Meta-analyses of the effect of hormone treatment on cognitive function in postmenopausal women

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Summary

As we age, most of us experience a certain degree of cognitive decline. In most cases, this decline is gradual. However, in some cases, cognitive impairment is so severe it can be classified as dementia and this impacts greatly on activities of daily living. Alzheimer's disease (AD), the most common form of dementia, has been linked to a reduction in estrogen (E) levels that come with aging. More specifically, many researchers have hypothesized that E, and hence E replacement via Hormone Therapy (HT), could protect against cognitive decline in women. However, recent randomised controlled trials (RCTs) did not reflect this. In fact, some reports showed that HT could be detrimental on cognition in older postmenopausal women. The most publicised of these has been the Women's Health Initiative Memory Study (WHIMS). However, studies have yielded conflicting results and conclusions. The reasons for this may be due to a number of factors, such as the age of participants, the time of HT onset ('window of opportunity' theory), type of treatment, type of menopause (surgical or natural) and, possibly, genetic risk factors. We performed quantitative and qualitative meta-analyses and reviewed each of these factors in detail. The future may lie in combining these factors in order to fully understand the potential mechanisms behind E and its effect on cognition.

Keywords

Hormone therapy, cognition, Alzheimer's disease, estrogen, postmenopausal, women

Introduction

We live in a world where people have increasingly longer, but not necessarily healthier lives. As we age, and brain cells gradually demise, there is a discernible decline in some cognitive functions, such as verbal memory, speed of information processing and complex spatial and verbal skills. The hippocampus, which is particularly important to memory function, loses approximately 5 percent of its volume every decade after the age of 65 years [1]. In pathological cognitive aging, such as dementia, people experience a more pronounced decline of cognitive functions, which impacts on activities of daily living. The most common form of dementia is Alzheimer's disease (AD). AD is a progressive dementia that initially usually manifests with memory deficiencies, one of its earlier and more pronounced symptoms, which are later followed by other cognitive deficits [2]. The speed and degree of cognitive decline shows great variability between individuals, ranging from "successful" aging to having more severe cognitive problems, such as dementia [3]. What determines this variability is not certain, but women may have a greater risk of developing AD than men [4]. This could be attributed to the fact that women reach an older age than men, and AD shows a greater incidence with age. However, the age-specific incidence of AD was also reported to be higher in women than in men [5]. This distinction could be linked to the more pronounced deficiency in steroid hormones, such as estrogen (E), in women after the menopause. Because of its biological plausibility to protect the brain, deficiency in E after the menopause has been suggested as a potentially important factor in the development of dementia. Therefore, it was believed that Hormone Therapy (HT) would be a beneficial intervention for treating or preventing dementia in older women [6,7].

1. Historical Background

The relationship between sex hormones (both endogenous and via HT) and cognitive function has been under extensive investigation over the last 3 decades. Results of many animal and cell culture studies have repeatedly shown potential protective effects of E on the brain. For instance, synaptic plasticity was shown to be enhanced through binding of E to its receptors in

the hippocampus and nucleus basalis of Meynert, areas both implicated in AD [8]. In animal models, E has been found to increase dendritic density in the hippocampus, which has the highest concentration of E receptors [9]. In affected AD brains, the hippocampal region is severely afflicted, suggesting that the biological effects of E in this area of the brain could perhaps preserve cognitive functioning by having an impact on cognitive decline prior to the onset of AD. It has been found that E use preserves regional cerebral metabolism, protecting against metabolic decline in postmenopausal women, again especially in the areas of the brain found to be adversely affected by AD [10]. Detailed reviews of the possible effects of E in protecting the brain are already available [11,12]. In fact, it was stated that there are almost innumerable biological reasons why E could be protective against both benign memory loss and senile dementia [13].

