2011).
Rivastigmine 1997	Reversible inhibitor of AChE and butyrylcholinesterase.	Dose-dependent effect on cognition, function, and activities of daily living.	Reduced cognitive decline in women AD patients treated (Scacchi et al., 2014). Delayed progression from MCI to AD in women (Ferris et al., 2009).
Tacrine	Reversible AChE inhibitor.	Largely replaced by other AChE inhibitors because of liver toxicity	Tacrine improved cognitive function to a greater extent in male, compared with female, e4 carriers (MacGowan et al., 1998).
Memantine 2002	NMDA antagonist (non-competitive, low- to medium-affinity). Also acts as an antagonist at 5HT3 and nicotinic (low-affinity) receptors.	Improves delusions, hallucinations, agitation, aggression, and irritability.	No published data on sex-related differences in efficacy. Women report difficulties with palatability (Ruiz et al., 2019).
Aducanumab June 2021	IgG1 monoclonal antibody against a conformational epitope on Aβ. Binds specifically to aggregated forms of Aβ. Recognizes Aβ plaques.	Approved by FDA (Accelerated approval pathway). Not approved by the European Medicines Agency, December 2021	Studies report benefit of aducanumab but sex differences have not been reported (Budd Haeberlein et al., 2022). An FDA report indicates no sex differences https://www.fda.gov/media/143577/download
Lecanemab July 2023	IgG1 monoclonal antibody. Binds with high affinity to Aβ soluble protofibrils.	Approved by FDA. Not yet approved by the European Medicines Agency.	Benefits of lecanemab were greater in men than women (van Dyck et al., 2023) or ineffective in women (Kurkinen, 2023).

recent studies assessed the effect of donepezil, rivastigmine and galantamine in a 3-year prospective study and reported that the decline in cognitive function, at least in the short term, was slower in cholinesterase inhibitor-treated individuals compared with controls and that efficacy was better in older persons and non ε4 carriers. Overall the response was better in males than females but data were not stratified and whether sex differences were observed for all 3 drugs is unclear (Wattmo et al., 2011).

Earlier investigations reported that donepezil-treated male AD patients performed better in the Boston Naming Test than females (Davis and Barrett, 2009), supporting earlier findings that reported greater efficacy of cholinesterase inhibitors in male AD patients (MacGowan et al., 1998). In contrast, others observed

that women AD patients responded better to donepezil and rivastigmine than men, exhibiting less marked cognitive decline (Scacchi et al., 2014), and that rivastigmine delayed progression from MCI to AD in females but not males (Ferris et al., 2009). These inconclusive findings are reflected in data from preclinical studies where donepezil preferentially improved cognitive function in male rhesus monkeys (Buccafusco et al., 2003) while rivastigmine antagonized scopolamine-induced spatial memory to a greater extent in female rats (Wang et al., 2000).

Variables that may contribute to a sex difference in response to these drugs include the influence of sex hormones and sex-related differences in the cholinergic system (Yoshida et al., 2000; Moen and Lee, 2021; Bennett et al., 2022). *APOE* genotype may also exert an impact. It was shown that female, but not male, ε2/ε3 carriers with mild-to-moderate AD responded better to tacrine than ε4 carriers (Farlow et al., 1998) and that tacrine improved cognitive function in male ε4 carriers more than male non-carriers and female ε4 carriers (MacGowan et al., 1998), but others reported that while ε4 carriers responded better to tacrine, there was no impact of sex (Rigaud et al., 2000). The therapeutic response to donepezil may also be affected by *APOE* genotype with evidence suggesting that ε4 carriers respond better (Choi et al., 2008); the effect of sex was not reported in this study.

To my knowledge, sex-related differences in efficacy to memantine have not been studied although palability issues have been reported in women (Ruiz et al., 2019). Analysis in 3xTg mice revealed that 3 months treatment with memantine increased plasma concentration and decreased Aβ oligomers to a greater extent in females than males but improved cognition and decreased tau and Aβ plaques similarly in male and female mice (Martinez-Coria et al., 2010).

