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REVIEW ARTICLE

Selective Estrogen Receptor Modulators (SERMs) as Sex-Specific Neuroprotective Therapies: A Comparative Review

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ABSTRACT: Alzheimer's disease (AD), a neurodegenerative disease that destroys memory, thinking, and reasoning skills, disproportionately affects postmenopausal women, highlighting a possible connection between estrogen loss and neuronal decline. While most studies have focused on estrogen-based therapies for women, recent research is exploring how selective estrogen receptor modulators (SERMs) could potentially offer neuroprotection in both sexes by mimicking estrogen's benefits on the brain. This review sought to explore the following: do male and female brains respond differently to SERMs in protecting against neurodegeneration? I hypothesize that SERMs might be a useful way to protect the brain from neurodegenerative diseases in both males and females, but many studies only focus on one sex or don't compare them; through synthesizing findings across multiple papers about both sexes, this paper aims to guide future research and potentially support the development of more inclusive and targeted SERM-based treatments. This review emphasizes that understanding the differences in how SERMs affect the male and female brain is integral to improving treatments against AD and possibly other neurodegenerative diseases.

KEYWORDS: Neuroscience, Neurodegenerative Diseases, Selective Estrogen Receptor Modulators (SERMs), Sex-Specific Neuroprotection, Estrogen Signaling.

Introduction

AD affects over 5 million people in the United States, with women making up nearly two-thirds of all affected individuals.[1] However, most pre-clinical studies rely primarily on male animal models, partially due to concerns that brain-synthesized estrogen in females can exert neuroprotective effects; this could alter experimental results in Alzheimer's models.[2] This inequity in research has hindered the effort toward establishing a treatment that considers the biological distinctions between the sexes, especially in the context of hormone-linked neurodegeneration. In this review, "sex" refers to biological characteristics, primarily chromosomal differences, as defined in most current pre-clinical studies. Intersex individuals, who have developmental sex differences, make up a significant yet often overlooked population. Their specific neurobiology is rarely examined in the existing literature, placing them outside the direct scope of this review; however, including them in future research will be essential for developing fully inclusive treatment strategies. This research gap is relevant for therapies that modulate estrogen receptors, like SERMs, because estrogenic signaling differs greatly between male and female brains.

Selective estrogen receptor modulators (SERMs), originally developed as a way to combat breast cancer and osteoporosis, are compounds that act as estrogen receptor agonists or antagonists in a tissue-specific manner. Clinically relevant SERMs include tamoxifen, an ER antagonist in breast tissue with partial agonist activity in the brain; raloxifene, which acts as an estrogen receptor agonist in bone and neural tissue; and genistein, a plant-derived phytoestrogen that exhibits SERM-like behavior. SERMs have recently drawn attention for their potential neuroprotective properties.[3] While estrogen replacement therapy (ERT) is capable of restoring cholinergic activity and neurotrophin expression, its risks are too grave and call for a safe alternative such as SERMs, which selectively target estrogen receptors in brain tissue. For example, a soy-based SERM could effectively decrease cognitive impairment and oxidative damage in an Alzheimer's mouse model.[4] Nevertheless, related studies among both males and females are still imbalanced.

This review examines the individual response of males and females to SERMs and their use as a neuroprotective agent in the management of various neurodegenerative diseases, as existing treatments of AD are expensive, symptomatic, and ineffective in slowing down the progression of the disease; thus, there is a need for a specific and affordable treatment such as SERMs.

For this literature review, I searched PubMed and ScienceDirect using terms such as "SERMs," "neuroprotection," "sex differences," and "neurodegeneration." I prioritized peer-reviewed studies that used experimental methods and included either male, female, or comparative sex-based data relevant to brain function. Articles were excluded if they lacked primary evidence on neural outcomes or didn't address SERM-related mechanisms. The studies I investigated used techniques such as *in vivo* electrophysiology to investigate synaptic plasticity, behavioral studies to assess memory, and molecular biology (like immunostaining and Western blotting) to investigate the health of the neurons. The studies were categorized based on the type of SERM, the area of the brain, and sex-specific effects to provide a clearer insight into the potential utility of SERMs as a potential treatment for neurodegenerative disorders in both sexes. Through synthesizing information from existing research and filling this knowledge gap, this review hopes to guide future research and promote more inclusive, effective therapeutic strategies.