The nineties showed great optimism about the benefits of E therapy in the treatment of AD, encouraged by an increasing number of positive observational studies and a number of small treatment trials, which provided evidence supporting the potentially biological beneficial effects of E. The basic biological mechanisms, as well as the supportive evidence from human observational studies, have been extensively reviewed [14,15,16,17]. The theoretical basis behind the idea that E could protect against AD was summed up as follows [18]:

(i) there is a positive relationship between AD and decreasing E levels after menopause

(ii) a sudden earlier loss of gonadal function seen in postmenopausal women compared to men is associated with an increased prevalence of AD in women

(iii) there is generally decreased incidence and delay in the onset of AD in observational studies of women using HT after the menopause [18]

While these arguments follow a logical system, they are, unfortunately, not always supported by research. Firstly, in contrast to initial findings, several well controlled observational studies actually reported higher levels of E in women with AD compared with controls (see for a review: [19]). Secondly, in contrast to European and Asian studies, observational studies in the US did not find increased incidence of AD in elderly women as compared to age-

matched men (see [20]). Lastly, more recent, but also several earlier observational studies did not show protective associations of HT use against AD (see for an overview [19]). Importantly, several sources of bias (e.g. healthy user bias, recall bias) exist in these observational studies, which also limits their predictive value.

These contra arguments are thus concerned with observational studies. However, there remains an abundance of evidence from *in vitro* and *in vivo* studies suggesting that E could act favourably upon almost all mechanisms known to be affected in cognitive decline and AD [21]. Prior to recent findings, the idea that HT could potentially reduce the risk for dementia in women was widely credited and accepted. Well controlled treatment studies ultimately provide the most compelling evidence. Most of the early treatment studies showed favourable effects of HT, in line with biological plausibility studies[15]. However, several of the initial treatment trials had methodological problems (size, statistical analyses etc), which had already earlier lead to scepticism about their results [22]. In addition, many treatment studies done in recent years have yielded opposing results. For example, several large well controlled recent randomized controlled trials (RCT) [23,24,25] showed that HT did not prevent cognitive decline and did not improve cognitive abilities in postmenopausal women with or without dementia.

Women's Health Initiative Memory Study

The largest and best known of these RCTs to date has been the Women's Health Initiative-Memory Study (WHIMS) [26]. The WHIMS was a large multi-centre, randomised, double-blind, placebo-controlled trial in which a subgroup of several thousand women from the Women's Health Initiative (WHI) study were assessed for the effects of HT on dementia and mild cognitive impairment. Participants were aged 65 or older (and were thus all postmenopausal), received conjugated equine estrogens (CEE) plus medroxyprogesterone (MPA) vs. placebo [27], or continuous unopposed CEE vs. placebo [28]. The combined trial arm was discontinued in 2002 after concerns arose regarding its safety (mainly an increased

risk in breast cancer). The CEE and MPA trial found, contrary to the earlier wealth of scientific evidence, which hailed HT as having a positive influence on cognitive function, that the widely used CEEs (both Premarin and Prempro) were detrimental to neurocognitive health and increased the risk for dementia [26,27]. Several scientists concurred with the WHIMS authors that HT should not be recommended as an effective preventive treatment against dementia [29]. However, a smaller subset of WHIMS participants receiving combined treatment (n=1417) showed some positive effects on visual memory, but only after 3 years of treatment [30]. This, once again, shows the variable results of HT and cognition studies.

In February 2004, the estrogen-only (CEE) arm of WHIMS (WHI) was also discontinued due to an unacceptable increased risk of stroke with treatment. The results were published in April of the same year [28,31]. Similar to WHIMS findings of CEE and MPA trial, it reported an increased risk in dementia onset, although it was of a smaller magnitude[31]. Meta-analyses on cognitive function (measured with the modified mental status examination) show an overall effect in favour of placebo ($z=2.04$, $p<0.05$, mean difference -0.15, 95% Confidence Interval or CI=-0.29 to -0.01 for combined trail and $z=2.49$, $p<0.0005$, mean difference -0.38, 95% CI=-0.60 to -0.17 for CEE alone). However, individual analyses per year show inconsistencies in risk over time in both studies. While the effect of the combined trial only showed a significant difference in favour of the placebo group at year 4 ($z=2.26$, $p<0.05$), this was seen after CEE alone only at year 1 ($z=2.25$, $p<0.05$) when taking into account the number of women who dropped-out each year.

The results of WHIMS are a far cry from earlier positive reports of the potential effects of HT. It has been argued that there may be some important reasons for the negative results found in WHIMS, as well as some rational behind the general discrepancy seen in the field as a whole. It has been suggested that differences in the age of participants, (resulting in the ‘window of opportunity’ theory [32]), type, form and route of treatment, and type of

menopause that participants had undergone (surgical or menopausal) are mostly responsible for the lack of uniformity in results. These factors shall be addressed in more detail below.