Monoclonal antibodies that target amyloid

Aducanumab, an Aβ-directed monoclonal antibody that binds to aggregated Aβ and recognizes amyloid plaques in brain, was the first immunotherapy that received US Food and Drug Administration (FDA) approval. Sex-related differences were not described in several published papers/commentaries that reported on the findings in the aducanumab trials ENGAGE or EMERGE (Knopman et al., 2021; Kuller and Lopez, 2021; Sabbagh and Cummings, 2021; Budd Haeberlein et al., 2022; Schneider, 2022; Rahman et al., 2023) even though policy suggests that appropriate recognition is given to this issue.

Lecanemab, which selectively binds to large soluble Aβ protofibrils, was approved in July 2023. Patients receiving lecanemab for 18 months showed a slower progression of disease, with reduced Aβ and better cognition compared with untreated patients (Swanson et al., 2021). The benefits were reported to be greater in men than women (van Dyck et al., 2023) reflecting data obtained in the Thy-Tau22-5xFAD (T5x) mouse model in which the decrease in soluble and insoluble Aβ was greater in brain tissue of male mice compared with females (Davtyan et al., 2019). The efficacy of lecanemab was greater, and the risk of amyloid-related imaging abnormalities (ARIA) was significantly reduced, in *APOE4* non-carriers compared with carriers. However, the data originally presented by van Dyck and colleagues in 2023 were recently reassessed and it was concluded that the impact of lecanemab was less than reported, and was ineffective in females (Kurkinen, 2023).

Is there evidence of sex-related differences in response to drugs in trial for AD?

In August 2023, 251 clinical trials related to AD and falling under the drug category (clinicaltrials.gov) are in progress or planned (ie described as Active not recruiting, Enrolling by invitation, Not yet recruiting and Recruiting). These include agents for image analysis which are not considered here.

Drugs that target neurotransmitter pathways

Agents designed to target different neurotransmitters include those acting on the cholinergic system (different formulations of the cholinesterase inhibitors donepezil and huperzine A, the cholinergic antagonist mecamylamine, choline alfoscerate that may increase brain ACh levels and the nicotine patch designed to directly activate nicotinic receptors), the NMDA receptor (memantine and other agents with antagonist action, SAGE-718, AVP-786, AXS-05, huperzine A, Chinese "Smart soup"), the β2-adrenergic receptor agonist CST-2032, and the sigma-2 receptor antagonist, CT1812.

Several agents are being investigated for their effectiveness in controlling AD-related agitation; these include agonists at cannabinoid receptors (cannabidiol, dronabinol and IGC-AD1), α2 adrenergic receptors (gabapentin) and D2 receptors (brexpiprazole), and NMDA receptor antagonists, AXS-05, AVP-786 and "Smart soup". Agonists and antagonists at different 5-HT receptors (masupirdine, a 5HT-6 receptor antagonist; piromelatine, a 5-HT-1A/1D receptor agonist as well as acting on melatonin MT1/2/3) and the selective serotonin reuptake inhibitor, escitalopram, are also in trial for treating agitation, while trazodone (agonist and antagonist activities at different 5HT receptors), is in trial for AD-related insomnia. Orexin receptor type 2 antagonists (Lemborexant, seltorexant and suvorexant) are also in trial for insomnia and KarXT (M1 receptor agonist) is in trial for the treatment of psychosis.

Clearly, sex-related differences in receptor density or receptor-related signaling opens the possibility that there may be differences in drug efficacy between males and females. Findings, mainly from preclinical studies, suggest that sex hormones influence expression and/or signaling of several receptors (Wilbert-Lampen et al., 2005; Kritzer and Creutz, 2008; Normandin et al., 2015; Bangasser et al., 2016), while sex-related differences in cholinergic activity (Giacobini and Pepeu, 2018) and NMDA receptor function (Wickens et al., 2018; Giacometti and Barker, 2020; Knouse et al., 2022) have been described. There are sex differences in gene expression in noradrenergic receptors (Mulvey et al., 2018) and in circuitry (Sun et al., 2020), and in 5HT transmission, concentration, metabolism and

