Role of Female Sex Steroid Hormones in Progression of Alzheimer's Disease: Results of Clinical Studies - A Narrative review

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Alzheimer's disease (AD) is the most common type of dementia, and it is caused by the abnormal build-up of proteins around brain cells. AD involves parts of the brain that control memory, thought and language leading to a great variety of symptoms ranging from mild forgetfulness to loss of the ability to carry on a conversation. All of the above significantly decreases the standard of living. This paper analyses articles concerning the effects of estrogen on the progression of Alzheimer's disease, gaps and contradictions in current studies and possible future directions. To answer these questions, PubMed database was searched, and two rounds of screening were conducted to identify articles that meet the inclusion criteria. Afterwards, the following data from each paper was extracted: title; author; year of publication; journal; academic field; citations and references; conclusions and gaps in research. Later, this data was used to make a comparison table to sum up the main findings of each paper. Even though there are several risk factors that might have contributed to sex difference in AD, such as deviation in brain structure and genetic background, clinical studies have been mainly focused on estrogens and their connection to AD. It has been proved that estrogen decreases the formation of amyloid-β plaques that are considered to be a major biomarker of AD by regulating APP processing. Moreover, clinical studies have shown that estrogen regulates synaptic plasticity and prevents neuronal Tau hyperphosphorylation. These findings suggest that due to estrogen's neuroprotective effects, it may become a potential cure for AD, since it already shows positive results in numerous clinical trials. However, inconclusive results of some studies slow down the use of estrogen in treating AD, since more long-term clinical trials are needed to identify correct dosage, time period and combination of hormones that will effectively relieve AD symptoms.

Keywords: Alzheimer's disease; estrogen; hormone therapy; dementia; female hormones; amyloids.

Introduction

According to the World Health Organization, more than 55 million people worldwide currently suffer from dementia. With it being the seventh leading cause of death, millions of dollars are spent on treatments, research and patients' care annually. Even though there are over one hundred causes of dementia[1], including well-known Parkinson's disease and less recognisable Corticobasal syndrome, Alzheimer's disease (AD) remains the most common cause of dementia, contributing to 60-70% of all cases[2].

Alzheimer's disease is thought to be caused by a build-up of amyloid proteins, deposits of which form plaques around brain cells[3]. Moreover, according to the NHS, the plaques decrease levels of chemical messengers called neurotransmitters being released, disrupting the signals between brain cells. One of the main neurotransmitters affected is acetylcholine (ACh). It is made from an acetyl group found in sugar molecule glucose and the nutrient choline which is present in different foods such as egg yolks, liver and legumes[4]. Britannica defines acetylcholine as playing a huge role in the autonomic nervous system, a branch of peripheral nervous system and regulates contraction of smooth muscles, dilation of blood vessels and heart rate[5].

The most likely early sign of Alzheimer's disease is forgetfulness. This symptom is a consequence of destroyed neurons in part of the brain responsible for memory, specifically the entorhinal cortex and hippocampus. According to the National Institute of Aging, this disease affects areas in the cerebral cortex involved in language, reasoning and social behavior, causing more severe symptoms such as dysphagia (difficulty eating and swallowing)[6] and loss of speech[7]. All of the above negatively affects the standard of living by causing disability and dependency among older people.

Nowadays, even with a growing body of literature concerning Alzheimer's disease, extensive research and clinical trials, there is still no cure for this type of dementia[8]. Even though there are a number of successful studies and approved drugs that relieve AD symptoms, the efficacy of these treatments is debatable in the clinical setting. However, there are some group therapies, like an art class or gardening, that improve cognitive functions (memory and problem-solving skills), therefore slowing down the progression of this disease. Several medicines may also

be prescribed to help with the symptoms. Acetylcholinesterase (AChE) inhibitors including donepezil, galantamine and rivastigmine work by increasing levels of acetylcholine, while memantine decreases effects of a chemical called glutamate which is associated with the progression of dementia[9]. Unfortunately, these drugs do not relieve symptoms in every patient, so finding a cure for Alzheimer's disease remains one of the most important goals in modern medicine.