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Discussion

Estrogen's Role in Neuroprotection and Alzheimer's Disease:

Estrogen protects neurons through multiple, interconnected mechanisms relevant to Alzheimer's disease (AD). This includes antioxidant activity that reduces oxidative stress, the buildup of harmful molecules called reactive oxygen species (ROS) that can damage DNA. Estrogen also promotes non-amyloidogenic processing of amyloid precursor protein (APP), a pathway in which APP is cleaved into harmless fragments rather than toxic amyloid-beta peptides that aggregate into plaques in the AD brain, thereby reducing amyloid-beta accumulation.[5,6]

Estrogen has gained traction recently as a protective factor in AD, especially because women, who experience a significant drop in estrogen levels after menopause, are disproportionately affected by the condition. While higher AD rates in women are often attributed to their longer average lifespans, research suggests that this drop in estrogen after menopause may play a more direct role in the development of neurodegenerative diseases.[6] The loss of estrogen, and with that its antioxidant properties, can partially explain this increased risk of disease; the hormone also regulates APP metabolism.[5,6] Both of these studies highlight two distinct but relevant neuroprotective mechanisms of estrogen: its ability to block oxidative stress and its ability to direct APP toward non-amyloidogenic pathways (where it is cut into harmless fragments as opposed to toxic ones). Understanding how estrogen works at these levels is extremely important to further develop and identify new treatment options, and explains why estrogen-mimicking drugs like SERMs have become more popular. Of these two neuroprotective effects, estrogen's antioxidant protection has been shown to work well in lab models, as it doesn't need to activate estrogen receptors to be effective.

Oxidative stress is a major contributor to neuronal damage in AD; estrogen has been shown to directly counteract this damage. 17-beta estradiol, the most active form of estrogen in the human body, and its non-receptor binding stereoisomer 17-alpha estradiol, help to prevent the buildup of intracellular peroxides in neurons exposed to hydrogen peroxide, glutamate, and amyloid-beta.[6] These findings were consistent across a variety of systems, from clonal hippocampal cells to primary cortical neurons, and occurred in the absence of estrogen receptors, suggesting that protection was receptor-independent.[6] This antioxidant effect was linked with a structural feature, the hydroxyl group at the C3 position on the A-ring of the steroid molecule, which allowed estrogen to directly neutralize harmful molecules called free radicals.[6] Only estrogens with this hydroxyl group were able to significantly improve cell survival, whereas modified estrogens like mestranol or testosterone showed no protective effects.[6] These results suggest that estrogen's antioxidant actions depend more on its molecular structure rather than standard hormone signaling; estrogen shows a uniquely promising future for usage as a therapeutic compound for protecting neurons from oxidative damage in AD.

Alongside its antioxidant role, estrogen also changes the processing of APP, a central molecule in AD pathology, by promoting non-amyloidogenic alpha-secretase pathways. Treatment with normal and healthy concentrations of 17-beta estradiol led to a 1.75-fold increase in the release of soluble APP (sAPP), a neuroprotective cleavage product that can't form amyloid beta.[5] This adjustment occurred without an increase in overall intracellular APP levels, suggesting that estrogen stimulates the cutting of existing APP molecules rather than increasing their production. Estrogen also protects the brain in two ways: by guiding APP down a safer path that avoids the formation of harmful cleavage.[5] Through reducing oxidative stress and steering APP away from toxic cleavage, estrogen offers double protection against AD progression. Together, these mechanisms strongly support the investigation of estrogen-mimicking drugs like SERMs as potential AD therapies.