2. Factors explaining the variability in outcomes between studies

2.1 Age

Some researchers have argued that the negative results found in WHIMS were partially due to the age of participants [33]. The advanced age (65+ years of age) and obesity of participants in this study was deemed not representative of the population that HT is aimed at. The majority of participants may have been beyond the scope of help in averting most of the negative outcomes (stroke, dementia). However, that would not explain the *negative* effects seen in the WHIMS. Another review [34] reported little support for beneficial effects of E (both alone and in combination with Progesterone – P) in women older than 65 years of age, and it was noted that potentially beneficial effects on specific cognitive functions were mainly seen in younger and more recently menopausal women. In a recent study, the relation between HT use and a lowered risk of developing AD in 971 postmenopausal women showed a protective association, but only in women of the youngest age tertile (50-63 years) [35]. This finding is in line with animal studies suggesting protective brain effects in young, but not older animals [36].

2.2 'Window of Opportunity' theory

Several authors have thus suggested that there is a critical period for HT treatment in order to obtain positive effects on the brain. It is hypothesized that initiating or continuing HT beyond this critical period would have little effect on the brain and cognitive function [32]. The 'window of opportunity' theory suggests that there is a critical time for the initiation of HT and could explain why no protective effects were seen in WHIMS. Results from animal studies suggest that the longer the delay between ovariectomy and onset of treatment, the less chance there is of detecting the favourable effects of HT on the brain [37].

However, the strongest argument against this theory is that in RCTs of women with AD, both Premarin and transdermal estradiol (E2) were seen to have similarly positive effects, but only for 2-3 months [38]. These women with AD (of whom the majority would be over 65 years of age) were at least 15 to 20 years older than the recently menopausal women (with a mean age of 48 years of age) in the successful E2 trails described in another meta-analysis [19]. This meta-analysis suggested that positive effects of E2 in women without dementia were also time-limited, resulting in an increase in memory, accuracy and abstract reasoning functions, but again only up to 2-3 months. For both older and younger, more recently menopausal women, a possible reversal of positive effects was seen on some cognitive functions after one year of treatment. Therefore, it seemed more likely that positive effects, if they were found, are only short lived, regardless of age. These findings also tie in with the WHIMS data. It has often been suggested that effects of HT are limited to particular aspects of cognitive function which could be an alternative reason for some studies not finding any effects. For this review, we performed quantitative and qualitative meta-analyses using Revman software provided by the Cochrane library standardized review system, employing both their inclusion criteria and their statistical methods (update) [39]. See textbox and Table 1 and 2

TEXTBOX **Meta-analyses of studies investigating the effects of HT on different aspects of cognitive function**

Verbal memory

Table 1 and 2 show that of all studies, only 23 of the tests used (22%, out of 106 cognitive tests used over all studies) showed a positive effect, while 3 tests had a negative result. Of these positive effects, a quarter of tests used (n=6) reflected a positive effect of HT on verbal memory, but 12 verbal memory tests used could not show this and one study (on WHIMS data, see below) showed that CEE with MPA had a negative effect on verbal memory over a longer period of several years.

Qualitative analyses using Table 1 shows that the positive effects on memory were only seen in four studies after treatment for a short duration of time (2-3 months). This was seen in a study using oral estradiol (E2) in younger postmenopausal women reporting insomnia (of an average age of 49 years of age) [40] and in studies using bolus injections of E2 in surgically menopausal women aged on average 48 [41]; 45 [42]; and 47 [43] years of age. In contrast, several other studies (using transdermal E2 in younger women with an average of 57 years of age)[44] and transdermal or oral E2 in older women of an average age of 71 years old [46] and 74 years old [45] respectively; 70 years old with oral E2 [25]; 69 years old with transdermal E2 [47]) did not reflect these effects. Studies with CEE did not report positive effects on verbal memory in younger (51 years old) [48] or older (82 years old) [49] women, although one study (sub-study of the WHIMS) reported a negative effect of CEE and MPA on verbal memory in older women (74 years old) [30]. These qualitative analyses were done using the reports of the investigators.

