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Seizure threshold, hormones and anti-epileptic drugs

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ABSTRACT

The concept of seizure threshold holds that everyone has a certain balance between excitatory and inhibitory forces in the brain. A low seizure threshold makes it easier for epilepsy to develop and easier for someone to elicit single seizure. The opposing effects of estrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold have been noted in animal and human studies. Estrogen has been shown to lower the seizure threshold. In contrast to estrogen, several studies have confirmed the anticonvulsive effects of progesterone and its metabolite. Anti-epileptic drugs (AEDs) are used to prevent or interrupt seizures. Limitation of sustained repetitive neuronal firing via blockade of voltage-dependent sodium channels, enhancement of GABA-mediated inhibition, and blockade of glutamatergic excitatory neurotransmission are the mechanisms of anti-epileptic drugs in preventing seizures. AEDs that induce hepatic cytochrome (CY) P450 enzymes can increase the metabolism of sex hormones and make hormonal contraception ineffective. In addition, AEDs may even increase seizure frequency or severity or change the seizure type.

Keywords: Seizure threshold, hormones, anti-epileptic drugs, proconvulsant, anticonvulsant

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INTRODUCTION

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have come to consensus definitions for the terms epileptic seizure and epilepsy. An epileptic seizure is a transient occurrence of signs/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.[1]

Physiologically, epilepsy is defined as a disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability. There is now clear evidence that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures. Both the enhanced excitability of the immature brain compared with mature brain and the unique pathologic consequences of seizures are related

to the sequential development and expression of essential signaling pathways. Although the immature brain is less vulnerable than the mature brain to seizure-induced cell death, seizures in the developing brain can result in irreversible alterations in neuronal connectivity. Developing novel strategies to treat and avert the consequences of seizures in children will require further understanding of the unique mechanisms of seizure initiation and propagation in the immature brain.[2]

Epilepsy is no more prevalent in women than in men but there are experimental data from animals, and observational studies in humans, which show that seizures can be influenced by "female" hormones.[3] Seizures patterns are often related to the reproductive cycles of a woman with epilepsy. Seizures are influenced by changes in hormone levels, which occur during the menstrual cycle and throughout the reproductive life of women with epilepsy. Establishing on early accurate diagnosis and initiating appropriate medical treatment may decrease seizure recurrence, reduce the number of anti-epileptic drug (AED) trial, and minimize the impact of seizures on the patient's quality of life.[4]

The importance of the following description is to disclose the relationship between seizure threshold, hormones and anti-epileptic drugs. Clinical practice in epilepsy, especially the principles of treatment, should consider the relationship. The understanding in such relationship will encourage physicians to be more rational in prescribing anti-epileptic drugs.

SEIZURE THRESHOLD

The concept of seizure threshold holds that everyone has a certain balance (probably genetically determined) between excitatory and inhibitory forces in the brain. The relative proportions of each determine whether a person has a low threshold of seizures (because of the higher excitatory balance) or a high threshold (because of a greater inhibition). Regarding this view, a low seizure threshold makes it easier for epilepsy to develop and easier for someone to elicit single seizure. Threshold means "the place or point of beginning", "the outset", "the lowest point at which a stimulus begins to produce a sensation", or "the minimal stimulus that produces excitation of any structure, eliciting a motor response". Meanwhile, as originally describe by J. Hughlings Jackson in 1870, a seizure is an "excessive discharge of nerve tissue on muscle". Jackson went on to say that "this discharge occurs in all degrees, it occurs with all sorts of conditions of ill-health, at all ages, and under innumerable circumstances".[5] These comments by Jackson are as true now as they were 130 years ago. Epileptic seizures are one of the most common, and frightening, neurologic conditions that occur in children.[2]

Normally, an action potential occurs in neuron 1 when the membrane potential is depolarized to its threshold level. Discharges in neuron 1 also may influence the activity of its neighbor, neuron 2. For example, a delay of several milliseconds from an action potential in neuron 1 may give rise to an excitatory postsynaptic potential (EPSP) in neuron 2. If cell 3, an inhibitory interneuron, also is activated by a discharge from neuron 1, then the activity in neuron 2 will be modified by an inhibitory postsynaptic potential (IPSP) that overlaps in time with the EPSP. The recorded event will be summed EPSP-IPSP sequence. If the IPSP occurs earlier, perhaps coincident with the EPSP, the depolarizing effect of the EPSP will be diminished. In this way, we can envision inhibition as "sculpting" or modifying ongoing excitation. If this concept is extrapolated to thousands of interconnected neurons, each influencing the activity of many neighbors, it is easy to see how an increase in excitation or

decrease in inhibition in the system could lead to hyper synchronous epileptic firing in a large area of brain. Normally, neurons fire single action potentials alone or in runs, and excitability is kept in check by the presence of powerful inhibitory influences.[6]

