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Review

Hormone replacement therapy and Alzheimer's disease in older women: A systematic review of literature

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The relationships between estrogen and cognitive functions have been explored in many experimental and observational studies with rather inconsistent outcomes. This study explored the relationship between hormone replacement therapy (estrogen-based) and Alzheimer's disease in postmenopausal women based on existing literature. A comprehensive search was conducted for relevant articles written in English language from 1990. PubMed, Medline search, Science direct and SCOPUS databases with keywords such as: 'Alzheimer's disease', 'hormone replacement therapy', 'pathogenesis of AD', 'epidemiology of AD in older women', 'biological role of oestrogen in neuroprotection', 'menopause and hormonal changes', and 'effects of HRT on cognitive functioning' were used for the search. The search strategy was based on Cochrane review recommendations and the relative risk was used to indicate the degree of relationship. A total of 898 citations were initially identified, of which 15 met the inclusion criteria for this study. Ten of the fifteen articles revealed that Estrogen Replacement Therapy (ERT) has a protective effect against Alzheimer's Disease (AD) in postmenopausal women with relative risks ranging from 0.28 - 0.95 (95% C.I. = 0.08 - 0.99), while the remaining five studies showed increased risk of AD in postmenopausal women exposed to ERT with relative risks ranging from 1.10 to 2.10 (95% C.I. = 0.60 - 3.50). Conclusively, longstanding commencement of HRT prior to the onset of menopause might be protective against the development of Alzheimer's disease on empirical basis, but does not seem to have any therapeutic value after the onset of the disease.

Key words: Alzheimer's disease, hormone replacement therapy, oestrogen and neuroprotection.

INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease characterized clinically by insidious onset of memory and cognitive

impairment, emergence of psychiatric symptoms and behavioural disorder, and impairment of activities of daily living (Honq-Qi et al., 2012).

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Apart from the deterioration of memory, Alzheimer's disease is also characterized by histopathological changes which include extracellular deposits of amyloid- β (A- β) peptides forming senile plaques, and the intracellular neurofibrillary tangles (NFT) of hyperphosphorylated tau in the brain which are commonly regarded as hallmarks of the disease (Dong et al., 2012).

Globally, it accounts for about 50 to 60% of all dementia cases (Janicki and Schupf, 2010). There are over 46 million people currently living with dementia worldwide and 58% of this figure reside in the low and middle income countries of world, and the number is estimated to increase to over 131.5 million people by 2050 (Baiyewu, 2003; Hall et al., 2009; World Alzheimer Report, 2015). With increasing life expectancy globally, the number of people of living with the disease will astronomically increase, since advanced age is one of the most consistent and important risk factors.

It is a disease of the aged with increased risk among postmenopausal women than their male counterparts (Plassman et al., 2007; Jamshed et al., 2014). Outcomes of various studies revealed that women are disproportionately affected and carry a significantly higher risk than men (Craig and Murphy, 2009; Hebert et al., 2013; Mielke et al., 2014; Gabelli and Codemo, 2015; Alzheimer's Association, 2016). Though longevity has been adduced as one of the reasons, the significantly higher risk of developing Alzheimer's disease in postmenopausal women exceeds the risk accounted for by their greater life expectancy (Andersen et al., 1999).

Thus, menopausal oestrogen withdrawal might be the most tenable explanation for the increased prevalence of Alzheimer's disease among women (Molsa et al., 1982; Epperson et al., 2013; Henderson et al., 2016). A meta-analysis of 7 sex-specific studies of the incidence rates of Alzheimer's disease concluded that AD is 1.5 times more likely to develop in women than men (Gao et al., 1998).

More recent studies by Hebert et al. (2013), Mielke et al. (2014), Jamshed et al. (2014), Gabelli and Codemo (2015) and Henderson et al. (2016) all confirmed that Alzheimer's disease is 1.5 times to twice commoner in postmenopausal women than men. Decreased oestrogen level might, therefore, be a risk factor for AD in postmenopausal women (Paganini-Hill and Henderson, 1994; Fillit and Luine, 1985; Fillit, 2002).

