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Short-term transdermal estradiol therapy, cognition and depressive symptoms in healthy older women. A randomised placebo controlled pilot cross-over study

Rebekah Schiff[a,*], Christopher John Bulpitt[a,1], Keith A. Wesnes[b,2], Chakravarthi Rajkumar[a,1]

[a]*Department of Medicine for the Elderly, Faculty of Medicine, Imperial College, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK*
[b]*Cognitive Drug Research Ltd, CDR House, Gatehampton Road, Goring-on-Thames RG8 0EN, UK*

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Summary The potential role of estrogen in protecting women from cognitive decline and reducing depressive symptoms is of great therapeutic interest. In a pilot randomised placebo controlled cross-over study, we aimed to determine the short-term effects of transdermal estradiol therapy on cognition and depressive symptoms in healthy cognitively normal post-menopausal women over 60 years of age. Nineteen cognitively normal women, without clinical depression whom had undergone a hysterectomy in the past were recruited. Women were randomised to receive either transdermal estradiol 50 μg/24 h (*Femseven*) or transdermal placebo for 12 weeks before crossing over to the other medication for a further 12 weeks. Cognition was assessed every 6 weeks by the cognitive drug research (CDR) computerised assessment which recorded both accuracy and speed in the following cognitive tests; simple reaction time, choice reaction time, digit vigilance, visual tracking, spatial working memory, immediate and delayed word recall and delayed face and picture recall. Depressive symptoms were measured using the brief assessment scale depression card (BASDEC) depression rating scale at baseline, 12 and 24 weeks. Participants had a mean age of 71, IQ of 115 and MMSE of 29. Simple reaction time and the BASDEC depression rating scale improved after 12 weeks of estradiol use. All other tests were unaltered by estradiol. Twelve weeks of transdermal estradiol therapy did not consistently improve the speed or accuracy of older women in various

* Corresponding author. Tel.: +44 208 383 3958; fax: +44 208 743 0798.
E-mail addresses: r.schiff@ic.ac.uk (R. Schiff), c.bulpitt@ic.ac.uk (C.J. Bulpitt), kwesnes@cdr.org.uk (K.A. Wesnes), c.rajkumar@ic.ac.uk (C. Rajkumar).
[1] Tel.: +44 208 383 3958; fax: +44 208 743 0798.
[2] Tel.: +44 1491 878700; fax: +44 1491 878701.

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cognitive tests. However, the results do support the concept that depressive symptoms may be reduced by estradiol, and not simply due to the relief of climacteric symptoms.

1. Introduction

Twenty percent of women who survive into their 80s will have dementia and others will have age-related cognitive impairment. Women are almost twice as likely to develop dementia as men (Launer et al., 1999). The potential effects of estrogen on cognition are therefore of great therapeutic interest.

Estrogen has multiple effects in the central nervous system, modulating systems involved with cognitive function. Effects mediated through estrogen receptors include protecting and promoting growth of neurons especially cholinergic neurons in the cortex and hippocampus, inhibition of β-amyloid protein formation and increasing expression of apolipoprotein E. Indirect actions include antioxidant effects and actions on the cerebral vasculature and immune system (Henderson, 2002).

There is conflicting evidence as to whether estrogen replacement enhances cognition in healthy post-menopausal women. Some observational studies have found improvements in discrete areas of cognition such as proper name recall (Robinson et al., 1994), verbal fluency (Kimura, 1995), language and abstract reasoning as well as memory (Jacobs et al., 1998).

There are relatively few randomised controlled trials in this area. Recently, the estrogen and progesterone arm of the women's health initiative memory study (WHIMS) found no improvement in cognitive function with combined hormone replacement therapy (Rapp et al., 2003) and the oestrogen-only study reported an adverse effect on cognition after 5.4 years follow-up, particularly in those with lower cognitive function when treatment was initiated (Espeland et al., 2004). A meta-analysis of the nine trials with adequate data for analysis prior to the WHIMS concluded that there was evidence of an improvement in verbal immediate recall, abstract reasoning and a test of speed and accuracy in young surgically menopausal women. They suggested further research was needed to address other issues including use by older women and route of estrogen administration (Hogervorst et al., 2002).

Depression is common in old age, prevalence varying between 10 and 20%, with a 50% greater prevalence in older women (Watkin and Katona, 1998). There is evidence to suggest that estrogen replacement therapy (ERT) is beneficial in the treatment of depressive symptoms either alone or as an adjunct to antidepressants (Schneider et al., 2001; Rasgon et al., 2002). However, some studies have suggested that these changes in affect are only evident in those with perimenopausal symptoms (Hlatky et al., 2002). Others have not found an effect in patients with mild to moderate depression using transdermal estradiol (Morrison et al., 2004).

In a pilot randomised placebo controlled trial, we aimed to determine whether transdermal estradiol:

a. altered the speed of responses in a variety of cognitive tests in older post-menopausal women without dementia or depression;
b. altered the accuracy of responses in a variety of cognitive tests in older post-menopausal women without dementia or depression;
c. improved affect in older post-menopausal women without clinical depression.

2. Method

A randomised placebo controlled crossover study. Women were recruited through advertisements in the hospital and local publications for older people. Women had to have had a previous hysterectomy since those still with an intact uterus would have required the addition of progesterone to their hormone replacement therapy. Other inclusion criteria for the study were; 60 or more years of age, no use of any form of ERT for at least 12 months prior to study entry, no use of any prescribed or non-prescribed drugs which might enhance cognition, no standard clinical contra-indication to ERT and a mini mental state examination (MMSE) score of 26 or above with a normal result (<7) on the brief assessment scale depression cards (BASDEC) (scale range 0–21) (Adshead et al., 1992). The BASDEC is a depression rating scale validated in the elderly. This scale performs as well as the 30 point geriatric depression