

Treatment of Women with Epilepsy in Perimenopause and Menopause

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With the attainment of midlife by the baby boomer generation, it becomes important to understand and manage the impact of accompanying reproductive hormone changes on epilepsy, and to review what is known about some ways the menopausal process may differ between women with epilepsy and women in the general population.

Reproductive steroids have neuroactive properties that modulate neuronal excitability and seizure occurrence. The absolute and relative levels of neuroactive reproductive steroids change throughout reproductive life, especially in relation to adrenarche, menarche, phases of the menstrual cycle, pregnancy and menopause. Menopause has been defined by the World Health Organization¹ and the Stages of Reproductive Aging Workshop (STRAW) working group² as “the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy, or radiation.” Menopause is recognized after a

woman has been amenorrheic for 12 consecutive months. It is usually associated with a serum follicle-stimulating hormone (FSH) level ≥ 50 mIU/mL. The development of natural menopause, however, involves a process that takes place over a protracted period of years, usually during midlife, and consists of a phase of changing menstrual cycle intervals (menopausal transition) and then a 12-month phase of amenorrhea (perimenopause). In this review, the term “perimenopause” will subsume both of these phases since most of the existing neurological investigations and reviews in the medical literature have not drawn a

distinction. The menstrual cycle changes are associated with a decline in reproductive steroid levels as well as changes in the ratios of these steroids. Specifically, serum levels of estrogen and progesterone decrease during perimenopause but the ratio of estrogen to progesterone increases with the development of anovulation until ovarian production of these hormones ceases. Knowledge of the neuroactive properties of reproductive steroids and the changes in reproductive steroid levels during a woman’s lifespan may be important to a more comprehensive understanding of the pathophysiology and treatment of women with epilepsy.

Reproductive Hormonal Effects on Epilepsy

Reproductive steroids have neuroactive properties that can affect neuronal excitability and seizure occurrence. The neuroactive properties of estradiol and progesterone follow.

Estradiol. Estradiol acts at the neuronal membrane to augment N-methyl-D-aspartate-mediated

glutamate receptor activity.^{3,4} This increases the excitability of neurons and facilitates repetitive firing, as has been demonstrated for hippocampal CA1 pyramidal neurons in response to Schaffer collateral stimulation.² Estradiol can also act intracellularly via estrogen receptor-mediated, genomically dependent mechanisms to lessen inhibitory neurotransmission by reducing the activity of glutamic acid decarboxylase, which results in decreased GABA synthesis.⁵

In adult experimental animals, the thresholds of limbic seizures in female rats fluctuate during the estrous cycle inversely to estradiol levels.⁶ Physiologic doses of estradiol activate spike discharges^{7,8} and lower the thresholds of seizures induced by electroshock, kindling, pentylenetetrazol, kainic acid, ethyl chloride, and other agents and procedures.⁷⁻⁹ The increase is seen within a minute of application to suggest a direct membrane rather than a genomic effect, and is more dramatic in animals with pre-existent cortical lesions.⁸

Clinically, Logothetis and colleagues¹⁰ showed that intravenously administered conjugated estrogen clearly activated epileptiform discharges in 11 of 16 women, and was associated with clinical seizures in four.

Progesterone. Some reduced progesterone metabolites, most specifically tetrahydroprogesterone (allopregnanolone-AP), exert direct membrane-mediated inhibitory effects by potentiating GABA-mediated chloride conductance.¹¹⁻¹³ AP acts as a positive allosteric modulator of the GABA_A receptor, inter-

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acting with a steroid-specific site near the synaptic receptor to facilitate chloride (Cl⁻) channel opening and prolong the inhibitory action of GABA on neurons.¹¹⁻¹³ It is likely that AP exerts tonic inhibition at an extrasynaptic GABA receptor site that has a different subunit composition (δ subunits) from the synaptic receptor where benzodiazepines are believed to act (γ subunits).¹⁴ Rapid withdrawal of progesterone makes the synaptic GABA receptor insensitive to the application of benzodiazepine, likely related to the loss of γ subunit-containing synaptic GABA_A receptors.¹⁴ This effect can be blocked by inhibiting the formation of the alpha 4 subunit of the GABA receptor, which is usually paired with the δ subunit in the extrasynaptic progesterone responsive receptor.^{14,15} The parent steroid, progesterone, enhances GABA-induced Cl⁻ currents only weakly and only in high concentrations.^{11,12} Plasma and brain levels of AP parallel those of progesterone in rats.^{11,12} In normal women, plasma levels of AP correlate with progesterone levels during the menstrual cycle and pregnancy.^{11,12} However,

brain activity of progesterone and AP is not dependent solely on ovarian and adrenal production, as they are both synthesized *de novo* in the brain, mostly by glial cells.¹⁶ Their synthesis is region-specific and includes the cortex and the hippocampus.¹⁶