To further buttress the role of oestrogen, postmenopausal women with AD tend to have lower levels of endogenous estrogen when compared to their counterparts without it (Jamshed et al., 2014). The positive cognitive effects of oestrogen are achieved in interrelated fashion via:

(1) Enhancement of the cholinergic system by stimulating Choline Acetyltransferase (ChAT) activity thereby increasing the synthesis of Acetylcholine and by raising the concentration of hypothalamic nicotinic Ach receptors (Morley et al., 1983; Luine, 1985; Toran-Allerand et al.,

1992),

(2) Neuroprotection against excitotoxins and has antioxidant effects which protects the neurones from oxidative stress and free radical damage (Behl et al., 1995; Goodman et al., 1996; McEwen, 1999; Grodstein, 2017).

(3) Influencing the glutamate system, a second neurotransmitter involved in learning and memory, via the expression of proteins of the NMDA receptors that are involved in glutamate activation and the enhancement of long-term potentiation (Gazzaley et al., 1996; Grodstein, 2017).

(4) Promotion of the non-amyloidogenic metabolism of the amyloid precursor protein through increasing the activity of amyloid- β degrading enzymes (ADE) by enhanced activity of Neprilysin (NEP-1 and NEP-2) enzymes (Jaffe et al., 1994; Xiao et al., 2009; Liang et al., 2010; Yoon and Jo, 2012)

(5) Increasing cerebral glucose transportation and regional blood flow which are all decreased in AD (Bishop and Simpkins, 1985; Ohkura et al., 1995; Resnick et al., 1998; Maki and Resnick, 2000).

The currently available treatments namely; the acetylcholinesterase inhibitors and the N-Methyl-D-Aspartate antagonists exert minimal impacts on the disease as they only decelerate the progression of the disease while only providing symptomatic relieve without definitive cure (Wenk et al., 2006; De Felice et al., 2007; Olivares et al., 2012; Mehta et al., 2012; Bond et al., 2012; Colovic et al., 2013; Lakhan et al., 2013; Zemek et al., 2014; Hogan, 2014; Bishara et al., 2015).

Despite the demonstrable neuroprotective and neurotrophic effects of estrogen, the outcomes of hormone replacement therapy (HRT), using either oestrogen alone or in combination with progesterone, were equivocal. The three largest clinical trials to date on the effect of HRT on memory and cognition among older women; the Women's Health Initiative Memory Study (WHIMS), the Cache County study and the Kronos Early Estrogen Prevention Study (KEEPS), though with some methodological differences, revealed variable outcomes (Zandi et al., 2002; Maki and Henderson, 2012; Gleason et al., 2015).

There is a very large body of literature on this important subject matter particularly at the turn of this millennium. There is also the compelling need to seek for other modalities of treatment for Alzheimer's disease apart from the currently available ones. This study, therefore, attempts to explore the relationship between Alzheimer's disease and hormone replacement therapy in older women based on available and accessible recent literature.

METHODOLOGY

Search strategy

A comprehensive search was conducted for relevant articles

published from 1990, with the final date of the search being 17th April, 2017. This period was chosen in order to cover at least three decades of research and to notice any variation therein. Databases searched were PubMed, MEDLINE, Science Direct and Scopus and other Cochrane Library Databases. The search terms used were 'hormone replacement therapy', 'Alzheimer's disease', 'epidemiology of Alzheimer's disease in older women', 'effects of hormone replacement therapy on cognitive functioning', 'menopause and hormonal changes' and 'hormone replacement therapy and incidence of Alzheimer's disease'. The reference lists of identified papers were also searched for further reference source articles. The search strategy was based on Cochrane review recommendations (Higgins and Green, 2011).

Inclusion and exclusion criteria

For any study to be considered for this study, it must meet the following eligibility criteria:

- (1) Must be a case-control or cohort study
- (2) Must have reported an association between hormone replacement therapy and Alzheimer's disease in the form of relative risk; and
- (3) Must have been published in English Language or if published in other language(s), must English translation.

The exclusion criteria were:

- (1) Unclear methodology
- (2) Studies with small sample size; and
- (3) Studies without cognitive endpoints.

