

## MORE IS NOT BETTER: HORMONES FOR MENOPAUSAL WOMEN WITH EPILEPSY?

### Hormone Replacement Therapy in Women with Epilepsy: A Randomized, Double-Blind, Placebo-Controlled Study.

Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, Labar DR, Hauser WA. *Epilepsia* 2006;47(9):1447–1451. **PURPOSE:** Previous reports have suggested that hormone replacement therapy (HRT) could increase seizure activity in women with epilepsy. We sought to determine whether adding HRT to the medication regimen of postmenopausal women with epilepsy was associated with an increase in seizure frequency. **METHODS:** This was a randomized, double-blind, placebo-controlled trial of the effect of HRT on seizure frequency in postmenopausal women with epilepsy, taking stable doses of antiepileptic drugs (AEDs), and within 10 years of their last menses. After a 3-month prospective baseline, subjects were randomized to placebo, Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or CEE/MPA) daily, or double-dose CEE/MPA daily for a 3-month treatment period. **RESULTS:** Twenty-one subjects were randomized after completing baseline. The subjects' ages ranged from 45 to 62 years (mean, 53 years; SD,  $\pm 5$ ), and the number of AEDs used ranged from none to three (median, one). Five (71%) of seven subjects taking double-dose CEE/MPA had a worsening seizure frequency of at least one seizure type, compared with four (50%) of eight taking single-dose CEE/MPA and one (17%) of six taking placebo ( $p = 0.05$ ). An increase in seizure frequency of the subject's most severe seizure type was associated with increasing CEE/MPA dose ( $p = 0.008$ ). An increase in complex partial seizure frequency also was associated with increasing CEE/MPA dose ( $p = 0.05$ ). Two subjects taking lamotrigine had a decrease in lamotrigine levels of 25–30% while taking CEE/MPA. **CONCLUSIONS:** CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. CEE/MPA may decrease lamotrigine levels.

### COMMENTARY

The possible effect of reproductive hormones on seizures was recognized over 2,000 years ago. Clinical observations of a relationship between the menstrual cycle and seizure occurrence in women of reproductive age were cited in medical journals as early as the turn of the 19th century. In 1942, experimental work in rats demonstrated the anticonvulsant properties of progesterone (1). Since then, many animal studies have confirmed the effects of progestins and estrogens on seizure threshold and epileptogenesis. Many cellular and molecular mechanisms contribute to the changes in brain excitability mediated by these hormones. Although an oversimplification, studies generally support the finding that the estrogens have proconvulsant properties and progestins have anticonvulsant properties. The three principal circulating estrogens are estrone, estradiol, and estriol. The progestins include progesterone and progesterone derivatives. Dihydroprogesterone is the immediate 5- $\alpha$ -reduced metabolite of progesterone and is further metabolized to allopregnanolone (3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one), a GABA<sub>A</sub>-receptor-modulating neurosteroid (1,2). Much of the

antiseizure effect of progesterone may be due to the conversion to this metabolite, and synthetic progestins are not converted to this or other known neurosteroids.

The findings of experimental studies parallel nicely the clinical observation that seizure frequency is increased in many women with epilepsy in association with certain phases of the menstrual cycle (catamenial epilepsy). In women with localization-related epilepsy, 39% demonstrate a catamenial pattern (3). The patterns described correlate with phases of relatively high estrogen/progesterone ratios: perimenstrual and periovulation in normal menstrual cycles and throughout the inadequate luteal phase in anovulatory cycles. Additionally, an open-label treatment trial with supplemental progesterone in women ( $n = 25$ ) demonstrated a 54% decline in the average frequency of daily complex partial seizures ( $p < 0.01$ ) and a 58% decline in secondarily generalized tonic-clonic seizures ( $p < 0.02$ ) (4). Nonetheless, no Class I evidence is available for the benefits of progesterone use in women with epilepsy during the reproductive years, although a multicenter, double-blind, randomized, placebo-controlled trial is currently underway (3).

Understanding the effects of endogenous and exogenous reproductive hormones on seizure control during the perimenopausal transition and postmenopause has been more elusive. Perimenopause is marked by erratic and frequently high estrogen levels, while postmenopause is characterized by stable,

low estrogen levels (5). Studies in women during these later life stages are very limited. Previously, Harden et al. performed a retrospective questionnaire study of perimenopausal and postmenopausal women with epilepsy ( $n = 81$ ) (6). Their findings suggest that seizure frequency can increase with perimenopause and can improve once the menopausal transition is complete, especially for women who had a catamenial pattern to her seizures. In the postmenopausal group, hormone replacement therapy (HRT) was significantly associated with an increase in seizures.

The present study by Harden et al. explores the effects of the combination of conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA) at two different doses, using a design that meets criteria for Class I evidence (i.e., double-blind, placebo-controlled, randomized trial). Several factors distinctive to the study design may have enhanced the likelihood of a positive finding regarding the effect of the combination hormonal treatment on seizure frequency. The authors astutely remark that postmenopausal women may be more susceptible to the effects of exogenous hormones on seizures, given that their hormonal milieu is one of low and stable estrogen and progesterone levels. Estrone is the primary estrogen after menopause, with its main source from subcutaneous fat. Each of the estrogens has distinct biological actions, although individual effects on seizure frequency are unknown. Similarly, the various equine estrogens are likely to have distinct actions from physiologic forms of estrogen in women, and the complex mixture of CEE extracted from horses includes androgens and progestins (1). CEE/MPA was commonly used as hormone replacement therapy at the time this trial was initiated. Moreover, the investigators utilized an elegant approach of randomizing a third of the patients to double-dose CEE/MPA, which was a common prescription dose for menopausal women who did not have symptom relief with single-dose CEE/MPA.