Recent evidence suggests that women are more likely to develop Alzheimer's disease than men[10]. Results of a study carried out in Sweden with 16,926 participants show that incidence rates of Alzheimer's disease were greater in women than men around the age of 80[11]. Moreover, a meta-analysis examining the incidence of Alzheimer's disease in Europe proved the hypothesis with the following results: thirteen women compared to seven men out of 1000 developed Alzheimer's disease[12]. These results lead to further research concerning the impact of female sex steroid hormones on Alzheimer's disease.

One of the main objectives of this paper are the effects of hormone therapy on mechanisms involved in the development of AD such as plaque formation. It is hypothesized that female sex steroid hormones may not only contribute to AD, but also be a part of possible treatment due to their neuroprotective effects.

A number of studies have reported that hormone therapy (HT) in postmenopausal women, in particular estrogen treatment (ET), decreases the risk for developing Alzheimer's disease[13]. Though there is a certain age period during which the results of this treatment are optimal, a significant number of clinical trials indicates a reduced risk for AD incidence. However, findings from the Women's Health Initiative Memory Study (WHIMS) contradict these promising results.

This paper is a systematic review that analyzes how estrogen affects Alzheimer's disease. Firstly, the results of the research are presented which compose of several sub-components: overview of AD in both genders; sex differences in the progression of AD; risk factors that might have contributed to sex differences in AD; how estrogen, sex steroid hormone, affects AD; analogue of estrogen, genistein, role in AD and estrogen's treatment effect for AD. Then, methodology of the review is presented describing all the steps taken in order to complete the review. This paper plays a significant role, since it summarizes current knowledge regarding the potential mechanism of estrogen's protective effect for AD. At the same time, some gaps in research are pointed out to guide future directions of further research.

The aim of this paper is to summarize current knowledge about female hormone estrogen and its effects on the nervous system, to describe how low estrogen levels due to menopause may contribute to AD, and to discuss further implications of hormone therapy as AD treatment.

Results

In this review, PubMed database was searched, and 120 articles were identified. None of them had duplicates or were marked as ineligible; therefore, zero records were removed before screening. During the first round of screening (title and abstract) 39 records were excluded, and during the second round of screening (whole text) 45 records were excluded. The remaining 36 articles were sorted, and data was summarized in the data extraction table. Data extraction table included abstract summary, authors, publication journal, years of publication, abstract, study type, number of participants, organism (humans, stem cells, different mice models), main findings and outcomes measured. This data allowed better comparison of articles that were further categorized into five main groups: studies with mice with positive outcomes; studies with mice with negative outcomes; studies with humans with positive outcomes; studies with humans with negative outcomes; studies with controversial outcomes. Majority of the studies were conducted with mice and rats, and only a few of them included humans, especially menopausal/postmenopausal women. Finally, 18 studies were included in the review.

Overview of AD in both genders

Alzheimer's disease is the most common form of dementia which is characterized by the deterioration of cognitive functions such as memory, learning and language. It can be classified into two main categories, sporadic (late onset) and familial (early onset). Familial AD accounts for less than 1% of all AD cases and results in the dysfunction of the amyloid precursor protein (APP) caused by genetic mutations[14], while sporadic AD accounts for the vast majority of AD cases ($> 70\%$). Age is the largest risk factor for late onset AD, however there are some additional risk factors including cardiovascular diseases, smoking and type two diabetes that contribute to higher AD incidence. The prevalence of AD for people over age of 65 is around 10%, and increases with aging, reaching 32% for the age of 85[15]. It is estimated that 6.7 million Americans age 65 and older have AD, and this number can increase up to 13.8 million by 2060[16].