Quantitative analyses showed only an overall positive effect on one test, the verbal paired associates immediate recall ($z=2.40$, $p<0.05$ effect size 1.02 95% CI=0.19-1.85)[41,42], but not on the delayed recall or recall of word lists or stories or on Verbal Fluency (which also tests language and executive functions). These analyses may be limited as standard deviations (SD) of the mean difference often had

to be recalculated which, in smaller studies, could lead to an overestimate of the SD, making these analyses vulnerable to type II error. However, it does indicate that effects, if present, are small.

Visual memory

On visual memory tests (where verbalization may occur), positive effects of E2 were seen on the memory of faces in women of 74 years of age (after 5 months of oral E2) [45]; and on picture recall and visual paired associates in women 65 of years of age (3 weeks E2 transdermal) [50] but also after CEE and MPA on figure recall after 3 years in women of 74 years of age [30]. Fifteen studies reported no effects on visual memory regardless of age or type of treatment [25,40,41,42,44,46,47,48,51,52,53]. Differences in tests could explain the differences between studies, but quantitative meta-analyses showed no significance for tests of heterogeneity. These analyses also revealed no overall significant effect of HT on visual memory. Traditionally, effects of E have been thought to be most apparent on verbal memory tests [54].

Speeded tests

However, several studies reported positive effects of HT on speed of information processing (found on a third of all tests used in studies). This was the case in 5 studies using transdermal E2 with women 65 years of age [50]; transdermal E2 with women aged 57 years old [44]; oral E2 with women aged 57 years [55]; transdermal E2 with women aged 71 years [46]; bolus E2 with women aged 45 years [43], although several other tests used in studies with transdermal E2 [44,46,47,50,53] could not reflect this. Three studies using CEE [56,57,58] reported no effects on speeded tests.

Quantitative meta-analyses found overall trends on simple tests (TMT-A and SRT, p=0.06) and more complex tests (TMT-B and Stroop, p=0.10). Surprisingly, for simple speed, these analyses involved studies with CEE and MPA for 9 months[1] [49] and transdermal E2 for 24 weeks [46], both in older women. For complex speed positive effects were seen in quantitative meta-analyses, again with CEE and MPA [49], after transdermal E2 in older women for two weeks [47] and three weeks [50] and also after oral E2 in younger women for a duration of ten weeks [44]. Other tests, such as CRT, Digit Vigilance and Digit Symbol Substitution Test, were not affected by HT.

Other

Several other tests showed positive effects, but only after bolus injections of E2 in surgical menopausal women [43] on executive functions (abstract reasoning) and accuracy or after oral E2 in symptomatic young women [55]. Meta-analyses showed that there was not an overall significant effect of HT on these types of tests (p=.14; p=.16) Three studies showed no overall effect of HT on the MMSE or CAMCOG [25,45; Greenspan 2005] and negative effects were found twice after HT on the modified 3MSE in WHIMS[27,8]. However, in sub- analyses [25], elderly women without stroke who had a normal MMSE (28-30) were found to significant less decline after E2 treatment compared to placebo after 3 years ($z=2.37$, $p<0.005$).

-insert Tables 1 and 2-

Summarizing the text box findings in Table 2 shows that E2 given orally or as a bolus injection was mainly effective in improving verbal memory for very recently menopausal younger symptomatic or surgically menopausal women, but this was only tested up to 3 months. Several earlier studies suggested that effects of E2 on memory actually may reverse after 6 months to a year [19]. The positive effect was also small, as it only held up in meta-analyses for one aspect of one test. For visual memory, effects were not clear. We saw some positive effects on visual memory after transdermal E2 and CEE and MPA, but only in older women. This may argue against the 'window of opportunity' theory. Similarly, the results for

1but the authors [49] did not report our finding having used the slope over 3 time points for analyses, but not the mean difference, as we did

speeded tests indicated that the successful type of E treatment could depend on age: the younger symptomatic group seemed to profit most from an oral or bolus injection of E2, while the older women could possibly profit from transdermal E2 and CEE and MPA. The only significant effect on accuracy and abstract reasoning was found in one study of surgically menopausal women after a bolus injection. Adding P did not seem to alter results substantially (see also [19]). None of the meta-analyses showed significant heterogeneity and the more conservative standardized mean differences with random effects (rather than weighted mean differences with fixed effects) were used throughout.