In most adult female animal models, progesterone depresses neuronal firing and lessens spontaneous and induced epileptiform discharges.⁷⁻¹⁵ It retards kindling and decreases seizure occurrence.⁷⁻¹⁵

Backstrom et al¹⁷ found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was associated with a significant decrease in interictal spike frequency in four of seven women with partial epilepsy. Progesterone (ie, natural progesterone as opposed to synthetic progestins) has been used effectively in oral form in open-label trials to lessen substantially and significantly seizure occurrence in women with catamenial epilepsy.¹⁸⁻²⁰

Catamenial Epilepsy

Seizures do not occur randomly in the majority of men and women with epilepsy;¹⁹ they tend to cluster in over 50% of cases.²¹ Seizure clusters may, in turn, occur with temporal rhythmicity in a significant proportion of men (29%) and women (35%) with epilepsy.²¹ In women, seizures may cluster in relation to the menstrual cycle, commonly known as catamenial epilepsy.²²⁻²⁵ This may be attributable to the neuroactive properties of steroid hormones and the cyclic variation of steroid hormone serum levels.

Physiologic endocrine secretion during the menstrual cycle influences the occurrence of seizures. In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol/progesterone ratio.²² This ratio is highest during the days prior to ovulation and menstruation, and is lowest during the early and mid-luteal phase.²² The premenstrual exacerbation of seizures has also been attributed to the withdrawal of the antiseizure effects of progesterone.²² Midcycle exacerbations may be due to the preovulatory surge of estrogen unaccompanied by any rise in progesterone until ovulation occurs.²² Seizures are least common during the mid-luteal phase when progesterone levels are highest.²² Inadequate luteal phase refers to subnormal progesterone secretion during the second half of the cycle, regardless of whether ovulation does or does not occur. The resulting elevation in the serum estradiol/progesterone ratio may promote increased seizure frequency throughout the second half of these cycles.^{22,26}

Herzog et al^{24,25} have presented statistical evidence to support the concept of catamenial epilepsy and the existence of at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle (Figure): 1) perimenstrual (C1: days -3 to 3) and 2) periovulatory (C2: days 10 to -13) in normal cycles and 3) luteal (C3: days 10 to 3) in inadequate luteal phase cycles. In these cycles, day 1 is the first day of menstrual flow and ovulation is presumed to occur 14 days before the subsequent onset of menses (day