receptor expression (Cosgrove et al., 2007; Sramek et al., 2016; Songtachalert et al., 2018). Analysis of serotonin synthesis by PET using α-[^{11}C]methyl-L-tryptophan as a tracer revealed that synthesis was 50% higher in the brains of males compared with females (Nishizawa et al., 1997). Sexual dimorphisms in dopamine receptor expression have also been reported (Williams et al., 2021) with recent metanalysis demonstrating greater binding of the selective D_2R antagonist [^{11}C]raclopride in putamen and caudate of females compared with males (Malén et al., 2022). Sex-related differences in the orexin system (Grafe and Bhatnagar, 2020), and cannabinoid receptors (Rubino and Parolaro, 2011; Normandin et al., 2015) and sigma receptors (Smith et al., 2018), have also been reported. It must be predicted that such differences are likely to significantly affect the efficacy of drugs that target these neurotransmitter receptors or pathways and provide a strong argument in favor of sex subgroup analysis and reporting in clinical trials.

Agents that target Aβ

Strategies designed to reduce Aβ remain at the heart of discovery in the context of AD. There are several ongoing clinical trials using antibodies that target specific epitopes of Aβ (Song et al., 2022) designed to reduce Aβ burden, including additional trials on the already-licensed aducanumab and lecanemab.

Donanemab, for which a decision from the FDA is expected in 2024, binds to the pyroglutamate-modified, N-terminal form of Aβ that is present in plaques. It retards progression of the disease and decreases Aβ plaques (Mintun et al., 2021; Reardon, 2023a) particularly in those with less tau pathology (Sims et al., 2023). Minimal attention has been paid to assessment of potential sex-related differences in the efficacy of donanemab although one paper suggested that sex did not impact on disease progression rates (Gueorguieva et al., 2023). As in the case of lecanemab, the risk of ARIA was greater in *APOE4* carriers compared with non-carriers.

Among others in trial are solanezumab, which targets the mid-domain of the Aβ peptide and recognizes soluble monomeric Aβ (Doody et al., 2014; Honig et al., 2018), crenezumab, which binds to stable oligomers and inhibits aggregation of Aβ (Ostrowitzki et al., 2022), ganteneumab, which binds to a conformational epitope on Aβ fibrils (Bateman et al., 2022). Data from a phase 2 trial with solanezumab suggested that there may be some sex differences in antibody distribution but this was not further investigated (Farlow et al., 2012). To my knowledge, there are no published data on sex-related differences in distribution, efficacy or pharmacodynamics on any other monoclonal antibody, except lecanemab (see above).

Targeting the N-terminal pyroglutamate Aβ epitope increases microglial-mediated phagocytosis of Aβ (Crehan et al., 2020) and therefore there are an increasing number of antibodies designed to exploit this including ABBV-916 and remternetug, which are currently in phase 2 and 3 trials respectively. Varoglutamstat (PQ912) also reduces production of pyroglutamate Aβ by inhibiting glutaminyl cyclase and is in phase 2 trials. In combination with a mouse pyroglutamate-3 Aβ antibody, it reduced Aβ accumulation and improved cognitive function, in APP/PS1 mice (Hoffmann et al., 2017). Targeting pyroglutamate-modified pE_3Aβ in the 5XFAD mouse model of AD reduced pyroglutamated and non-pyroglutamated Aβ plaques in male and female mice. Highlighting a sexual dimorphism, soluble Aβ was decreased only in male mice whereas insoluble Aβ was decreased only in female mice (Zagorski et al., 2023). Of course, there is no guarantee that the sex differences identified in mice will translate into humans, but the fact that there are indications of sex-related responses to lecanemab and solanezumab presents a forceful argument for stratification by sex in all clinical trials.

Other approaches to interfere with Aβ accumulation are being investigated, including small molecules designed to prevent oligomer formation, or to block the impact of these oligomers. For instance, ALZ-801, described as anti-oligomer and as an aggregation inhibitor, is currently in phase 2 trials, as is CT1812, a sigma-2 receptor allosteric antagonist, designed to inhibit binding of Aβ oligomers to oligomer receptors thereby reducing Aβ-induced synaptic toxicity. Autoradiographic analysis has shown sex-related differences in sigma 2 receptors binding and suggested that a reduction in receptors is associated specifically with Aβ pathology specifically in female APP/PS1 mice (Sahlholm et al., 2015).