Both neuroprotective mechanisms provide a compelling case for further researching estrogen-related therapies in AD.[5,6] Given the ability of these mechanisms to occur without estrogen receptor activation, compounds capable of mimicking estrogen's structure or selectively targeting estrogen receptors within the brain could offer the same benefits without the risks of hormone therapy. The existence of SERMs, which regulate estrogen receptors in a tissue-selective way, may thus represent a promising approach within the study of AD treatment. Yet, many critical questions still have to be answered, amongst which are the understanding of these mechanisms' differences between sexes and hormonal conditions, the similar relevance of both neuroprotective mechanisms within the aging brain, and the capacity of estrogen-related therapeutic strategies to provide long-term neuroprotection.

Hormonal Changes and the Therapeutic Potential of SERMs in Both Sexes:

As humans begin to age, their hormone levels decline drastically, altering neuroprotective signaling in both sexes, ultimately increasing vulnerability to neurodegenerative diseases like AD. In women, menopause causes an abrupt decline in circulating estrogen. This loss is associated with impaired cholinergic function, reduced neurotrophin expression, and increased neuronal vulnerability.[7] Similarly, in men, aging comes with a gradual decline in testosterone levels. Because testosterone is converted to estradiol through aromatase in neural tissues, reduced testosterone availability leads to decreased estrogenic signaling in the brain. A loss of estradiol, playing an essential role in neuroprotection, impacts synaptic plasticity, mitochondrial health, and inflammatory regulation.[8] While estrogen therapy can restore some of these protective functions, its systemic effects and risks limit long-term use. SERMs show lots of promise as an alternative treatment, as they are able to selectively activate estrogen receptor pathways in brain tissue without stimulating estrogen-sensitive tissues in the breast or uterus.[8]

The transition to menopause in women causes a lasting drop in ovarian steroid production, resulting in a prolonged estrogen-deprived state for up to a quarter of a woman's life.[7] This decline compromises basal forebrain cholinergic neurons, as seen by reduced high-affinity choline uptake and decreased

acetyltransferase (ChAT) activity in the frontal cortex and hippocampus, as demonstrated in ovariectomized rat models.[7] ERT helped to prevent these deficits, preserving both cholinergic function and neurotrophin expression, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which promote neuron survival and synaptic plasticity.[7] Because NGF and BDNF are produced by neurons and glia in brain regions containing estrogen receptors, the restoration of their expressions as a result of ERT suggests that estrogen affects these cell types.[7] That being said, standard ERT carries many risks, including increased chances of certain types of cancer, limiting clinical utility, and further underscoring the importance and need for alternatives that retain neuroprotective efficacy without harmful side effects. SERMs can engage estrogen's protective pathways specifically within the brain, while avoiding harmful effects in other tissues.

While men don't experience as drastic a hormonal shift as menopause, gradual declines in testosterone with aging can indirectly reduce estrogenic neuroprotection. Testosterone is converted to estradiol through aromatase in neural tissue, where it aids synaptic plasticity, modulates neuroinflammatory responses, and enhances mitochondrial function.[8] Reduced androgen and estrogen signaling in men may therefore contribute to oxidative stress and impaired neuronal repair mechanisms, increasing susceptibility to AD pathology.[8]

Despite being different kinds of hormone decline, both males and females suffer from similar issues: increased susceptibility and reduced levels of neuroprotective hormones within an aging brain. This similarity underlines why SERMs could be an excellent treatment approach for both sexes. Unlike systemic ERT, SERMs such as raloxifene and tamoxifen derivatives act as estrogen receptor agonists in the brain while functioning as antagonists in estrogen-sensitive peripheral tissues.[8] Through targeting estrogen receptor beta and alpha with neurons and glia, SERMs can activate neuroprotective pathways, like enhancing antioxidant defenses, regulating synaptic plasticity proteins, and preserving cholinergic function, without the oncogenic risks of standard estrogen therapy. SERMs' receptor-selective nature means that they could benefit both sexes. Preclinical studies suggest that SERMs can improve cognitive outcomes, reduce oxidative stress, and maintain neurotrophin signaling.[7,8] However, sex-specific responses to SERMs remain underexplored; this gap in knowledge emphasizes the need for comparative studies assessing SERM efficacy across male and female models of neurodegeneration.