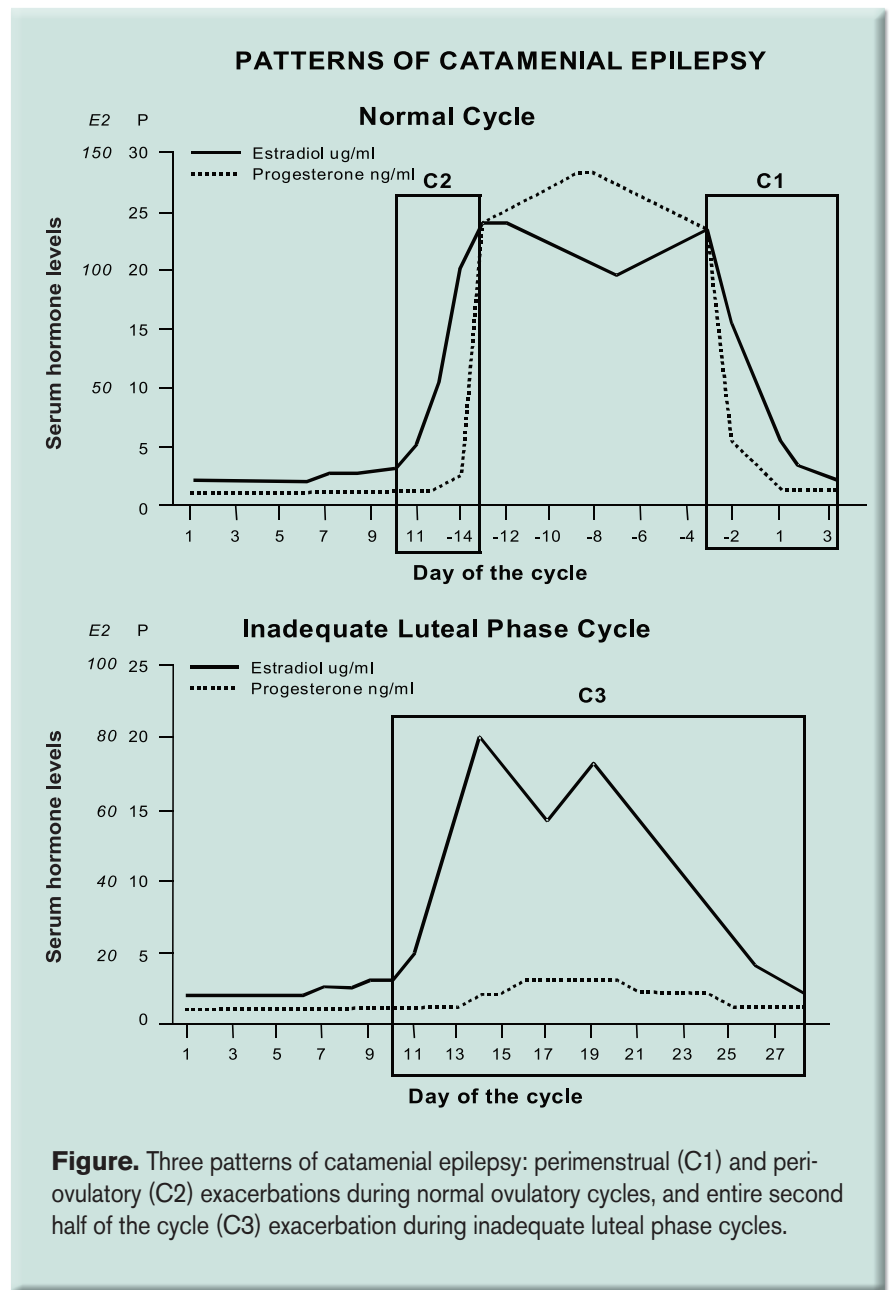


Figure. Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles, and entire second half of the cycle (C3) exacerbation during inadequate luteal phase cycles.

-14). These three patterns can be demonstrated simply by charting menses and seizures, and obtaining a midluteal phase serum progesterone level to distinguish between normal and inadequate luteal phase cycles. Some level of catamenial seizure exacerbation was demonstrated in 71.4% of 184 subjects, with 34.7% showing a twofold or

greater increase in seizure frequency during the phase of exacerbation.²⁴

Epilepsy and Menopause

The age at which women experience menopause may be influenced by epilepsy.²⁷⁻²⁹ In an investigation of 68 naturally menopausal women with epilepsy, high lifetime seizure frequency and the use of enzyme-

inducing antiepileptic drugs were associated with the earlier development of menopause (ie, 3-4 years earlier than the average age of 51.9 years in the general population).²⁹

Historically, there have been differences of opinion regarding the effects of menopause on epilepsy. In 1907, Turner³⁰ stated that while menopause generally has little influence on epileptic attacks, there are a few cases in which seizures may become arrested. The beneficial results of ovariectomy in animal experiments were subsequently cited in support of the notion that clinical improvement occurs at the time of menopause.³¹ Other reports, however, have described exacerbation of seizures at the time of the climacteric.³² It is important to be aware that the term “menopause” refers to a complex process and a variable end point that may differ significantly among individuals. Early during menopause, for example, anovulatory cycles may develop and lead to increased estrogen-to-progesterone ratios, which would be expected to promote the occurrence of seizures. At the end of the process, ovarian estrogen production may become essentially undetectable and potentially lead to a beneficial effect. Adrenal steroid secretion, however, continues beyond menopause. Some adrenal androgens are converted to estrogens by adipose tissue. The resulting estrogen-to-androgen ratio may exert a significant influence on seizures in the absence of gonadal secretion, and may vary in relation to body mass. Prospective investigations to correlate changes in seizure and brain wave patterns with reproduc-

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tive and adrenal endocrine profiles during menopause need to be carried out in order to clarify these issues.

