

## THE CURRENT STATE OF POSTMENOPAUSAL HORMONE THERAPY: UPDATE FOR NEUROLOGISTS AND EPILEPTOLOGISTS

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*Appropriate and safe use of hormone replacement therapy (HRT) in postmenopausal women is an evolving saga, triggered by the unexpected results from the first publication of the Women's Health Initiative (WHI) Trial in 2002. These results showed a slight but significantly increased risk of breast cancer, stroke, and dementia with standard HRT compared with placebo. A reanalysis of these results shows that use of HRT within the first few years after the onset of menopause may be associated with decreased risk of dementia and coronary artery disease. However, HRT in its commonly used form of conjugated equine estrogen and medroxyprogesterone acetate can increase seizure frequency in menopausal women with epilepsy; this outcome may be an adverse effect of these neuroactive steroids on the epileptic female brain, which is already in a hormonally deprived state. To explore this possibility, more information about the neurophysiologic activity of medroxyprogesterone acetate is needed and alternatives to this specific HRT regimen should be considered for women with epilepsy.*

Relevant information for neurologists and epileptologists about the use of hormone replacement therapy (HRT) continues to emerge. A recent analysis of the risks and benefits of postmenopausal HRT once more provide some surprising results (1). This new analysis emerges against a body of information that caused a sea change in the outlook of both the medical community and the public toward the medical treatment of postmenopausal women. When the first results of the Women's Health Initiative (WHI) study (a large, double-blinded, placebo-controlled, randomized trial of hormone therapy in postmenopausal women) were published in 2002 (2), a

wave of shock reverberated through the women's health community, since the findings were contrary to those demonstrated by previous observational studies and to dogma prevalent at that time.

The specific findings of the 2002 clinical trial, which are considered to have employed the highest level of evidence-based methodology, differ depending on the hormone regimen used (i.e., estrogen only for hysterectomized women and combined estrogen/progestogen for women with an intact uterus). Within the estrogen-only hormone replacement group, significant increases were found for stroke (3), deep vein thrombosis (4), and gall bladder disease (resulting in a greater number of corrective procedures) (5); these risks (2,5,6), plus increases in breast cancer (7) and dementia, were found with combined estrogen/progestogen use in women over 65 years of age (8). Particularly counter to expectation was the fact that coronary heart disease (CHD), which was found to be associated with a lower risk of events in observational studies (9), did not bear out a reduction in risk in either arm of hormone therapy of the WHI study (10,11). Hip fracture and total fractures were reduced in both treatment arms (2,3), and colorectal cancer was decreased in the combined treatment arm beginning in the third year (2).

Between 1993 and 1998, the WHI trial enrolled 27,347 healthy postmenopausal women, ages 50 to 79 years, across 40 sites in the United States. Of the subjects, 10,739 had undergone a hysterectomy and, therefore, were randomized to 0.625 mg per day of conjugative equine estrogen (CEE) or placebo, and the 16,608 who had an intact uterus were randomized to 0.625 mg per day of CEE plus 2.5 mg per day of medroxyprogesterone acetate (MPA) or placebo (2). The study was stopped approximately 1 year before scheduled because of increased risks found during an interim analysis. Current treatment guidelines indicate that the therapy should be used only for the short-term treatment of moderate-to-severe symptoms, aiming for the lowest effective dose throughout treatment (12). The U.S. Food and Drug Administration (FDA) has added a black box warning to estrogen preparations, stating that they should not be used for the prevention of CHD, and a rewording of the indications that specifies that they should not be prescribed as a first-line therapy for prevention of osteoporosis (13). Per expert opinion, an ideal candidate for HRT is a woman 45 to 60 years of age with moderate-to-severe symptoms; however, she should not use hormone therapy for more than 3 years (14).

Since the publication of the first WHI results (2), several aspects of the findings have been debated. In particular, the dose and formulation of hormone therapy used in the WHI study have been scrutinized, as clinicians and researchers have asked

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whether lower doses of more simple hormonal compounds or naturally derived hormones would be safer. The formulations approved for this large trial were the form of hormone therapy for postmenopausal women most commonly prescribed at the time, which was one of the reasons they were selected for evaluation. Topical hormone formulations, lower hormone dose, and natural formulations may provide similar benefits but fewer risks; however, large, well-controlled trials designed to assess the safety of other hormone formulations compared with CEE and MPA are not available and are not likely to be forthcoming.

The study that recently reanalyzed the WHI trial (1) examined an aspect of the study design that has long raised questions for investigators and clinicians trying to interpret the results of the 2002 study (2). Specifically, can subjects spanning such a broad age range (50–79 years), and therefore broadly ranging in their health risks, be lumped together for analysis? The concern of the investigators of the 2007 study was that the discrepancy between observational studies and the 2002 clinical trial outcomes, especially regarding CHD, in part may be due to a differential effect of hormone therapy on the age-related, variable state of the underlying vasculature. Evidence to support a differential effect involves the theory that estrogen may delay the onset of the early stages of atherosclerosis, as might occur in younger women, but may be ineffective or trigger events in the presence of advanced atherosclerosis, which is more likely to be found in older women. The findings of this time-since-menopause and age-stratified analysis indicated that CHD risk was reduced in women taking HRT within the first 10 years of the onset of menopause (keeping in mind age at menopause closely correlates with age in general). However, there was a trend toward an escalated risk of CHD as the number of years increased from the onset of menopause; this trend did not meet the investigator's strict criteria for significance (1). A nonsignificant trend was also present for total mortality. Importantly for neurologists, stroke risk was elevated regardless of years since menopause: no trend for reduced risk in younger women or those closer to menopause was seen. Therefore, the risk of stroke with exogenous hormones, including oral contraceptives, remains clear. Furthermore, the 2007 report does not clarify whether the risk of dementia imparted by combined hormone therapy (previously analyzed in subjects 65 years of age and older [8]), if given in the years near to menopause, is associated with a lowered risk of developing dementia later in life. However, in a recent presentation at the American Academy of Neurology, a reanalysis of the WHI data, addressing just this point, found that women who had used hormones prior to the trial experienced significantly lower risks of Alzheimer's disease and all-cause dementia during WHI trials (15).