These analyses thus showed, as stated earlier [15], that possibly not all cognitive tests may be equally sensitive to HT and that different treatments may show different cognitive effects, which may also depend on age. Of course, the WHIMS, as the largest study which included older women, reported that women who used CEE and MPA after 2 years and CEE alone after 3 years had less improvement on the 3MSE and a greater risk of dementia, but the effects were small. As also mentioned, while a decrease in verbal memory was seen, the WHIMS sub-study actually reported improvements in visual memory after combined HT at this time point.

2.3 Treatment Form / Route and duration

Whether HT given for a longer period of time to older women could actually increase dementia risk was reviewed by others and several possible mechanisms for this relation were suggested [59]. These mechanisms were based on the theory that a longer life span, a lower prevalence of vascular dementia, and lower levels of testosterone (T) in women may contribute to the higher prevalence of AD. The mechanisms, that may have been active in WHIMS and potentially responsible for an increase in dementia, could be:

1) use of MPA and Estrone (E1), which is a major metabolite of CEE, which may have different effects on neuronal and cerebrovascular function than P and E2 (the most potent E);

2) a greater risk of stroke (caused by the use of MPA [60] or through accidental inclusion of those at risk for stroke) leading to dementia;
3) and, lastly, a decrease of bioavailable T (through the increase in sex hormone binding globulin or SHBG, which CEE induces to a greater extend than E2 does [61]. T can, directly or through conversion into E2, protect against AD[62].

Arguments against these mechanisms are the following. Firstly, as we saw in the meta-analyses, while on verbal memory only E2 had positive effects in relatively younger postmenopausal symptomatic women, small positive effects of CEE with or without MPA were seen on some cognitive tests, but only in older women. In addition, exclusion of women with stroke, in the CEE alone or CEE with MPA trial, did not substantially alter the negative effect of HT on the overall improvement on the 3MSE [28]. Lastly, while SHBG may increase with CEE, so would the amount of E when treating with CEE. The role of bioavailable T and E2 (and the ratio of T:E2) on cognitive function in elderly women is not well understood and requires further investigation. It is unclear whether CEE metabolites would have worse effects than E2, but brain E receptors are more sensitive to E2 than E1 [63]. However, in a recent RCT focusing on Event Related Potentials in women with an average age of 60 years, a positive effect of CEE was found [64]. The results showed a shortening of P300 latency which is consistent with normalisation of cognitive function. This result casts further uncertainty into the understanding of the role of CEE in cognitive treatment. One observational study reported that higher E1 levels were associated with detrimental effects on cognition. In the Study of Osteoporotic Fractures [65], women in the highest E1 quartile showed worse scores than women in the lower E1 quartiles on two cognitive tests. In contrast with this, the majority of observational studies showed a protective association (although tainted by several potential confounds, such as the healthy user bias [19]). Most women in the U.S.-based studies would have used CEE (in the form of Prempro and Premarin) and would have thus been exposed to E1 metabolites. Lastly, as mentioned above, CEE (similar to transdermal E2) has also shown positive effects on cognition in

women with dementia [39] and, as our most recent meta-analyses suggest, also on some tests in older women without dementia.

Taken together, these findings suggest that as well as the form of HT, the route of administration may also be of importance and may depend on the age of the women. Where oral and bolus injections of E2 with or without P may be more suitable for relatively recently menopausal women, transdermal E2 and possible CEE could be more suitable for older women. However, it is not clear whether and which positive effects, if they exist at all, reverse after longer periods of usage.

2.4 Surgical Menopause

Our quantitative meta-analyses of women without dementia [39] and the current updated meta-analyses analyses indicated that significant effects of HT were strongest in women who had undergone for surgical menopause. A significant drop in cognitive function after ovariectomy has been shown [43,66,67]. In contrast, researchers could not find any evidence suggesting that natural menopause causes a drop in cognitive functions [68]. Therefore, one conclusion that could be drawn from these results is that surgical menopause in itself is a risk factor for accelerated cognitive impairment and that E therapy would be particularly indicated for this group. However, in another observational study [69], surgically menopausal women who had an E2 implant for approximately 10 years had worse long term episodic memory and mental flexibility, and more psychological and somatic menopausal symptoms than untreated surgically menopausal women. These negative results are in line with other findings of an association between better Verbal Fluency and HT use in younger (<58 years) surgically menopausal women, but not in older surgically or younger and naturally menopausal women [70]. These findings also tie in with an observational study which indicated that former -but not current- users of HT were protected against AD [71]. However, interactions of duration of use and protective effects were not always found. For example, in another observational study [72], surgically menopausal women using HT compared to surgically menopausal women

who were not using HT had better verbal memory and constructional abilities at age 65. As duration of treatment was not reported in this study, it is possible that the majority of women in this study had only used HT for a limited period of time. .