Buntanetap reduces Aβ by inhibiting APP synthesis (Fang et al., 2023) and is currently in phase 2 trials. It improved cognition in APP/PS1 mice and improved synaptic function (Teich et al., 2018) but only female mice were investigated. To date, trials targeting γ-secretase have been unsuccessful (Yiannopoulou et al., 2019) but newer agents have shown some promise (Rynearson et al., 2021). Many trials on BACE1 inhibitors have also been unsuccessful but new classes of drugs that modulate BACE1 activity are in development (Monteiro et al., 2023). It is worth noting that sex differences in γ-secretase and BACE1 have been reported in mice, Increased activity of γ-secretase and increased expression of nicastrin and presenilin have been reported in tissue from 24 month-old female mice (Placanica et al., 2009), while estrogen downregulates BACE1 transcription (Cui et al., 2022). It is also interesting that circulating BACE1 concentrations were significantly higher in a cohort of females compared with males that were at risk of AD (Vergallo et al., 2019).

Agents that target Tau

Agents in clinical trials aimed at modulating tau are mainly monoclonal antibodies and inhibitors of tau aggregation. Monoclonal antibodies that are currently in trial include Lu AF87908, which recognizes phosphorylated tau (p-tau) protein, APNmAb005, which recognizes a conformational epitope in tau oligomers and JNJ-63733657 and E2814 which recognize the microtubule binding region of tau. The epitope to which E2814 binds, plays a role in seeding and propogation, and is a predominant component of tau tangles (Roberts et al., 2020). Tau-targeting antisense oligonucleotides, NIO752 and BIIB080, that inhibit translation of tau mRNA into the tau protein, and drugs designed to inhibit tau aggregation/self-association LY3372689, TRx0237 and OLX-07010 are also in clinical trial as is nicotinamide riboside, which has been shown to decrease tau phosphorylation (Hou et al., 2018), attenuate cognitive deterioration and improve synaptic plasticity in mouse models of AD (Gong et al., 2013; Hou et al., 2018).

To my knowledge, there are no published reports of sex-related differences in responses to such agents although it

is well documented that there are marked differences in tau accumulation in males and females, with greater tau accumulation in brains of female AD patients compared with males (Oveisgharan et al., 2018). A recent study designed to assess tau propagation using regional [^{18}F]flortaucipir PET analysis suggested a more widespread increase of tau in female MCI patients compared with males (Shokouhi et al., 2020) and it was shown that naturally-occurring tau antibodies were lower in CSF from female AD patients compared with males (Krestova et al., 2018). Even in cognitively-intact elderly individuals, the age-related increase in p-tau in postmortem brain tissue is enhanced to a greater extent in women than men (Hu et al., 2021). Tau has been coupled with sex-specific genetic variants in men and women that are linked with enhanced risk of AD. SNPs within *DNAJA2*, *FERMT2*, and *TYW5* were associated with tau in women whereas SNPs within *CR1* were associated with Tau in men (Wang X. et al., 2022).

In the absence of clinical data, the findings of preclinical studies that identified sexual dimorphism related to tau are worthy of note. The recombinant protein/tau vaccine AV-1980R, which induces antibodies that inhibit tau aggregation, decreased soluble p-tau in the brains of male and female T5x double transgenic mice but its effect on insoluble p-tau was confined to male mice (Davtyan et al., 2019).