There are many different ways to diagnose AD including medical history, mental status tests, diagnostic tests, brain imaging, physical and neurological exams. However, two major biomarkers of AD that are very common are senile plaques made out of amyloid-β (Aβ) aggregates and neurofibrillary tangles (NFTs) of hyperphosphorylated tau which deposit in the brain[17]. Neurofibrillary tangles are formed from many tau molecules which stick together resulting in poor communications between neurons. Aβ peptides are formed from a breakdown of a larger amyloid precursor protein (APP) and their accumulation is considered to induce a series of events including inflammation,

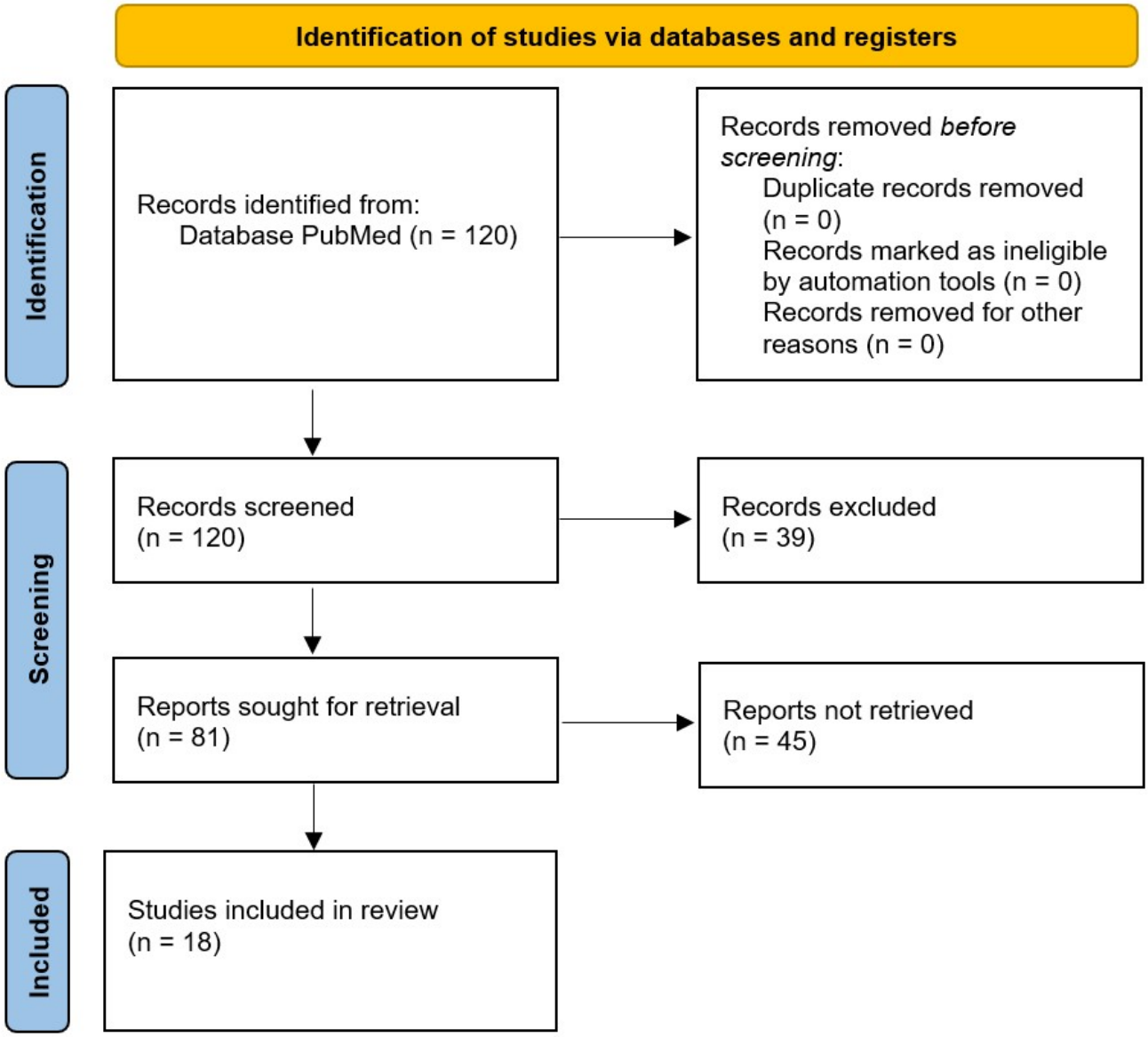

Fig. 1 Flow Chart

neurodegeneration and oxidative damage[18].