Thus, it must be kept in mind that several clinically important questions are left unanswered, such as effect of duration of use and the generalisability of WHIMS to women for whom HT is an indication, i.e. perimenopausal women who have menopausal symptoms [73]. While our quantitative meta-analyses identified surgical menopausal women as those most effectively treated for cognitive deficiency by HT [39], other reviewers suggested that women who were highly symptomatic (which would include most of the surgically menopausal women) showed largest treatment effects [74]. Although when statistically tested [15], menopausal symptoms did not explain improvement on cognitive function, these issues need to be further elucidated. There is no doubt that the findings of these trials have had and will continue to have a huge influence on the industry and the use of HT. Further, more controlled studies need to be done in order to fully understand, support or refute the findings so far. The key to future understanding may lie in focusing on interactions of the factors mentioned above and genetic risk factors.

3. Genetics

It is possible that an interaction exists between HT and genetic factors. More specifically, the effect of HT may depend on a woman's particular genetic profile. It is has been found that having at least one APOE ε4 allele is at least 2-3 times more likely in AD cases [75] Some studies found that cognitive decline was prevented with HT, but only in women without the ε4 allele [76,77]. However, at least 5 other studies did not find any significant difference when taking the APOE genotype into account [7,35,71,78,79].

We and others, using highly sensitive assays, have found that E2 levels were actually slightly elevated in women with AD [19,59]. It could be hypothesized that women with AD have a

genetic predisposition to higher E2 levels. Certain genes are involved in the metabolism and synthesis of E2. For example, the enzyme cytochrome P450c17a is involved in E synthesis, which is regulated by the CYP17 gene. This gene is located on chromosome 10 and has 2 allele variants. A polymorphism (or variation) of this gene is the A2 allele, which causes an increase in the quantity of enzyme produced, resulting in higher E levels. The allele versions of this gene without this variation are known as A1. It has been reported by several studies that people who are A2 homozygotic (have both A2 gene allele versions: A2:A2) or who are heterozygotic (with just one A2 allele: A2:A1) have higher levels of E than people with two A1 alleles (A1:A1) [80]. Therefore, using HT to increase the levels of E in women who are homozygotic (A2:A2) and already have higher levels of E could have a detrimental effect. It is possible that there may be optimal levels of E for the brain to function at the most efficient level. Therefore, increasing E2 above this optimal level could result in negative effects on the brain. If our review data relating type of treatment to age are correct, possibly this is related to different optimal levels of E with age (e.g. lower plasma levels of E2 are reached with CEE and transdermal E2 compared to oral and bolus E2, see figure 1). Similar mechanisms have been postulated for actions of T in elderly men [19]. Lower levels of E may thus be more effective in older women when compared to younger menopausal women, particularly for those who already have higher endogenous E levels.

DNA damage has been associated with AD pathology [81]. P450 (CYP) 1B1 is a key enzyme in the metabolism of E2. 4-hydroxylation of E2 [regulated by expression of cytochrome P450 (CYP)] results in a reduction of estrogenic activity. A toxic metabolite, that has been associated with DNA damage, is a product of this [82]. The Val432 allele variant is associated with higher 4-hydroxy E2 levels than the Leu432 variant. In women who would have high E levels, this variant could result in dangerous metabolites, potentially leading to DNA damage which could be implicated in AD risk.

Additionally, the inactivation of reactive metabolites, such as catecholestrogens, is regulated by Catechol-O-MethyTransferase (COMT), which is regulated by the gene COMT (Val108/158) Met). The COMT Met/Met polymorphism may be a risk factor when compared with the COMT Val/Val genotype, in that reactive metabolites are not inactivated [83]. If women have genotypes CYP17 A2, P450CYP1B1 Val432 and COMT Met/Met and are then given HT, they might produce very high levels of toxic metabolites, which might put them at risk for dementia.