Drugs to modulate immunity/inflammation

The burgeoning volume of data that implicates perturbation in the immune system and microglial function has triggered a search for agents that modulate both in the hope of altering the course of AD. GWAS has identified polymorphisms in several genes that code for proteins involved in immune function and endow significant risk of AD. One is TREM2 (Guerreiro et al., 2013; Jonsson et al., 2013), which is expressed on microglia and is essential for the clustering of microglia around amyloid plaques (Jay et al., 2017; Lewcock et al., 2020). There is evidence that TREM2 is protective (Zhao et al., 2017; Brown and St George-Hyslop, 2021) as is soluble TREM2, which binds Aβ, prevents its oligomerization and improves cognition in a mouse model of AD (Zhong et al., 2019; Sheng et al., 2021). Consistently, knocking out TREM2 resulted in greater plaque burden; this effect was greater in female mice compared with males (Meilandt et al., 2020). APOE genotype, as well as sex, affects the TREM2-mediated interaction between plaques and microglia. Microglial-plaque interaction correlated with TREM2 expression and was approximately 5 times higher in 5xFAD/APOE3$^{+/+}$ male, compared with female, mice and markedly reduced in 5xFAD/APOE4$^{+/+}$ female mice (Stephen et al., 2019).

Clinical trials on AL002, an antibody targeting TREM2, are ongoing and a second antibody, DNL919, has been placed on clinical hold while further assessment of its safety/toxicity is investigated. These trials make no specific reference to analysis of sex-related differences though this is clearly relevant given the available preclinical data.

Other drugs in clinical trials that are designed to modulate microglia include sodium oligomannate (GV-971), mastinib and the CSF1R antagonist JNJ-40346527. Another CSF1R antagonist, PLX3397, has been assessed in a clinical trial but the EU Clinical Trials Register reports that the trial was ended prematurely. However because its action is similar to that of JNJ-40346527, it is relevant to consider the data which indicate that PLX3397 exerts sex-dependent effects. It depleted microglia to a greater extent in female, compared with male, rats (Sharon et al., 2022) and, in Tg2541 mice, it decreased tau, and extended the life span of female, but not male mice (Johnson et al., 2023). It was further shown that plasma and brain PLX3397 levels were increased to a greater extent in male, compared with female, mice indicating that sex impacts on PLX3397 pharmacokinetics. This suggests that PLX3397 treatment should be tailored to sex to ensure benefit in males and females, in mice in the first instance.

Masitinib modulates microglia probably through inhibition of the M-CSF receptor kinase 1, although it also inhibits the tyrosine kinases c-kit, fyn and lyn, and PDGF and FGF receptors. Analysis in cancer patients has identified sex-related differences in pharmacokinetics and, in particular, slower elimination of tyrosine kinase inhibitors in females (Huang et al., 2022; Özdemir et al., 2022). Other inhibitors of tyrosine kinases that are also in clinical trial for the treatment of AD include dasatinib, a potent inhibitor of Abl and Src and the JAK inhibitor, baricitinib (Matsushita et al., 2023), although sex-related differences in the pharmacokinetics of these have not been reported.

Semaphorin 4D and galactin 3 redirect microglia toward an inflammatory phenotype (Smith et al., 2015; Tan et al., 2021) and are upregulated in AD (Tan et al., 2021; Evans et al., 2022); antibodies directed at both are currently in Phase 1 and/or 2 trials. There is some evidence of a sexual dimorphic effect of galactin 3 in mouse models of stroke (Mijailović et al., 2022). Daratumumab, a CD38 antibody is also being assessed as a potential disease-modifying strategy in AD since CD38 also modulates microglial activation and has been shown to enhance Aβ accumulation (Blacher et al., 2015).

Mutations in the gene encoding sortilin1 have been linked with increased risk of AD and an anti-sortilin 1 antibody, AL-001, is currently in clinical trials for AD. One mutation, SORL1 SNP 4 (rs661057), is associated with an increased risk of AD in women (Cellini et al., 2009).

Other agents in clinical trials designed to impact on microglia and reduce neuroinflammation include those that aim to reduce inflammatory cytokines, or the impact of these cytokines, like lenalidomide (Valera et al., 2015), L-serine (Ye et al., 2021) and XPro1595 (MacPherson et al., 2017) and, at least in the case of XPro1595, its modulatory effects on stress-induced inflammatory changes were shown to be sex-dependent (Eidson et al., 2019). The antiretroviral agent, lamivudine, which improves age-related cognitive function and modulates genes related to the Type 1 interferon response (Li et al., 2021), is currently in early phase trials and is known to exert sex-related effects (Anderson et al., 2003). The cannabinoids, SCI-100 and palmitoylethanolamide (Landucci et al., 2022), are also in clinical trial because of their reported anti-inflammatory action and, when assessed for the treatment of neuropathic pain, responses to palmitoylethanolamide were shown to be sex-dependent (Morera et al., 2015).