In a retrospective questionnaire study of 61 menopausal women by Abbasi et al,³³ 49 had established epilepsy before the onset of menopause. Of these, 20 (41%) reported worsening of their seizures with menopause, 13 (27%) noted improvement, and 16 (33%) described no changes. In another questionnaire study, Harden et al³⁴ found that the majority of subjects (39 perimenopausal and 42 menopausal) who reported a catamenial pattern of seizure exacerbation during their reproductive years experienced an increase in seizure frequency during perimenopause, but a decrease in seizures 1 year or longer after menopause. This finding is consistent with the notion that hormonally sensitive seizures may be exacerbated by the increase in estrogen/progesterone ratio associated with perimenopausal anovulation, and that seizures may decrease when estrogen levels are very low menopausally.

A recent randomized, double-blind, placebo-controlled trial to assess the effect of hormone therapy—using conjugated estrogen and

medroxyprogesterone—on seizure frequency in menopausal women with epilepsy showed a significant dose-related increase in seizure frequency for the most severe seizure type (decreasing order of severity: generalized convulsive > complex partial > simple partial).³⁵

Hormonal Therapy

If neuroactive reproductive steroids contribute to seizure occurrence, they may also have a role in the treatment of epilepsy during perimenopause. The development of anovulatory or inadequate luteal phase cycles during perimenopause results in a higher serum estradiol-to-progesterone ratio; that is, a higher neuroexcitatory-to-neuroinhibitory ratio. Treatment strategies may, therefore, involve the supplementation of progesterone or the elimination of estrogen. The latter can be accomplished by the reversible suppression of ovarian endocrine function using gonadotropin-releasing hormone (GnRH) analogue and then adding back a stable, balanced estradiol and progesterone supplement. To date, there is no FDA-approved hormonal treatment for epilepsy or class 1 evidence to support hormonal treatment, although a large multicenter, randomized, double-blind, placebo-controlled trial of cyclic progesterone supplement is under way.

Progesterone. Progesterone therapy benefits some women with catamenial epilepsy¹⁸⁻²⁰ and has the potential for doing so during perimenopause as well. In one open-label investigation of women who had inadequate luteal phase cycles with catamenial exacerbation of

intractable complex partial seizures, six of eight women experienced improved seizure control with a 68% decline in average monthly seizure frequency over 3 months for the whole group.¹⁸ In a subsequent open trial of supplemental cyclic progesterone versus the optimal antiepileptic drug regimen alone in 25 women (14 with inadequate luteal phase or anovulatory cycles and 11 with normal cycles and perimenstrual seizure exacerbation), 18 (72%) experienced fewer seizures, with an overall average monthly decline of 54% for complex partial and 58% for secondary generalized seizures over 3 months.¹⁹ Progesterone was more efficacious when administered during the entire second half of the cycle, rather than just premenstrually, and then tapered and discontinued gradually over 3 or 4 days at the end of the cycle.¹⁸ At 3 years, examination of the average daily seizure frequency per patient showed that the 15 women who remained on cyclic progesterone therapy and their original antiepileptic drugs continued to experience improved seizure control in comparison to their own baselines (Table, 3-year follow-up).²⁰ Three women were entirely seizure-free, four had total seizure reductions of 75%-99%, and eight had reductions of 50%-74%.

Progesterone is available as an extract of soy and yams in lozenge and micronized oral capsule forms in variable dosages ranging from 25 mg to 200 mg, and should be administered 3 times daily because of its brief half-life (approximately 6 hours).¹⁸⁻²⁰ The daily regimen to achieve physiologic luteal range serum levels measured 4 hours after

Table. Adjunctive Cyclic Progesterin Therapy

	Medroxy-progesterone (Mattson 1984) ²⁹	Progesterone Suppositories (Herzog 1986) ¹⁸	Progesterone Lozenges (Herzog 1995) ¹⁹	Progesterone Lozenges (Herzog 1999 3-yr follow-up) ²⁰
Regimen	5-10 mg q.d. days 15-28 of cycle	100-200 mg t.i.d. days 15-28 of cycle	100-200 mg t.i.d. days 15-28 of cycle	100-200 mg t.i.d. days 15-28 of cycle
Assessment	@ 3 months	@ 3 months	@ 3 months	@ 3 years
Subjects	24	8	25	15 of original 25
Number/percent improved	10 (42%)	6 (75%)	18 (72%)	15 (100% of 15 followed for 3 years, 60% of initial 25)
Seizure frequency	-10%	-68%*	-54% [†] CPS -58%* SGMS	-62% [†] CPS -74% [†] SGMS

