Estrogen therapy in postmenopausal women: effects on cognitive function and dementia

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Authors' objectives
To determine whether postmenopausal oestrogen replacement therapy improves cognition, prevents development of dementia, and improves the severity of dementia.

Searching
MEDLINE was searched from 1966 to 1997 using the keywords provided. The bibliographies of retrieved papers were examined and experts were consulted for further literature. The search was limited to articles published in peer-reviewed journals.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), non-randomised controlled trials (including cohort and case-control) and cross-sectional studies were included in the review. Case reports were excluded.

Specific interventions included in the review
Oestrogen replacement therapy given either orally or by intra-muscular injection. This included estradiol, piperazine estrone and conjugated equine oestrogen.

Participants included in the review
Postmenopausal women, including perimenopausal and surgically menopausal women. The age range of the included women varied.

Outcomes assessed in the review
The possible biological mechanisms of oestrogen on the central nervous system were reviewed. The primary outcomes were: the effect of oestrogen on cognitive function in nondemented women; the effect of oestrogen on the risk of developing Alzheimer's disease (AD) or other dementia; and the effect of oestrogen treatment in women with AD. Multiple outcome measures were used to estimate the effect of oestrogen on cognitive function in nondemented women and in women with AD.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The validity of the studies does not appear to have been formally assessed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were combined by both a meta-analysis and a narrative synthesis. Those studies that examined the effect of oestrogen on cognition in nondemented women, and the effect of oestrogen therapy on cognition in women with AD, were discussed narratively as there were a variety of study designs and multiple outcome measures which precluded...
quantitative summary.

Those studies which evaluated the use of oestrogen therapy and risk of dementia were combined by a formal meta-analysis. Separate meta-analyses of risk estimates for developing any dementia (AD and other dementia types), and for developing AD in oestrogen users compared with non-users, were conducted. Studies that reported risk for AD based on US national criteria were summarised separately. For each study, the most adjusted risk estimate was used to calculate the summary odds ratio (OR). In studies where the control group included men, the ORs and confidence intervals (CIs) were recalculated for women. A random-effects model and the general variance-based method were used.

How were differences between studies investigated?
A test for heterogeneity was performed, where a P-value of less than 0.10 was considered statistically significant.

Results of the review
There were 5 observational studies (1,379 women), 7 RCTs and 1 non-RCT (294 women) which evaluated the effect of oestrogen on cognition in non-demented women. There were 8 case-control studies (2,381 women) and 2 prospective cohort studies (1,596 women) which evaluated the use of oestrogen therapy and risk of dementia. There were also 1 RCT, 1 non-RCT and 2 uncontrolled trials (58 women) of oestrogen therapy in women with AD.

Effect of oestrogen on cognition in nondemented women.

Of the 5 observational studies, 2 reported inconclusive results, 2 reported no association, and 1 found that oestrogen use improved cognition. Of the 8 controlled trials, 6 found that oestrogen improved cognitive function. All of the available evidence had significant methodological problems. There was no clear evidence of a beneficial effect from oestrogen in asymptomatic women.

Effect of oestrogen therapy on cognition in women with AD.

All 4 identified studies (2 controlled and 2 uncontrolled) found some beneficial effect from oestrogen on cognition on at least one measure of dementia severity, but generally not on all measures used. The studies were all extremely small with short duration of therapy, and included participants with a wide range of dementia severity.

Use of oestrogen therapy and risk of dementia.

The 10 identified studies (8 case-control and 2 prospective cohort studies) produced results ranging from a suggestion of a protective effect from oestrogen, to an increased risk of developing AD in oestrogen users. The meta-analysis of all 10 studies produced a summary OR of 0.71 (95% CI: 0.53, 0.96) for developing any dementia. The 8 case-control studies gave an OR of 0.79 (95% CI: 0.56, 1.12) for any dementia, and the 2 prospective cohort studies gave an OR of 0.48 (95% CI: 0.29, 0.81) for AD. The definition of dementia had very little impact on the results of the meta-analysis.

Authors' conclusions
There was evidence that oestrogen therapy improved cognitive performance in recently menopausal women, but no evidence of a beneficial effect in asymptomatic women. The evidence of a protective effect from oestrogen in terms of the risk of developing dementia was weak; large, controlled, blinded trials are required. Oestrogen should not currently be used to treat women with AD. A large RCT of oestrogen therapy should be completed as soon as possible given the current lack of available treatment for dementia.

CRD commentary
This was a relatively well-conducted systematic review with a very clear objective, detailed description of primary studies, and a comprehensive pooling of studies. No formal validity assessment of the included studies appears to have been undertaken, but there was a knowledgeable and detailed discussion of the methodological problems inherent in using non-randomised studies. The literature search was quite limited and appeared to use only US spellings. This could have introduced some retrieval bias and significant publication bias. The inclusion criteria for the review could have
been more clearly stated. It should also be noted that one of the review's authors is employed by a pharmaceutical company investigating a new treatment for AD. On the whole, the authors' conclusions are justified. Although there was some suggestion of benefit from oestrogen in terms of the risk of developing dementia, an RCT is required to fully evaluate its use.

**Implications of the review for practice and research**
The authors state that a large blinded RCT is required to evaluate the use of oestrogen to improve cognition in women with AD, and to evaluate its use in reducing the risk of developing dementia.

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