It is abundantly clear that microglial phenotype and function are markedly affected by sex with an ever-growing literature suggesting a disproportionate impact of microglial activation and inflammation in females in the context of AD (Kodama et al., 2020;

Casaletto et al., 2022; Lynch, 2022). This means that particular attention should be paid to sex when agents that affect their function are in clinical use and demands that clinical trials should be designed with specific emphasis placed on specifically assessing sex-related responses to drugs.

As indicated in the paragraphs above, a significant part of the work investigating the role of inflammation in AD has been derived from animal studies. While many of these suggest that inflammation drives amyloid accumulation, there are contradictory data, perhaps arising from differences between the different models of AD, as pointed out in a recent review (Xie et al., 2021). Furthermore, it is without doubt that amyloid contributes to inflammatory changes (Wang S. et al., 2022) and therefore further study is necessary to clarify the temporal relationship between inflammation and amyloid accumulation.

Studies using positron emission tomography (PET) have reported that microglial activation, as assessed by ^{11}C-PBR28, correlates with accumulation of amyloid (^{18}F-flutemetamol) more so in MCI, compared with tau (^{18}F-AV1451) where the correlation is stronger in established AD (Dani et al., 2018). This indicates that an important factor in consideration of treatments that target microglial activation/inflammation is timing, which was emphasized by others who reported a "biphasic trajectory of inflammation" where the correlation between inflammation and amyloid accumulation varied with the stage of disease (Ismail et al., 2020).

Drugs targeting oxidative stress

Oxidative stress is a feature of AD and homocysteine concentration, which is a marker for oxidative stress, was greater in men with AD compared with women (Tenkorang et al., 2018). This is significant because a number of agents that target oxidative stress are currently in trial for AD including n-3 fatty acids, DHA and EPA, the fatty acid synthase inhibitor, CMS121, the free radical scavenger, hydralazaine hydrochloride and Flos gossypii flavonoids. Sex-related differences in responses to n-3 fatty acids have been reported in mice with DHA reducing social isolation-induced anxiety and depressive-like behaviors in male mice but not in female mice (Davis et al., 2017). In human studies, a strong positive correlation between dietary n-3 fatty acids and cognition was observed in females but not males (Lassek and Gaulin, 2011) while dietary supplementation with n-3 fatty acids improved episodic memory in females but not males (Stonehouse et al., 2013). Hydralazine hydrochloride eexerts its antioxidative effects by activating the Nrf2 pathway and the evidence indicates that sex is a variable in Nrf2 activation. Specifically, dimethylfumarate (DMF), which increases Nrf2 activation, exerted an effect in microglia prepared from the cortex of female mice but not male mice (Mela et al., 2022).

Drugs targeting metabolism

Disruption of metabolic processes are well-described features of AD and these include glucose hypometabolism (Hammond et al., 2020; Hammond and Lin, 2022) and a shift from glucose to lipid metabolism (Demarest et al., 2020). A recent analysis revealed that brain metabolism decreased over a 2 year period in women with AD, as assessed by ^{18}F fluorodeoxyglucose-PET, and that this was correlated with circulating Aβ42:Aβ40. Further transcriptomic analysis identified that the number of differentially expressed genes, particularly those related to glucose metabolism, was 3 times greater in female, compared with male AD, patients (Park et al., 2023). Similar sex-specific differences have been reported in animal models of AD (Guillot-Sestier et al., 2021; Strefeler et al., 2023). Impaired mitochondrial function is also a recognized change in the brains of AD patients (Wang et al., 2020) and animal models of AD (Fang et al., 2019; Demarest et al., 2020) and the evidence indicates that mitochondrial metabolism is particularly compromised in female APP/PS1 mice (Demarest et al., 2020; O'Neill et al., 2022).