Sex differences in the progression of AD

Molecular cytogenetic analysis showed that somatically acquired X chromosome aneuploidy (chromosomal anomaly) may contribute to brain aging and neurodegenerative processes. Furthermore, premature centromere division (PCD) which is associated with increased aneuploidy, is correlated with AD. It has been shown that average frequency of PCD of patients with AD is approximately three times higher than that of control subjects[19].

Evidence suggests that frequency of AD in women is a lot higher than in men; almost two thirds of all AD patients are female[20]. Earlier, this was explained only by the fact that women live longer than men on average of 4.5 years, and older age is the greatest risk factor for AD[21]. Nowadays, theories suggest that sex can influence AD in a number of different social and biological ways that are further discussed in the next section.

However, there is some discrepancy in the results of studies carried out in different countries. For example, in the United States, studies often report that AD incidence does not differ by sex, even after the age of 85 years, while studies in several European countries report that women have a higher incidence of AD dementia after the age of 80[22]. The reasons for these discrepancies are not well understood, but they may depend on the time period and genetic predisposition according to geographical region.

Risk factors that might have contributed to sex differences in AD

Risk factors of developing AD can be divided into two sections: biological risk factors and social risk factors.

Biological factors: Sexual dimorphism can be explained by following differences: deviation in brain structure, genetic background and sex hormones. Specifically, men tend to have larger brain volume so they are less sensitive to pathological agents for AD and suffer lower structural loss compared to women[23]. Moreover, during the transition time before menopause, levels of female sex steroid hormones (estrogen and progesterone) significantly decrease. This drop has been associated with higher AD incidence in women leading to many preclinical and clinical studies about estrogen and its connection to AD. Finally, approximately 70% of the risk of developing AD can be contributed to genetics[23]. It has been proven that women are more vulnerable to risks associated with the apolipoprotein E (APOE4) gene, one of the most significant risk factors for AD[24]. Around 25% of people carry one copy of APOE4 gene and approximately 3% carry two copies, although inheriting APOE4 does not necessarily mean that a person will develop AD[25].

Social factors: Investigations carried out using data from Framingham Heart Study suggested that lower risk of dementia in men can be explained by 'survival bias'. Additionally, women usually have lower education and lower income which can lead to physiological risk factors like depression and various sleep disorders[26]. Undoubtedly, more studies with large sample size are needed to prove these correlations.

How estrogen, sex steroid hormone, affects AD

Over the past few years, sex steroid hormones have been associated with the progression of AD, and the age-related depletion of estrogens in women is also viewed as a potential risk factor for AD development. Estrogen is a hormone produced by the ovaries and it is primarily known for its role in the achievement of sexual maturation and fertility[27]. However, a significant amount of estrogen, especially 17β-estradiol (E2) is synthesized in the brain. During menopause, which usually occurs at the age of 50 to 52, women suffer a reduction in estrogen synthesis that decreases estrogen production. This estrogen deficiency has been associated with cognitive decline – one of the main characteristics of AD[28].

Observational and clinical studies have shown that estrogen has neuroprotective effects. For instance, estrogen can rapidly activate the extracellular signal-regulated kinases (ERK) which act as an information superhighway, and phosphoinositol-3-kinase (PI3K)-Akt pathways in cortical and hippocampal cells that regulate cell growth[29]. Moreover, estrogen regulates synaptic plasticity, promotes neural survival, and mediates sex-specific behaviors[30], but there are some risks associated with the use of estrogen. It is proven that estrogen has carcinogenic and proliferative effect (increases the division of cancer cells) on non-neuronal (mammary gland and endometrial) cells[31].

Estradiol is found in circulation and it is able to cross the blood-brain barrier (BBB) which protects the brain from toxic substances found in blood. After crossing the BBB estradiol uses estrogen receptors to alter genetic transcription and act on neurons. This signaling results in the regulation of APP processing[32].