Data extraction

The first two investigators, AWI and OAS, independently searched and selected relevant literatures based on the search terms. The third investigator, IAM, extracted the data while disagreements were jointly discussed with the fourth investigator, BKM, who served as an arbiter. The extracted data included; the first author, the year of publication, the study type, and the association between Alzheimer's disease and hormone therapy as indicated by the relative risk (RR). For the purpose of interpreting the associations, relative risk of >1 indicates increased risk, while, relative risk of <1 confers protection against Alzheimer's disease with estrogen replacement therapy.

Ethical approval

This article is a systematic review of the effects of hormone replacement therapy on Alzheimer's Dementia, therefore, Ethics committee approval was not required.

RESULTS

Figure 1 summarises the search process conducted. Electronic literature searches originally identified a total of 898 citations comprising of: PubMed (n=217), Medline (n=258), Science Direct (n=92) and, Scopus (n= 331). After accounting for duplicates, a total of 196 papers were excluded while 702 remained. Additional 679 citations were rejected when their titles and abstracts were reviewed and found not to be relevant to the index

study. Some of the reasons for the rejection included: referring to other forms of hormone therapy such as testosterone and growth hormone therapy, treatment for postmenopausal osteoporosis or cancer chemotherapy. The full texts of the remaining 23 publications were examined and 8 articles were further excluded. The reasons for their exclusion were: lack of cognitive endpoints (n= 5) and, unclear methodology (n=3). Finally, fifteen (15) articles met the inclusion criteria and were included in this study.

Summary of study outcomes

Table 1 summarises the key findings of the included studies; the association between hormone replacement therapy and the risk for developing Alzheimer's disease, the relative risks, the type of study and the references. Ten of the studies were conducted in United States and 5 from Europe. The European ones included studies from the United Kingdom, Finland, Italy and the Netherlands. It must be observed that no study from Africa or Asia met the criteria for inclusion of this research.

DISCUSSION

Hormone replacement therapy and Alzheimer's disease in postmenopausal women

This study attempts to look at the association between hormone replacement therapy and Alzheimer's disease in postmenopausal women. Based on the outcomes of the various studies explored, hormone replacement therapy could either serve as a protective factor or could increase the risk of Alzheimer's disease in postmenopausal women. The associations from the two perspectives are discussed below:

Protective association between HRT and Alzheimer's disease

The epidemiologic trials that revealed the protective effects of hormone replacement therapy against Alzheimer's disease included those of Tang et al. (1996), Paganini-Hill and Henderson (1996), Kawas et al. (1997), Baldereschi et al. (1998), Waring et al. (1999), Slioter et al. (1999), Zandi et al. (2002), Henderson et al. (2005), Shao et al. (2012), Imtiaz et al. (2017a) and Imtiaz et al. (2017b).

In all the trials, the relative risks of developing Alzheimer's disease in the study participants subjected to hormone replacement therapy were less than one (<1) which indicated protective effects (these findings are presented in Table 1). Despite the several methodological issues raised with respect to the selection of the