Treatments other than hormones for relief of menopausal symptoms are certainly needed; for example, women with a history of breast cancer cannot use hormone therapy. Symptomatic

relief of menopausal symptoms, in this patient population or other populations that are not candidates for hormone therapy, may be possible with transdermal clonidine, venlafaxine, fluoxetine, or paroxetine. Gabapentin, at 900 mg per day, also has been shown to improve hot flushes in women with breast cancer (16). The spectrum of the risks and benefits of hormone therapy use in postmenopausal women still is not completely clear. However, the current recommendation of short-term treatment of moderate-to-severe symptoms, aiming for the lowest effective dose, seems appropriately cautious, yet humane. The use of lower doses and topical hormonal formulations and non-hormonal treatments are reasonable alternatives to CEE and MPA, and more information on their safety and effectiveness is anticipated.

New information on HRT use in women with epilepsy raises further concerns for epileptologists and neurologists working with these patients. Investigators found that the standard HRT therapy, using CEE and MPA, may increase seizure frequency in a dose-related manner (17). The investigators also demonstrated that lamotrigine levels are reduced by HRT use, resulting in effects similar to those of reproductive hormones, which induce lamotrigine metabolism. This clinical trial was inspired by a previous study in which women reported, by questionnaire, that they had had seizure increase with HRT use (18). Results of both clinical studies prompt consideration of the neurophysiologic effects of the reproductive hormones used in HRT, which are neuroactive steroids, also termed *neurosteroids*.

Interestingly, although these two clinical reports have consistent outcomes of adverse effects on seizure, there are no supportive laboratory counterparts of these findings. Accordingly, ovariectomy in adult female rats (used as an analogous state to menopause) is associated with increased severity of seizure activity. Ovariectomized rats showed a significantly more rapid progression to status epilepticus compared with intact animals, using the pilocarpine model (19). In a similar experiment, using an NMDA seizure-induction model, ovariectomized rats had a significantly increased total seizure number and more severe hippocampal damage compared with age-matched intact female animals (20).

How does hormone replacement affect seizure activity in a rodent postmenopausal model? Again, contrary to the findings of the recent human studies, several experiments have shown an overall neuroprotective effect of estrogen and progesterone. In a kainate-induced model, estrogen pretreatment had no effect on seizure severity but significantly decreased "spread," neuronal loss, and mortality in ovariectomized rats compared with ovariectomized rats without pretreatment. Progesterone pretreatment in this model had a slightly different profile of effects; it decreased seizure severity and hippocampal damage (21). Using the NMDA-induced model, estrogen pretreatment

decreased total seizure number in ovariectomized rats compared with ovariectomized rats without pretreatment; and in fact, estrogen replacement restored seizure number to that of the intact state (20). In the lithium-pilocarpine model of status epilepticus, estrogen pretreatment is neuroprotective in ovariectomized rats compared with oil-treated ovariectomized controls (22).

There are problems with extrapolating these laboratory results to the effects of HRT on menopausal women with epilepsy, and several factors may explain the seeming difference in the findings. First, ovariectomized rats may not have an analogous hormonal brain milieu to naturally menopausal women. The rats were likely not in surgical postmenopause for a long period of time prior to the experiments; however, the postmenopausal women had years to develop changes to neurons and glia following hormone withdrawal. Second, the doses of HRT used by menopausal women are actually relatively higher than the doses used in these laboratory experiments. Finally, and probably most important, the human studies used a synthetic progestin, MPA, about which little is known regarding the effects on brain excitability. It is widely accepted that estrogen generally facilitates seizure activity, while progesterone (through the action of its reduced metabolite, allopregnanolone) has anticonvulsant properties (23). However, MPA clearly has a different profile of activity in the brain and is not neuroprotective in rodents (24). In one study of ovariectomized rats with and without estrogen replacement, the effect of progesterone versus MPA pretreatment on kainate-induced seizures was evaluated. Both progesterone and MPA blocked the neuroprotective effects of estrogen in these experiments (a result differing from previous experiments for progesterone), and seizure severity was somewhat but not significantly worse in the MPA-treated group (25). Obviously, there is more to learn about the effects of MPA in the brain, but it may be the bad actor in terms of seizure worsening.

Since progesterone in its natural form is readily available, it is a reasonable option for the progestin component when HRT is needed for women with epilepsy, since there is evidence that it has active anticonvulsant properties (26). HRT remains a clinical dilemma and options outside of the standard HRT regimen must be considered and investigated, such as a simplified estrogen compound, 17- $\beta$ -estradiol, and natural progesterone in the FDA-approved form of Prometrium. Evidence for gabapentin as beneficial in reducing hot flashes (16) raises the possibility that other antiseizure medications also may be of benefit for menopausal symptoms and may be worthy of further investigation.

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