These theories have not been fully investigated, but may have important implications in our knowledge of the causes of AD and need to be substantiated in further studies.

In an observational study from the Mayo Clinic, Minnesota, it was found that women who underwent surgical menopause had a 40% increased risk of dementia. Women who had bilateral ovariectomy by the age of 46 had a 70% increased risk of dementia. The removal of one ovary before 38 years of age resulted in a 260% increase in the risk of dementia [59]. The reason for this trend could be due to early exposure to low levels of potentially protective E levels. However, life long exposure to E (calculated from age of menopause and onset of menses) has shown controversial associations with the onset of dementia [19]. Alternatively, surgical menopause and increased risk of dementia may be linked because women usually undergo surgical menopause because of endometrial cancer. The type of genetic risk markers mentioned above, leading to high levels of toxic estrogenic metabolites, could be implicated in the mechanism explaining the association between endometrial cancer and AD. If this is so, other steroid-sensitive cancers, such as breast cancer, could also have a higher incidence in women who survive this and then to go onto develop AD.

4. Conclusion

The question that needs to be asked is whether oral E2 can have a positive effect on cognitive function in recently postmenopausal women for a longer period of time. It is unclear whether

this effect pertains to women who have undergone surgical menopause and/or those with menopausal symptoms, and whether this effect is mediated by symptom alleviation. As can be seen from previous studies, it seems that CEE is not an effective form of HT when addressing memory problems in this younger, more recently menopausal group.

It has also previously been stated that the primary reason for a lack of effect of HT on menopausal cognitive decline in women is their age. Some believe that there is a critical window of time after which HT is ineffective, as it will not only have no effect on cognitive decline, but may also result in additional detrimental effect and impair cognition further. However, some treatment studies do show positive effects of HT in older women. Some aspects of cognition are possibly more sensitive to these effects than others.

Whether women have undergone natural or surgical menopause may play a crucial role in this debate. A sudden and early loss of E may not the most important factor in this association. Instead, it is possible that the same genetic predisposition to reasons for having to undergo surgical menopause, underlie the increased risk of AD. Especially if women who are genetically at risk take HT and increase their levels of endogenous E2, this could potentially affect the production of toxic metabolites and lead to DNA damage, which is implicated in a variety of age-related morbidity factors, such as some cancers, but also AD.

To conclude, the studies to date suggest that short term (up to 3 months) oral E2 treatment (with P for women with an intact uterus) for symptomatic recently natural and surgically menopausal women is the most favorable combination to benefit verbal memory but also to improve symptoms, the main indication for treating women with E. Whether genetic predispositions associated with E metabolism modify a women's risk for dementia remains to be investigated.

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5. Future Perspective

In a world with constant advances in ways to prolong life and improve standards of living, it is evident that the prevalence of age-related disease, such as dementia, is bound to increase. This creates not only a higher demand on society's resources, but also the economy as a whole. In a report published by the London School of Economics via the Alzheimer's Research Society, the United Kingdom alone is estimated to be faced with double the costs of care for the elderly in the next 30 years. Therefore this is a topic which will have even greater significance and importance in the future.

The general confusion and conflicts seen in this area are worrying, particularly for postmenopausal women who are plagued by symptoms, such as hot flushes, night sweats and mental instability. However, just as history has shown a shift in perspective over the last ten years, what the next ten years bring will hopefully result in the clarification of the effects that HT has on cognition in menopausal women with and without dementia. The future lies in more RCTs which take into consideration all the variables that have been seen to influence the impact of HT on cognition. A change in perspective is needed to focus on which variables result in a positive effect of HT, instead of just those aspects that may result in negative findings. The inclusion and exclusion criteria used in future studies should take into consideration such as the influence of age, window of time, treatment form/route, surgical vs. natural menopause, and more recently, possibly genetics.

6. Executive summary

Introduction

- As we age, there is a decline in certain cognitive functions, such as verbal memory, complex spatial and verbal skills
- Cognitive decline with age ranges from 'successful' aging to more severe deterioration and dementia, of which Alzheimer's disease (AD) is the most common.
- Women may be at greater risk of developing AD than men.
- The fact that women reach an older age than men does not explain this difference in dementia prevalence, because age-specific AD incidence is also higher in women.
- It was theorised that a more severe deficiency in estrogen (E) in elderly women, when compared to men after menopause, may increase their risk of AD
- Hormone therapy (HT) consisting of E has been suggested as a way of treating/preventing AD in older women and observational studies have found protective associations.