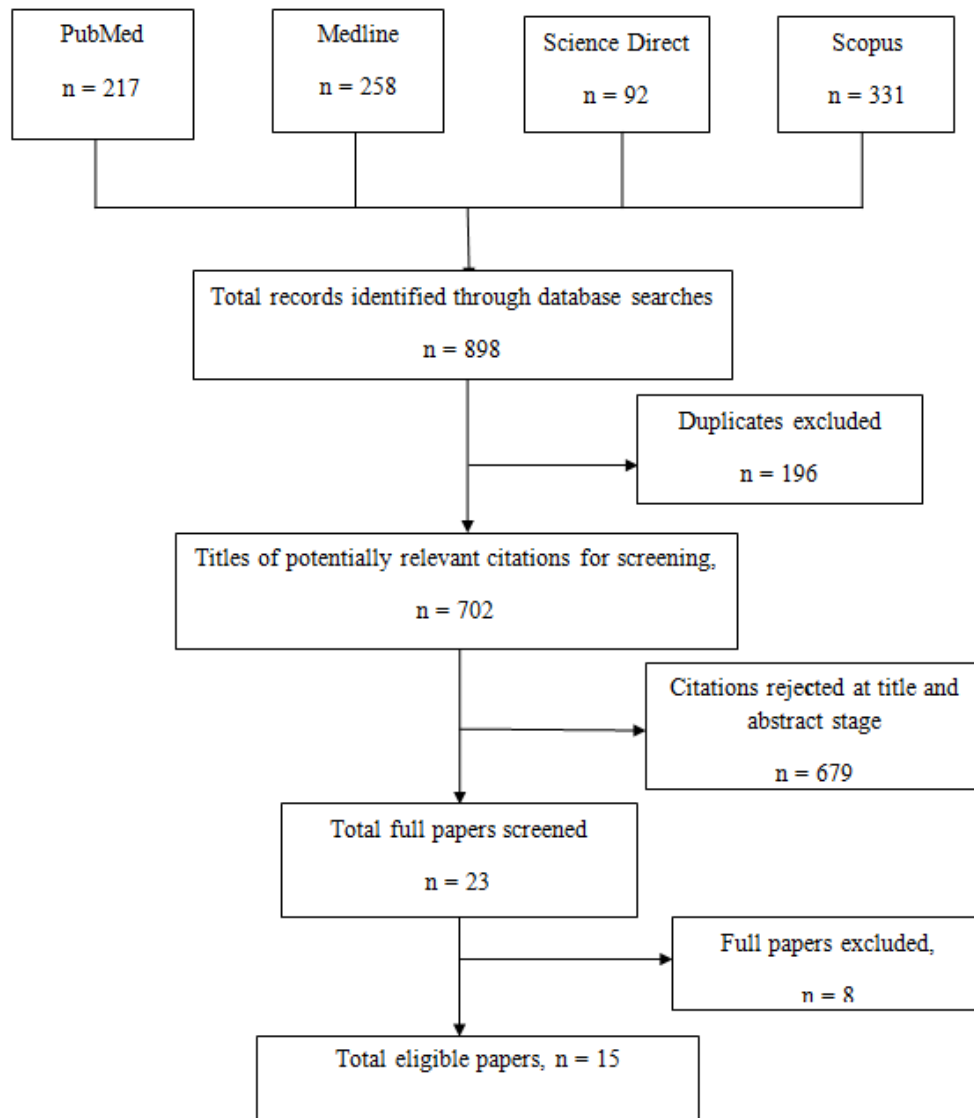


Figure 1. Study selection flow chart.

participants, the timing of the estrogen therapy, as well as the dosage and the formulation of the hormone(s) used in the studies cited, the common denominator amongst them is that the protective effects of estrogen against cognitive deterioration seems to be more pronounced when initiated in the early phase of menopause or at the early stages of the disease.

The Cache County Study, for instance, that examined the relationship between HRT and AD in postmenopausal women revealed that women who used HRT had a reduced risk of AD compared with non-HRT users (adjusted HR, 0.59; 95% CI, 0.36 - 0.96) (Zandi, 2002). The risk also varied with the duration of use, so that a woman's sex-specific increase in risk disappeared entirely with more than ten years of treatment. Adjusted

HRs were 0.41 (95% CI, 0.17 to 0.86) for HRT users compared with non-users and 0.77 (95% CI, 0.31 to 1.67) compared with men. Almost all of the HRT-related reduction in incidence reflected former use of HRT (adjusted HR, 0.33; 95% CI, 0.15 to 0.65). There was no effect with current hormone replacement therapy (adjusted HR, 1.08; 95% CI, 0.59 to 1.91) unless duration of treatment exceeded 10 years (adjusted HR, 0.55; 95% CI, 0.21 to 1.23). The study, therefore, concluded that prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current use unless such use has exceeded 10 years (Zandi et al., 2002).

Similarly, more recent studies by Imtiaz et al., 2017a,b in both the Kuopio Province prospective cohort study and the MEDALZ nested case-control study of the entire

Table 1. Relationship between hormone replacement therapy and Alzheimer's disease.