Sex Differences in Estrogen Signaling and SERM Effects on Brain Function:

Differences in male and female brain functions, such as brain estrogen synthesis, receptor distribution, and hormone signaling, may shape how SERMs protect against AD. While sex-specific pathways are well documented, most current SERM research still doesn't directly compare male and female responses, resulting in a gap in understanding SERMs' true potential.

Estrogen can be produced in the brain through the action of aromatase enzymes within neurons and glial cells; within the brain, estrogen has roles related to memory and neuronal survival.[9] Certain tissues are able to produce their own estrogen on site, without relying on estrogen traveling through the bloodstream; this is critical in postmenopausal women when their hormone levels drop, because their tissues can still maintain estrogen activity locally.[9] In brain regions vulnerable to AD, like the hippocampus and amygdala, men and women have different aromatase activity, receptor distribution, and downstream estrogen signaling.[9] Additionally, since these regions are key to the aspects of memory and the regulation of emotions, these sex differences may directly influence the susceptibility to neurodegeneration as well as the responsiveness to estrogen therapies. These differences suggest that drugs targeting estrogen pathways, like SERMs, may not have the same effect in men and women.

Genistein, a soy-derived SERM, has been shown to cross the blood-brain barrier, reduce amyloid-beta toxicity,[10] lower tau phosphorylation in AD models,[11,12] and protect cholinergic neurons.[13] These protective effects overlap with ER pathways in the hippocampus, suggesting that differences in receptor distribution can influence how strongly genistein acts in different brains. While these results are extremely promising, data on whether these effects are consistent in males and females is unknown.

To understand how SERMs might differently affect male and female brains, it is important to acknowledge sex differences in estrogen synthesis and receptor distribution. Women with AD show significantly lower levels of brain aromatase activity compared to cognitively healthy women, suggesting that local estrogen synthesis deficits, not just lower estrogen levels, could contribute to higher disease vulnerability.[9] Estrogen receptor (ER) alpha and beta expression also varies between males and females, with females tending to show greater ER beta density in hippocampal CA1 neurons, whereas males show greater levels of ER alpha in certain amygdalar regions. These patterns influence the activation of pathways regulating synaptic plasticity, oxidative stress responses, and mitochondrial stability. Lowered local estrogen synthesis and sex specific receptor distributions could not only influence standard vulnerability to neurodegeneration, but also how effectively individuals would respond to a SERM therapy. Given that SERMs target ER alpha and ER beta, these sex linked differences could alter drug efficacy at both molecular and functional levels.

Hyperphosphorylated tau is a distinguishing pathological feature in AD, and estrogen is able to help regulate tau; it models key kinase pathways.[2] Genistein is able to counteract tau phosphorylation through suppression of CAMKII/CaMKIV and GSK-3beta (types of kinases) activity, essentially supporting synaptic plasticity.[14,15] It also combats oxidative stress, typically suppressed by estrogen, through enhancing mitochondrial antioxidant enzymes like MnSOD and through preserving ATP synthesis.[4] Because the efficiency of mitochondria decreases with age in both sexes, but appears more prone to estrogen loss in women, these antioxidant and mitochondrial-protective actions of SERMs could result in greater benefits for postmenopausal women.