The Harden et al. trial was ended early because of results from the Women's Health Initiative study ( $n = 16,608$ ). It was a shock to the medical community that not only was HRT not a useful preventive medicine tool, but it could actually increase the risk for invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism (7). The Harden et al. study initially predicted that 120 women, 40 in each treatment arm, would be needed for a power of 80% and a two-tailed significance level of 0.05. Because recruitment had to be terminated, only six subjects were randomized to the placebo group, eight to the single-dose CEE/MPA group, and seven to the double-dose CEE/MPA group. The groups were similar by other characteristics, except that the frequency of simple partial seizures was higher in the double-dose CEE/MPA group, which may have influenced the outcome data. What is truly remarkable is that despite discontinuing the study prematurely and limited enrollment, the results were still positive and even were able to demonstrate statistical significance for a dose-related response for CEE/MPA and increased seizure frequency.

After the report of the Women's Health Initiative study, the prescriptions for oral HRT in the United States decreased by approximately one-third by June 2003, from their peak in 2000. However, 59.6 million prescriptions for these products were still dispensed in 2003, another 7.5 million dispensed for transdermal products, and an additional 8.9 million for oral progestins (8). Although long-term HRT is no longer recommended for health maintenance, short-term HRT is still prescribed for the management of menopausal symptoms, such as hot flashes, insomnia, and vaginal atrophy (9). Thus, the findings of the Harden et al. study remain clinically relevant. Updated results of dispensing practices are not yet available; however, the search for products for menopausal symptom relief continues and has moved firmly into the alternative therapy arena (10,11). The possible effects of various alternative agents on seizure threshold are not known.

Although the Harden et al. trial cautions against use of CEE/MPA in postmenopausal women with epilepsy, it cannot differentiate between the possible effects of the many different equine estrogens, equine androgens, or even the equine progestins and synthetic progestin MPA. In addition, a possible confounder is that in the two lamotrigine-treated patients, lamotrigine levels decreased by 25% to 33% with single-dose CEE/MPA. No changes were observed in other antiepileptic drug levels, but the number of subjects on each AED was small. A possible alternative to the CEE/MPA combination medicine may be one that uses a more pure human-like estrogen derivative, such as estradiol or possibly estrone, and natural progesterone, which can be metabolized to the beneficial neurosteroid allopregnanolone.

The early termination of this trial resulted in limited enrollment and may have reduced it to a Class II study, as there were a high percentage of subjects who discontinued, many subjects who were evaluated after just 30 to 60 days, a higher number of simple partial seizures in the double-dose group, and comparisons by seizure-frequency strata could not be performed, as originally planned. The investigators state that the seizure frequency increases were mild, but details were not provided; any increase in daily seizure rate from baseline was counted as a positive response. It would have been helpful if the authors had reported on the magnitude of seizure increases, as it could help put their findings into the context of everyday treatment decisions and patient counseling.

Nonetheless, having Class I or Class II evidence from a treatment trial assessing the influence of reproductive hormones on seizures in humans is unique at this point in time. These findings further the understanding of the impact of hormones on seizure control in women with epilepsy, and the principles learned can be extended to other life epochs, including puberty, menstrual cycles, pregnancy, and perimenopause. Future studies on whether other estrogens with natural progesterone could

circumvent the risk for increased seizures would be beneficial for postmenopausal women with epilepsy.

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## References

- Scharfman HE, MacLusky NJ. The influence of gonadal hormones on neuronal excitability, seizures, and epilepsy in the female. *Epilepsia* 2006;47:1423–1440.
- Smith SS, Woolley CS. Cellular and molecular effects of steroid hormones on CNS excitability. *Cleve Clin J Med* 2004;71(suppl 2):S4–S10.
- Herzog AG, Harden CL, Liporace J, Pennell P, Schomer DL, Sperling M, Fowler K, Nikolov B, Shuman S, Newman M. Frequency of catamenial seizure exacerbation in women with localization-related epilepsy. *Ann Neurol* 2004;56:431–434.
- Herzog AG. Progesterone therapy in women with complex partial and secondary generalized seizures. *Neurology* 1995;45:1660–1662.
- Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocr Rev* 1998;19:397–428.
- Harden CL, Pulver MC, Ravdin L, Jacobs AR. The effect of menopause and perimenopause on the course of epilepsy. *Epilepsia* 1999;40:1402–1407.
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–333.
- Wysowski DK, Governale LA. Use of menopausal hormones in the United States, 1992 through June, 2003. *Pharmacoepidemiol Drug Saf* 2005;14:171–176.
- Lobo RA, Belisle S, Creasman WT, Frankel NR, Goodman NE, Hall JE, Ivey SL, Kingsberg S, Langer R, Lehman R, McArthur DB, Montgomery-Rice V, Notelovitz M, Packin GS, Rebar RW, Rousseau M, Schenken RS, Schneider DL, Sherif K, Wysocki S. Should symptomatic menopausal women be offered hormone therapy? *Med Gen Med* 2006;8:1.
- Ma J, Drieling R, Stafford RS. US women desire greater professional guidance on hormone and alternative therapies for menopause symptom management. *Menopause* 2006;13:506–516.
- Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Gultinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med* 2006;145:869–879.