Association	Study	Relative risk (95% C.I.)	References
Protective	Baltimore longitudinal study	0.46 (95% C.I. = 0.21 - 1.00)	Kawas et al. (1997)
	Northern Manhattan Cohort, NY	0.50 (95% C.I. = 0.25 - 0.90)	Tang et al. (1996)
	Italian longitudinal study	0.28 (95% C.I. = 0.08 - 0.98)	Baldereschi et al. (1998)
	Leisure world retirement	0.65 (95% C.I. = 0.49 - 0.88)	Paganinini-Hill and Henderson (1996)
	Muti-Institutional research on Alzheimer's disease	0.70 (95% C.I. = 0.51 - 0.95)	Henderson et al. (2005)
	Cache county study	0.59 (95% C.I. = 0.36 - 0.96)	Zandi et al. (2002)
	Rochester population-based	0.42 (95% C.I. = 0.18 - 0.96)	Waring et al. (1999)
	Rotterdam population-based	0.34 (95% C.I. = 0.12 - 0.94)	Slooter et al. (1999)
	Kuopio prospective cohort	0.53 (95% C.I. = 0.31 - 0.91)	Imtiaz et al. (2017a)
	MEDALZ-finnish nationwide case-control	0.91 (95% C.I. = 0.84 - 0.99)	Imtiaz et al. (2017b)
Increased Risk	Cache county (New)	0.80 (95% C.I. = 0.60 - 1.10)	Shao et al. (2012)
	Seattle group health population-based	1.10 (95% C.I. = 0.60 - 1.80)	Brenner et al. (1994)
	Rochester, MN	1.10 (95% C.I. = 0.60 - 1.90)	Roberts et al. (2006)
	United Kingdom	1.20 (95% C.I. = 0.60 - 2.40)	Seshadri et al. (2001)
	Women's Health Initiative memory study (WHIMS)		
	Estrogen-Progesterone Trial	2.1 (95% C.I. = 1.20 - 3.50)	Schumaker et al. (2003)
	Estrogen Alone	1.5 (95% C.I. = 0.80 - 2.70)	Schumaker et al. (2004)

Finnish population with clinically verified AD from 2005 to 2011, both studies showed that long term use of estrogen was protective against AD. Other studies such as the Baltimore Longitudinal study (Kawas et al., 1997), Rochester population-based (Waring et al., 1999), Rotterdam population-based (Slooter et al., 1999), and the Multi-Institutional Research on Alzheimer's disease (Henderson et al., 2005) all revealed the protective effects of estrogen in AD after adjusting for other covariates such as age and educational status. This 'estrogen effect' could be attributed to Cholinergic mechanisms and other neuroprotective effects (Henderson, 1997).

To further buttress on the protective role of hormone replacement therapy in Alzheimer's disease, after an extensive literature review, Fillit, 2002, concluded that the role of hormone (oestrogen) replacement therapy seems to be confined to primary rather than secondary prevention of AD. Similarly, meta-analyses conducted suggested risk reductions of about a third conferred by HRT on AD (Hogervorst et al., 2000; LeBlanc et al., 2001).

Increased risk of Alzheimer's disease with HRT

The outcomes of five studies in this review which included the Seattle population-based (Brenner et al., 1994), UK-based Practice Research Database (Seshadri

et al., 2001), Estrogen-Progestin and the Estrogen alone trials of the Women's Health Initiatives Memory Study (WHIMS) (Shumaker et al., 2003; Shumaker et al., 2004), and the Rochester study (Roberts et al., 2006) all revealed an increased risk of developing AD in postmenopausal women subjected to HRT. These are all indicated by relative risks of >1 which showed positive associations (these findings are depicted in Table 1).

In the WHIM study, the randomized controlled trial that assessed the effect of estrogen plus progestin and estrogen alone on global cognitive functioning in postmenopausal women, the outcomes varied but were all associated with increased risks (Rapp et al., 2003). In postmenopausal women aged 65 years and above, estrogen plus progestin did not improve cognitive function when compared with placebo (Rapp et al., 2003). There was even a more than twice increased risk of clinically meaningful cognitive decline in the estrogen plus progestin group as indicated by a relative risk of 2.1 (95% C.I. = 1.20 to 3.50) (Shumaker et al., 2003). While in the estrogen alone group, the relative risk was 1.5 (95% C.I. = 0.80 to 2.70) (Shumaker et al., 2004).