* Treatment comparison with baseline seizure frequency $P < .05$.
[†] Treatment comparison with baseline seizure frequency $P < .01$.
 CPS = complex partial seizures; SGMS=secondary generalized motor seizures.

administration ranges from 50 mg to 200 mg, taken 3 times daily, with the usual optimal daily dose ranging from 300 mg to 600 mg.¹⁸⁻²⁰ The maintenance dosage and regimen should be individualized and based on a combination of clinical response and serum progesterone levels between 5 and 30 ng/mL. Progesterone should always be tapered rather than abruptly discontinued at the end of the cycle. Progesterone should be avoided during or in anticipation of pregnancy (unless used specifically as part of a fertility program under the supervision of a gynecologist) and in the absence of adequate birth control measures. It should also be used cautiously in the presence of undiagnosed breast lumps since synthetic

progesterin use has been associated with mammary nodule development and, in high doses, malignancy in experimental animals.

Adverse effects occur with overdosage, and include sedation, emotional depression and asthenia.¹⁸⁻²⁰ Constipation and exacerbation of asthma are observed as well, although rarely. Progesterone use may also occasionally be associated with breast tenderness, weight gain and irregular vaginal bleeding. The vehicle used to dissolve progesterone for suppository use may rarely be responsible for the development of an allergic rash. Discontinuation of the hormone or lowering of the dosage resolves these side effects.¹⁸⁻²⁰

Drug interactions are an important consideration. Higher progester-

terone dosages may be required to achieve luteal range levels in women who take enzyme-inducing antiepileptic drugs³⁶ such as phenobarbital, carbamazepine or phenytoin. Progesterone is not known to have any substantial systematic effect on antiepileptic drug levels, unlike estrogen, which is known to affect glucuronidation, and the serum level of lamotrigine³⁷ and, possibly, valproate.³⁸

Progestin. Parenteral depomedroxyprogesterone (Depo MPA) may lower seizure frequency when given in a dose sufficient to induce amenorrhea.^{38,39} In one open-label study of 14 women with refractory partial seizures and normal ovulatory cycles, parenteral depomedroxyprogesterone administration in doses large enough to induce amenorrhea (ie, 120-150 mg every 6-12 weeks) resulted in a 39% seizure reduction.³⁹ It was unclear whether the effect was due to direct anticonvulsant activity of medroxyprogesterone or to the hormonal consequences of the induced amenorrhea. One patient who had absence rather than partial seizures did not improve. Side effects included those encountered with progesterone; however, depot administration is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding and a lengthy delay (6 to 12 months) in the return of regular ovulatory cycles.³⁹ Long-term hypoestrogenic effects on cardiovascular and emotional status need to be considered with chronic use. Bone density is generally maintained. Perhaps the greatest difficulty arising out of Depo MPA administration is that

Menopausal use of progesterone may, therefore, be preferred to the more standard synthetic medroxyprogesterone.

following discontinuation it may take months—or sometimes even a couple years—to eliminate stores of the hormone. During this time, the persistent partial suppression of the hypothalamopituitary axis results in anovulatory cycles with concomitantly high estradiol-to-progesterone ratios and associated increases in seizure frequencies.

Oral synthetic progestins administered cyclically or continuously have not proven to be an effective therapy for seizures in clinical investigations,^{39,41} although individual successes with continuous daily oral use of norethistrone and combination pills have been reported.⁴² Menopausal use of progesterone may, therefore, be preferred to the more standard synthetic medroxyprogesterone.

GnRH analogue. Intractable seizures in the setting of anovulatory cycles during perimenopause may be treated via reversible elimination of the menstrual cycle using GnRH analogue, especially in the setting of catamenial seizure exacerbation and inadequate response to cyclic progesterone therapy. Bauer et al⁴³ used triptorelin, a synthetic GnRH analogue, in a con-

trolled-release depot form (3.75 mg) given intramuscularly every 4 weeks for an average of 11.8 months in 10 women (ages 20-50) with catamenial seizures intractable to high therapeutic doses of carbamazepine, diphenylhydantoin, phenobarbital and valproic acid (monotherapy or combined). They remained on a stable dose of the anticonvulsant throughout the period of treatment with triptorelin. The authors reported that three patients became seizure-free, four showed a decrease in seizure frequency of up to 50%, one experienced shortened duration of seizures, and two experienced no therapeutic effect. These results were attained within the first 2 months of starting triptorelin. The study was not controlled and longer follow-up was not available for some of the patients. Serum luteinizing hormone (LH) and estradiol were measured in one patient before and during the second month of triptorelin treatment; as expected, marked inhibition of LH and estradiol production was seen. All of the women became amenorrheic. Eight of the ten patients experienced hot flashes, headache or weight gain.