The APP is the precursor of Aβ, which forms the central core of senile plaques, and it is cleaved by enzymatic activity; α-secretase cuts the Aβ peptide and yields a large fragment of the soluble non-amyloidogenic APP (sAPP), that does not form senile plaques, β-secretase cuts the Aβ peptide, generating an amyloidogenic fragment which is processed by a third enzyme - γ-secretase. γ-secretase cuts the APP and produces a soluble Aβ[33].

Furthermore, not only estradiol affects the production of Aβ peptide by blocking the APP, it also prevents neural Tau hyperphosphorylation, which along with Aβ induces oxidative stress and disrupts Ca2+ homeostasis resulting in neurodegeneration[34].

However, there are studies with controversial findings. In

some animal models estradiol failed to protect brain cells from death. It is possible that after certain degree of injury estradiol fails to attenuate cell death[35].

Analogue of estrogen, Genistein, role in AD

Background: Genistein (Gen) is a phytoestrogen that belongs to a class of compounds known as isoflavones, which have similar structure as estrogen. It is an active molecule in soybean and it is consumed by humans via soy products[36].

Mechanism: Genistein is used as a medicine to treat women's diseases, and it has been shown in in vivo studies that Gen has neuroprotective effects, it decreases amyloid β-protein toxicity and improves brain function[37]. Genistein inhibits BACE1 enzyme and, therefore, reduces Aβ production[38]. Moreover, in AD model rats Gen decreased the hyperphosphorylation of tau protein by regulating CAMK4 (a protein coding gene)[39].

Applications: One recent double-blind, placebo-controlled, bicentric clinical trial examined the effect of daily oral supplementation of genistein for 12 months on Alzheimer's disease patients. Due to mechanisms by which genistein acts such as lowering inflammation and Aβ deposition, all nine parameters measured in this study showed a tendency of improvement after treatment with genistein when compered with placebo. However, owing to certain limitations associated with this study like small sample size and low duration, further clinical trials are necessary to prove that Gen is a potential candidate to become an estrogen substitute in AD treatment[40].

Estrogen's treatment effect for AD: All of the risks associated with estrogen depletion due to menopause lead to a great number of studies investigating the effects of hormone therapy on the progression of AD. A number of studies were successful, while some of them resulted in inconclusive data and others suggested the adverse effects on cognitive functions.

- **Studies with mice:** There are two types of studies that can be conducted in order to prove the importance of sex steroid hormones in AD: injecting mice with estrogen or performing OVX in order to stop estrogen production and induce artificial menopause transition.

  For example, in one of the studies female hemizygous APP/PS1 mice (sample size not specified) were bilaterally ovariectomized (OVX) at the age of 4 months. A pellet containing 0.18 mg of E2 was implanted at the following three time points: immediately after OVX, 2 months after OVX (6-month-old), or 4 months after OVX. At the end of each period of E2 treatment, specimens were collected and behavioral tests were carried out. Ovariectomy-induced depletion of estradiol in APP/PS1 mice resulted in elevated Aβ levels, and worsened memory performance[41].

  Moreover, in one of the more recent studies female 5xFAD mice (10 mice, 4 to 5 weeks of age) and female C57BL/6 mice (5 mice, 5 weeks of age) were injected with estrogen at the age of 11 weeks, and after 6 more weeks the mice were made to perform the Barnes Maze test to assess the spatial learning and memory of the AD mice. The results suggested that estrogen alleviated neurotoxicity in the brain and protected neurons in AD models. It was concluded that estrogen has potential as a treatment agent for AD[42].

  Authors of both studies declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

- **Studies with humans:** After discovering correlation between estrogen and AD, a great number of preclinical and clinical studies were conducted, most of them addressing menopause transition and menopause treatments.

  During 3-year longitudinal brain imaging study participants at the age of 40-60 with clinical, laboratory, neuropsychological, and brain imaging were examined. All subjects received MRI, PiB- and FDG-PET scans at baseline and at least 2 years later following standardized protocols. Results showed that older age and APOE4 status are associated with higher rates of Aβ deposition. Moreover, postmenopausal women exhibited the highest rate of hippocampal volume loss and higher rates of Aβ deposition than males[43]. Due to relatively small sample size, it was impossible to test for interactions between groups and APOE4 genotype.