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Male and female brains have many differences in estrogen synthesis and receptor distribution; these factors are likely to shape how SERMs like genistein engage neuroprotective pathways.[9] Genistein has been shown to balance amyloid and tau pathology, enhance mitochondrial function, and improve cognition in an AD model.[4] However, this data does not affect the outcome when it comes to sex analysis. The existing gap between known inequities concerning the existence of sex differences and the lack of relevant data concerning SERMs is a gap that needs to be filled. In an effort to fill the gap, research studies with sex as a controlled variable will offer an opportunity for improvement concerning SERM treatments based on sex differences. If this and related gaps persist, there is a risk of developing therapies that produce uneven and potentially ineffective outcomes across individuals.

Conclusion

This review has investigated and explored the neuroprotective potential of SERMs in AD, emphasizing the critical but frequently overlooked sex differences in estrogen signaling, brain estrogen synthesis, and receptor distribution. Estrogen's antioxidant effects and its role in regulating APP processing help to develop the foundation for SERMs' promise as a safer, targeted therapy for both males and females. Although substantial evidence from preclinical studies demonstrates the multi-pathway neuroprotective activity of SERMs such as genistein, most investigations fail to directly compare outcomes between males and females.[4]

Despite the promising results obtained, a significant amount of evidence discussed stems from animal and *in vitro* studies. While these studies are invaluable in shedding light upon the fundamental mechanisms at work in neurodegenerative disorders, they do not necessarily reflect the complexities of human neurodegeneration. Differences in hormone dynamics, brain aging, and disease progression between AD models and humans serve as a reminder of the care that must be exercised when translating these findings to patient populations.

Local estrogen production deficits and sex specific receptor profiles could influence disease vulnerability and the ability to respond to a therapy.[9] This highlights the need to factor sex as a variable in future research. This imbalance that exists between the complexity of sex differences and the way clinical trials of SERM drugs are conducted is still potentially contributing to the development of drugs that aren't equally effective in men and women. This review seeks to provide a basis through which SERMs may be tailored according to the unique neurobiological profile of each sex.

In order to address this gap, future experiments and clinical trials should be sure to compare male and female responses to SERMs, specifically examining hormone fluctuations, receptor engagement, and downstream neuroprotective outcomes. Future studies could also benefit from sex-specific molecular imaging, longitudinal hormone profiling, and multi-omics analyses to further understand nuanced mechanisms in sex-dependent drug efficacy.

Building on this information, I propose the development of a new personalized treatment strategy using SERMs that is tailored to individuals' ER profiles and hormone levels. This treatment approach would use imaging and biomarker analysis to identify the use of ER-alpha or ER-beta preferring SERMs, or the addition of treatments that increase local estrogen production through the use of aromatase inhibitors or modulators. This personalized therapeutic procedure is expected to maximize neuroprotection while avoiding adverse effects. This treatment is expected to enable the patient to retain enhanced mental and quality-of-life benefits.