In a UK-based population-based nested case-control study to determine whether exposure to postmenopausal estrogen replacement therapy is associated with reduced risk of AD, Seshadri et al., 2001; using prior and current use of ERT in cases compared with controls as main outcome measures reported that; among 59 newly diagnosed cases of AD, 15 (25%) were current estrogen

users while among the controls 53 (24%) were current users. The adjusted odds ratio comparing all current estrogen recipients with non-recipients was 1.18 (95% CI, 0.59 to 2.37).

In estrogen users who took the drug for 5 years or longer compared with non-users, the odds ratio was 1.05 (95% CI, 0.32 to 3.44). Odds ratios were similar for estrogen recipients who received estrogens alone and recipients who received combined estrogen-progestin treatment (Seshadri et al., 2001). The conclusion was that, the use of ERT in women after the onset of menopause was not associated with a reduced risk of developing Alzheimer's disease (Seshadri et al., 2001).

In a relatively more recent study, the Kronos Early Estrogen Prevention Study (KEEPS), which was a randomized, double-blinded, placebo-controlled clinical trial conducted in nine US academic centres, a total of 693 women participated in the ancillary KEEPS-Cog, with the participants randomized into oral conjugated equine estrogen, micronized progesterone, transdermal estradiol and placebo groups, in order to assess the effects of HRT on cognitive function (Gleason et al., 2015), it was concluded that postmenopausal HRT did not have any treatment-related benefits on cognitive outcomes (Gleason et al., 2015).

Future trends in HRT Trials in Alzheimer's disease

The use of either estrogen alone or estrogen-progestin combinations have been tried in different observational studies and randomized trials such as the WHIMS (Shumaker et al., 2003; Shumaker et al., 2004) and KEEPS-Cog (Gleason et al., 2015) with varying outcomes but there are limited research evidence regarding the roles of selective estrogen receptor modulators (SERMs) and Phytoestrogens in Alzheimer's disease (Henderson, 2008; Henderson, 2014).

The selective estrogen receptor modulators (SERMs) lack the basic steroid structure of sex hormones but exert tissue-specific estrogenic effects by inducing conformational changes in the estrogen receptor. The available ones include Tamoxifen and Raloxifene used in breast cancer and osteoporosis. Research data are sparse regarding the cognitive effects of these drugs (Paganini-Hill and Clark, 2000; Yaffe et al., 2001; Yaffe et al., 2005).

The Phytoestrogens, on the other hand, are dietary estrogens of plant origin which are present in high concentrations in certain foods such as the soy products. The most studied phytoestrogens are the Isoflavones which have been shown to have selective affinity for the Beta estrogen receptors (Kuiper et al., 1998). There are controversies regarding the effects of the Isoflavones on human cognition (White et al., 2000; Henderson et al., 2012). There are no current clinical trials of these micronutrients for the treatment or prevention of Alzheimer's disease (Henderson, 2014).

Based on preliminary evidence of the effects of the SERMs and the Phytoestrogens, they might, therefore, be candidate agents for consideration in the future role of HRT in the primary and secondary management of Alzheimer's disease in older women.

Conclusion

Despite the seeming protective role of HRT against Alzheimer's disease and other forms of cognitive impairment based on theoretical perspectives and observational studies, the findings have been inconsistent. After synthesizing many literature and highlighting the findings of the Women's Health Initiative Memory Study (WHIMS), McCarrey and Resnick (2015) inferred that although observational studies suggested that HRT would benefit cognitive function and reduce the incidence of cognitive impairment, including dementia, the results of the WHIMS randomized controlled trials in postmenopausal women did not support the observational findings and even showed poorer cognitive outcomes in women randomized to HRT (McCarrey and Resnick, 2015). Similarly, in a comprehensive review of more than 200 published works, Barrett-Connor and Laughlin (2009), concluded that there is no evidence that convincingly supports the prescription of early or late postmenopausal estrogen therapy to preserve cognitive function or prevent dementia (Barrett-Connor and Laughlin, 2009). It could, however, be concluded on empirical basis that longstanding commencement of HRT prior to the onset of menopause might be protective against the development of Alzheimer's disease but does not seem to have any therapeutic value after the onset of the disease at menopause.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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