Historical Background

- Animal models have shown that estrogen increases dendritic density in the hippocampus, and estrogen receptors are highly concentrated in the hippocampus.
- People with AD have severely affected hippocampal regions, and therefore a lack of estrogen in this area may be a precursor for the development of AD.
- Estrogen may protect against metabolic decline of certain regions susceptible to AD in postmenopausal women.
- The early nineties provided a wealth of research which supported the idea that HT is an effective treatment method against AD.
- However, methodological problems of earlier studies and the opposing results found by more recent studies have lead to a change in perspective.

Women's Initiative Memory Study (WHIMS)

- The WHIMS was a randomized, placebo-controlled trial (RCT) which used conjugated equine estrogens (CEE) with medroxyprogesterone (MPA) vs. placebo, or continuous unopposed CEE vs. placebo. Both treatments in this study found detrimental effects of HT on cognition in postmenopausal women.
- Some WHIMS researchers advice that the popularly used CEEs, Premarin and Prempro, are detrimental to neurocognitive health and therefore do not recommend HT as an effective therapy for dementia.
- There are several possible reasons for the differences reported in results between WHIMS, earlier studies and other more recent HT trials.

Factors explaining the variability in outcomes between studies

- Age – It is believed by some that women over 65 years of age can not benefit from the beneficial effects of HT. However, some studies found positive short lived effects of HT in women with dementia
- 'Window of Opportunity' – there may be a critical period of time in which HT is effective. This may be in younger, symptomatic recently menopausal women with a minimal delay between ovariectomy and HT onset. However, studies suggest that, these effects, when found, are only short-lived (up to 2-3 months).
- Treatment form / route – Conjugated equine estrogens (CEE) is the main treatment used in studies that showed no effects of HT on verbal memory, whereas oral and bolus injections of estradiol (E2) (alone or combined with progesterone) have yielded positive results in recent menopausal women, particularly if they were symptomatic.
- Orally administered CEEs and transdermal E2 has also been found to be effective in older women suggesting that optimal type and treatment route may be modified by age.
- Surgical menopause – Some treatment trials have shown that HT may be most effective in women whom have undergone surgical menopause

Genetics

- The effect of HT may depend on a woman's specific genetic polymorphisms associated with E synthesis and metabolism, resulting in higher endogenous E2 levels which may be detrimental.
- DNA damage has been associated with AD onset. 4-hydroxylation of E2 may result in a toxic metabolite, which has been associated with DNA damage. Certain genetic polymorphisms are associated with higher production or lower break-down of these toxic metabolites
- The genotypes CYP17 A2, P450CYP1B1 Val432/Val and COMT Met/Met in combination with HT may increase levels of E2 and toxic metabolites which could result in DNA damage and which could put women at risk of AD.

Conclusion

- From previous studies, it seems that CEE is not an effective form of HT for cognitive complaints in recently menopausal women. E2 has yielded more positive results, with or without P
- It is argued that there is a critical window of time in which women are at the optimal age for the beneficial effects seen with HT, after which it is not effective or even detrimental. However, other positive treatment studies of older women refute this
- Positive effects of HT may be seen particularly in younger, surgical menopausal women, using oral E2 as the treatment form and seem to affect some components of cognition and not others. Effects are short lived and small, whether they are detected in older or younger postmenopausal women. We may need to further investigate the genetic make-up of the individual before treating women with HT

Future Perspectives

- There is, and will continue to be, a great demand on societies resources due to the fact that we are living longer lives and therefore prevalence of age-related cognitive decline is likely to also increase .
- The confusion seen in the last ten years about the effects of HT in the treatment of cognitive decline is worrying. Future studies must take into consideration all the variables that have come from the multitude of previous investigations and combine knowledge to come to a more concrete foundation
- Researchers should possibly look carefully at the inclusion criteria of their participants and take into consideration the findings that others have shown, such as window of time, treatment form/route, surgical vs. natural menopause and also genetic factors that may tie all this together.

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