  Another study analyzed plasma biomarkers of Aβ pathway, tau pathophysiology and neuronal loss. Women with a history of hysterectomy or in women with a levonorgestrel-releasing intrauterine system, natural oral or transdermal estrogen was prescribed. All other women were prescribed a combination of estrogen and natural progesterone, since it protects the endometrium and does not interfere with the beneficial effects of estrogen. Statistical analyses were conducted on the 224 participants 67 of whom were genotyped as carriers of at least one APOE ε4 allele. Results showed that Menopause hormone therapy (MHT) may reduce the risk of developing late-life cognitive decline due to Alzheimer's disease (AD)[44]. Women at genetic risk of AD seem to be particularly benefiting from MHT, since they have smaller reduction of Aβ1-42 than APOE ε4-negative treated women.

  However, the Cache Country Study that examined the history of former HRT use among 1889 women (mean age, 74.5 years) did not show such promising results. Even though women who used HRT had a reduced risk of AD compared with non-HRT users, there was no effect with current HRT use unless duration of treatment exceeded 10 years[45].

Moreover, one very recent nationwide, nested case-control study was conducted to assess the association between use of MHT and development of dementia according to type of hormone treatment, duration of use, and age at usage. 5589 incident cases of dementia and 55890 age matched controls were identified from a population of all Danish women aged 50-60 years with no history of dementia or contraindications for use of menopausal hormone therapy. Combined estrogen and progestin treatment were used, duration of treatment was estimated using a medicinMacro program. Estrogen-progestin treatment was given in one combined drug formulation or as two drugs, one with estrogen and one with progestin. The dosage was regulated up or down according to the symptoms of the women. Compared with people who had never used treatment, people who had received estrogen-progestin therapy had an increased rate of all cause dementia even in women who received treatment at the age of 55 years or younger[46].

Despite the promising positive cognitive effects estrogen therapy has displayed in laboratory studies, this has yet to be strongly replicated in human studies.

Discussion

This paper reviewed the role of female sex steroid hormones in the progression of Alzheimer's disease. Due to a significantly higher AD incidence rate in women (it was stated in U.S. and most European reports that two-thirds of clinically diagnosed cases of dementia and AD are women)[47], many sex-specific biological and gender-specific sociocultural factors have been studied in order to identify the reason for these results. A strong relationship between sex steroids hormones and their role in progression of AD has been reported in literature. Evidence suggests that AD pathogenesis is regulated by estrogen and progesterone in females, and that age-related decline in sex hormones significantly contributes to AD risk[48].

This research was aimed to determine the effects of estrogen on the brain function, role of menopause in AD progression and whether clinical studies with HRT and estrogen treatments have consistent positive results that would indicate a potential finding of AD cure. It was discovered that a significant amount of estradiol is synthesized in the brain and that it blocks APP, affecting the Aβ peptide production, therefore, decreasing the formation of senile plaques[49].

A number of studies investigating estrogen depletion due to menopause and possible AD treatments were successful. It was recently discovered that MHT may reduce the risk of developing late-life cognitive decline due to Alzheimer's disease[50], and that estrogen alleviated neurotoxicity in the brain and protected neurons in AD models[51].

Surprisingly, only a few studies resulted in inconclusive data. In the Cache Country Study, it was concluded that there is no effect with current HRT use unless duration of treatment exceeded 10 years[52]. Moreover, findings from the Women's Health Initiative Memory Study (WHIMS) suggested the adverse effects of HT on cognitive functions. WHIMS was a multicenter, randomized, double-blind, placebo-controlled clinical trial with two groups of women. One involving 4532 postmenopausal women who received continuous combined estrogen (conjugated equine estrogens [CEE] plus medroxyprogesterone acetate) or placebo, and the other involving 2947 hysterectomized women randomized to continuous unopposed CEE or placebo. All participants were age 65 years or older. It was discovered that CEE with or without medroxyprogesterone acetate, given to women age 65 years and older, not only did not protect against dementia or cognitive decline, but also increased the risk of dementia[53].