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References

1. Thies, W.; Bleiler, L. 2013 Alzheimer's Disease Facts and Figures. *Alzheimer's & Dementia* **2013**, *9* (2), 208–245. https://doi.org/10.1016/j.jalz.2013.02.003.2
2. Li, R.; Cui, J.; Shen, Y. Brain Sex Matters: Estrogen in Cognition and Alzheimer's Disease. *Molecular and Cellular Endocrinology* **2014**, *389* (1-2), 13–21. https://doi.org/10.1016/j.mce.2013.12.018.
3. Arnott, J.; Martinkovich, S.; Planey, S. L.; Shah, D. Selective Estrogen Receptor Modulators: Tissue Specificity and Clinical Utility. *Clinical Interventions in Aging* **2014**, 1437. https://doi.org/10.2147/cia.s66690.
4. Duan, X.; Li, Y.; Xu, F.; Ding, H. Study on the Neuroprotective Effects of Genistein on Alzheimer's Disease. *Brain and Behavior* **2021**, *11* (5), e02100. https://doi.org/10.1002/brb3.2100.
5. Jaffe, A. B.; Toran-Allerand, C. D.; Greengard, P.; Gandy, S. E. Estrogen Regulates Metabolism of Alzheimer Amyloid Beta Precursor Protein. *The Journal of Biological Chemistry* **1994**, *269* (18), 13065–13068.
6. Behl, C.; Skutella, T.; Lezoualc'h, F.; Post, A.; Widmann, M.; Newton, C. J.; Holsboer, F. Neuroprotection against Oxidative Stress by Estrogens: Structure-Activity Relationship. *Molecular pharmacology* **1997**, *51* (4), 535–541.
7. Simpkins, J. W.; Singh, M.; Bishop, J. The Potential Role for Estrogen Replacement Therapy in the Treatment of the Cognitive Decline and Neurodegeneration Associated with Alzheimer's Disease. *Neurobiology of Aging* **1994**, *15* (Suppl. 2), 195–197. https://doi.org/10.1016/0197-4580(94)90205-4.
8. Arevalo, M. A.; Santos-Galindo, M.; Lagunas, N.; Azcoitia, I.; Garcia-Segura, L. M. Selective Estrogen Receptor Modulators as Brain Therapeutic Agents. *Journal of Molecular Endocrinology* **2010**, *46* (1), R1–R9. https://doi.org/10.1677/jme-10-0122.
9. Li, R.; He, P.; Cui, J.; Staufenbiel, M.; Harada, N.; Shen, Y. Brain Endogenous Estrogen Levels Determine Responses to Estrogen Replacement Therapy via Regulation of BACE1 and NEP in Female Alzheimer's Transgenic Mice. *Molecular Neurobiology* **2012**, *47* (3), 857–867. https://doi.org/10.1007/s12035-012-8377-3.
10. Youn, K.; Park, J.-H.; Lee, S.; Lee, S.; Lee, J.; Yun, E.-Y.; Jeong, W.-S.; Jun, M. BACE1 Inhibition by Genistein: Biological Evaluation, Kinetic Analysis, and Molecular Docking Simulation. *Journal of Medicinal Food* **2018**, *21* (4), 416–420. https://doi.org/10.1089/jmf.2017.4068.

11. Park, Y.-J.; Jang, Y.; Kwon, Y. H. Protective Effect of Isoflavones against Homocysteine-Mediated Neuronal Degeneration in SH-SY5Y Cells. *Amino Acids* **2010**, *39* (3), 785–794. https://doi.org/10.1007/s00726-010-0523-5.
12. Park, Y.-J.; Ko, J.; Jeon, S.; Kwon, Y. Protective Effect of Genistein against Neuronal Degeneration in ApoE−/− Mice Fed a High-Fat Diet. *Nutrients* **2016**, *8* (11), 692. https://doi.org/10.3390/nu8110692.
13. Jhamandas, J. H.; Cho, C.; Jassar, B.; Harris, K.; MacTavish, D.; Easaw, J. Cellular Mechanisms for Amyloid β-Protein Activation of Rat Cholinergic Basal Forebrain Neurons. *Journal of Neurophysiology* **2001**, *86* (3), 1312–1320. https://doi.org/10.1152/jn.2001.86.3.1312.
14. Ye, S.; Wang, T.-T.; Cai, B.; Wang, Y.; Li, J.; Zhan, J.-X.; Shen, G.-M. Genistein Protects Hippocampal Neurons against Injury by Regulating Calcium/Calmodulin Dependent Protein Kinase IV Protein Levels in Alzheimer's Disease Model Rats. *Neural Regeneration Research* **2017**, *12* (9), 1479–1484. https://doi.org/10.4103/1673-5374.215260.
15. Xi, Y.-D.; Zhang, D.-D.; Ding, J.; Yu, H.-L.; Yuan, L.-H.; Ma, W.-W.; Han, J.; Xiao, R. Genistein Inhibits Aβ25–35-Induced Synaptic Toxicity and Regulates CaMKII/CREB Pathway in SH-SY5Y Cells. *Cellular and Molecular Neurobiology* **2016**, *36* (7), 1151–1159. https://doi.org/10.1007/s10571-015-0311-6.

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