Unsurprisingly, a number of drugs that aim to restore metabolism are in development, and a few are in clinical trials including nicotinamide riboside and dapaglifozin, which are designed to improve mitochondrial function and reduce blood glucose by inhibiting the sodium-glucose co-transporter-2 (SGLT2). There is some evidence suggesting that SGLT2 may exert sex-specific effects (Rivera et al., 2023).

The medium chain triglyceride, tricaprilin, is also in clinical trial. It is ultimately metabolized to ketones which appear to exert beneficial effects in AD (Jensen et al., 2020) with evidence from preclinical studies indicating that ketone supplementation decreased β-hydroxybutyrate and increased blood glucose in older female rats and had the opposite effect in male rats, while body weight increased to a greater extent in males (Kovács et al., 2020). Interestingly, in TBI, the protective effect of β-hydroxybutyrate appears to be confined to males (Greco et al., 2020).

Type 2 diabetes confers a significant risk of developing AD and a recent study that analyzed data from 450,000 individuals determined that females with type 2 diabetes had a higher risk of developing AD than men with type 2 diabetes (Zhou et al., 2023). Significantly, the evidence suggests that type 2 diabetes is more prevalent in women than men (Ashraf et al., 2021). Type 2 diabetes and AD share similarities, particularly insulin resistance (Arnold et al., 2018). These similarities and the evidence from animal studies demonstrating that intranasal insulin improved cognition in APP/PS1 mice (Mao et al., 2016) and also in 3xTg AD mice, aged animals and Aβ-treated animals (Ohyagi et al., 2019), triggered an interest in assessing insulin as a potential therapy in AD. Intranasal insulin was reported to exert no significant effect on cognition in a recent study in which data from males and females were combined (Craft et al., 2020). However an earlier study reported sex-dependent effects in MCI and AD patients; improved cognitive function was observed in males but not females and the effect was greater in ApoE ε4-negative males, but not females (Claxton et al., 2013). Further studies are clearly required to gain clarity on effects and there are currently 2 trials in progress.

Other agents designed to improve insulin sensitivity and signaling are also in clinical trial, including semaglutide, a glucagon-like peptide-1 (GLP-1) agonist that enhances insulin signaling in the brain. A recent analysis of 3 large trials concluded that treatment of patients with type 2 diabetes with semaglutide or liraglutide reduced the incidence of dementia (Nørgaard et al., 2022). Although similar results were reported in males and females, sex-related differences in the effects of GLP-1 agonists have been observed; for example, weight loss, a greater decrease in glycated

hemoglobin and a greater improvement in β cell function were all recorded in females (Rentzeperi et al., 2022). GLP-1 agonists were also more effective in reducing cardiovascular events in females with type 2 diabetes compared with males (Raparelli et al., 2020).

Metformin is currently in trial as a potential disease modifying agent in AD. A study in the PDAPP (J9) mouse model (AβPP mice) of AD revealed that cognitive function improved in metformin-treated, compared with control-treated female AβPP mice whereas it deteriorated in males (DiTacchio et al., 2015). There are no reports on sex-related differences in response to metformin in AD patients as highlighted recently (Chaudhari et al., 2020).

Conclusion

Until relatively recently, recruitment for clinical trials did not give due consideration to the possible impact of sex on outcomes and reports often did not stratify findings by sex. In the context of AD, recruitment now commonly reflects the greater prevalence of the disease in women. However reporting of sex-specific responses to drugs remains an issue. Indeed a recent metanalysis found that only 7 studies out of the 56 assessed, specifically evaluated and reported on the impact of sex (Martinkova et al., 2021) although it has been observed that some data are publicly available on the US FDA website, Drugs@FDA (Schwartz and Weintraub, 2021).

In this review, drugs in clinical trial for AD have been grouped into those targeting neurotransmitters, Aβ, tau, immunity/inflammation, oxidative stress and metabolism. For each of these targets, there is reason to predict sex differences in responses to drugs, based on evidence mainly from preclinical analysis. However this speculation requires rigorous assessment and emphasizes the importance of evaluating sex as a variable. There is a strong argument favoring a move toward including analysis of changes by sex in all clinical trials and reporting the results of trials in a sex-stratified manner.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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