Haider and Barnett⁴⁴ reported on their use of subcutaneous goserelin (3.6 mg) administered every 4 weeks to a 41-year-old woman who had experienced frequent catamenial status epilepticus despite therapeutic anticonvulsant drug levels and a trial of levonorgestrel/ethinyl estradiol. They reported a decrease in frequency, from 10 to 3 hospital admissions for status epilepticus over a similar period.

GnRH analogues basically create a medical oophorectomy. Common

side effects are menopausal symptoms, such as flushing, sweats, vaginal dryness and dyspareunia. Long-term risks include osteoporosis. These side effects and risks can be managed with the use of balanced estradiol and progesterone supplementation as well as the use of bisphosphonates. Although neither Bauer et al⁴³ nor Haider and Barnett⁴⁴ reported exacerbation of seizures with GnRH analogues, Herzog⁴⁵ found that during the first month, when there is an initial stimulation of estrogen before its production is inhibited, some women experienced such a marked exacerbation of their seizures and auras that they could not tolerate further use of GnRH analogue. This can be largely eliminated with the use of progesterone supplementation during the first 2-3 weeks. Following the total suppression of estrogen secretion after these early weeks, low doses of estrogen can sometimes be added back cautiously along with the progesterone with continued good control of seizures. The proconvulsant property of estrogen may be outweighed by the proconvulsant effect of sleep disruption related to menopausal symptoms. Some women, however, may show remarkable seizure sensitivity to even tiny amounts (eg, low doses of estradiol lotion) of estrogen.

Summary and Conclusions

Reproductive steroids have neuroactive properties that can modulate neuronal excitability and seizure occurrence. In most seizure models, estradiol is neuroexcitatory and lowers seizure thresholds; progesterone is neuroinhibitory and raises

Potential benefits need to be weighed against potential risks of hormone use at any age, perimenopausally as well as postmenopausally.

seizure thresholds. Although perimenopause is associated with a decline in serum estradiol and progesterone levels, the perimenopausal development of anovulation is associated with an increase in estradiol-to-progesterone ratios that can increase neuronal excitability and exacerbate seizures. Perimenopause is associated with increased seizure frequency, especially in women who have a past history of catamenial seizure exacerbation (catamenial epilepsy), which would imply hormonal sensitivity.

There is a rational scientific basis for the use of reproductive hormonal treatment of epilepsy. Molecular biological, neuronal, experimental animal and clinical evidence shows that steroid hormones have neuroactive properties that modulate kindling of epilepsy and seizure occurrence. Preliminary clinical trials of hormonal therapy show promise of efficacy. Hormonal therapy may also be important for comprehensive management of menopausal symptoms, including emotional as well as physical changes that may occur dur-

ing perimenopause and menopause. Potential benefits need to be weighed against potential risks of hormone use at any age, perimenopausally as well as postmenopausally.

While there is limited class I evidence to guide us in the use of reproductive hormones in women with epilepsy, preclinical evidence and clinical experience raise considerations for the use of cyclic progesterone supplementation perimenopausally to balance the epileptogenic effects of unopposed estrogen, which characterize the anovulatory cycles of perimenopause. This may be particularly important in women who have had a history of catamenial seizure exacerbation during their reproductive years. Menopausally, perhaps especially after surgical menopause, there may be reason to consider estrogen supplementation in some select cases; specifically, when menopause is accompanied by vegetative (atypical) depression that is refractory to standard psychotropic interventions, when there is an unusual decline in verbal memory and cognitive function, and when such supplementation is indicated for short-term distressing vasoreactive symptoms. Administration of estrogen should be accompanied by natural progesterone to minimize seizure risk. Risks for cardiovascular disease and dementia may be more favorable for the menopausal cohort that is started on HT between 50 and 59 years of age, as compared with older women.^{46,47} ■

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This article includes discussion of off-label use of medications.

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