Unfortunately, there is no definite explanation for such contradicting results; however, one of the main theories is the wrong time period for HRT. It was found that women reporting the use of HT in mid-life (but not late-life) had a 26% reduced risk of a dementia diagnosis, while women using HT only in late-life had a 48% elevated risk compared to women not using HT at either time point[54].

Now, that the protective effects of estrogen on the brain, as well as some dangerous side effects of HT are well-known, it would be worth exploring possible treatment implementations, especially among a higher risk population, in order to see if the benefit of the treatment would outweigh potential risks.

Data from many human and mice studies, including treatment methodology was considered and included in this review. The paper has a high-level accuracy due to two reviewers on every step of the process. However, there were some limitations; only published papers have been assessed, and no primary studies were conducted on this topic.

Methods

***Review question*:** Why women are more likely to develop Alzheimer's disease than men? What are the effects of estrogen on the brain and on the progression of AD? Which clinical studies have been carried out concerning hormone therapy and dementia? What are the knowledge gaps in the impact of female sex steroid hormones on Alzheimer's disease?

***Types of participants*:** This review does not have any exclusion criteria. However, it is likely that most of the participants will be menopausal women (age 45-49) and postmenopausal women (age 50-80).

***Context*:** The context in this review includes all countries where clinical studies have been conducted.

***Source of evidence* :** In this review, PubMed database was searched for articles written in 2018-2023 time period. Grey

literature in WHO, NHS and Harvard databases were also covered. To perform citation chaining, key articles containing most relevant information have been identified. Afterwards, citation chaining was conducted in order to identify other appropriate articles.

***Keywords and PubMed search strategy for literature on Alzheimer's disease and estrogen therapy*:** ("Alzheimer's disease"[MeSH Terms] OR "Alzheimer's disease"[All Fields] OR "dementia"[MeSH Terms] OR "dementia"[Title/Abstract] OR ("Alzheimer's disease"[Title/Abstract] AND 2020:2023[pdat])) AND ("estrogen"[MeSH Terms] OR "estrogen"[All Fields] OR "estrogen"[tw] OR "hormone therapy"[MeSH Terms] OR "hormone therapy"[All Fields] OR "HT"[MeSH Terms] OR "HT" [Most Recent] OR "progesterone"[MeSH] OR "progesterone"[Title/Abstract]) AND ("amyloid"[MeSH Terms] OR "amyloid"[mh:noexp] OR "amyloid"[tw]) AND ("female"[MeSH] OR "female"[Title/ Abstract])

Two rounds of screening have been conducted to identify articles that meet the inclusion criteria. During the first pass titles and abstracts were examined to remove obviously irrelevant material. During the second pass the whole text was examined for compliance with the eligibility criteria.

***Extracting the results* :** There was no need in translation of articles written in foreign-language, so the use of Google Translator was not required. In order to achieve the goal of the paper, the following data was extracted: title; author; year of publication; journal; academic field; citations and references; conclusion and gaps in research.

***Ethics* :** This research does not pose any risks to human subjects. It is based on published papers and literature review so there is no need for ethics approval.

Conclusion

AD is the most common type of dementia that affects the lives of tens of millions of people every year. It is thought to be caused by a build-up of amyloid proteins, deposits of which form plaques around brain cells and it results in a variety of symptoms ranging from mild forgetfulness to loss of speech. AD incidence in women is a lot higher than in men, which is explained by the estrogen depletion due to menopause. A great number of studies with successful results concerning HRT as AD treatment are carried out; however, causation of AD has not yet been proved. More long-term studies with high sample size are essential in order to identify optimal time period (midlife or late-life), methodology including duration and active element (estrogen alone, combination of estrogen and progestin, genistein or 17β-estradiol) and any side effects of hormone replacement therapy that can be used as AD treatment in the future. Thus far, estrogen therapy prescribed alone, only for preventing AD, appears to be most beneficial for women under 65 years.

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