The term seizure refers to a transient alteration of behavior due to abnormal synchronized and repetitive bursts of firing of neurons in the central nervous system. Different definitions emphasize different features of an epileptic seizure: nature of onset and termination, clinical manifestations, and enhanced neuronal synchrony. Some previous definitions also considered issues of etiology, classification, and diagnosis, although none of these strictly fits within the task of a definition.[1]

Seizure threshold is changed by thyroid hormones in experimental animal and human. Seizures occur in patients with Graves disease or with excess administration of thyroxin for hypothyroidism. Thyroid hormones have profound effects on several aspects of early brain development and seizure threshold. Increased level of myelin and thyroid hormones could increase the excitability of the central nervous system (CNS) by lowering the threshold for various types of stimuli.[7]

More than 50% of all partial epilepsy originates from foci in temporal lobe structures. The high incidence of temporal lobe foci may occur because of the low seizure threshold found in many temporal lobe structures, especially in the limbic structures of the mesial temporal lobe.[8]

HORMONES

General view

Male and female sexuality and reproductive functions are complex systems with cortical, limbic system, hypothalamic, pituitary, and end organ interactions. Sexual steroids are produced in the sexual glands, the adrenals, and the brain. They undergo interconversion in the brain, bind to different brain areas, and have multiple effects behaviorally and neurologically. Progesterone, estrogen and testosterone have neuroendocrine effects that alter epileptogenicity. Seizure frequency may change throughout the life cycle as a result of hormonal status. Changes in the central control, peripheral hormone levels, and or medication effects may all contribute to decreased libido, potency, and fertility. AEDs interact with hormone-binding metabolism, resulting in altered human reproductive function. AEDs alter contraceptive hormone treatment.[9]

Hormone such as estradiol, progestin, and androgen that are secreted by the ovaries can have a profound effect on seizure vulnerability. Estradiol has long been known to decrease seizure threshold. Although a preponderance of clinical and experimental data suggests that estradiol has proconvulsant effects, antiseizure effects of estrogen have also been reported. Indeed, the precise impact of estradiol (and other steroid hormones) on seizure sensitivity may relate to both proximate levels and changes in those levels. The effects of progestin and androgens on seizure appear clear, with both genetically increasing seizure thresholds. Nonetheless, some reports suggest that progestin or androgen either lack antiseizure effects or that they can have proconvulsant effects.[10]

Women with epilepsy face additional challenges. Some AEDs reduce levels of physiologic ovarian sex steroid hormones and may reduce the efficacy of contraceptive steroids. Women with epilepsy have a greater risk for syndromes associated with infertility, such as hypothalamic-pituitary axis disruption, polycystic ovary-like syndrome, and anovulatory cycles.[11]

The menstrual cycle is fundamentally a neurological event. Normal reproductive function requires an interaction between

hypothalamic, pituitary and ovarian hormones. Gonadotropin releasing hormone (GnRH) is secreted in a pulsatile fashion by neurons in the arcuate nucleus of the hypothalamus. Its secretion is modified by catecholamines e.g., dopamine which acts as an inhibitor and norepinephrine which is a stimulator. The GnRH travels to the gonadotropic cells of the anterior pituitary through the portal system where it binds to receptors stimulating the production of follicle-stimulating hormone (FSH), and luteinizing hormone (LH). In children secretion of GnRH is extremely low, increasing slowly over the 3-4 years prior to the development of menses.[12]

Ovarian steroid hormones alter excitability of neurons of the central nervous system. Estrogen reduces inhibition at the gamma aminobutyric acid ($GABA_A$) receptor, enhances excitation at the glutamate receptor, and increases the number of excitatory neuronal synapses. Progesteron enhance GABA-mediated inhibition, increases GABA synthesis, and increases the number of $GABA_A$ receptors. In animal models of epilepsy, estrogen increases and progesterone decreases the likelihood that a seizure will occur.[13]

Estrogen and progesterone affect the central nervous system – primarily, the regulation of endocrine functions and sexual behavior. Experiments in animals have shown that the ovarian sex steroid hormones also modulate the seizure threshold.[14] The opposing effects of estrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold have been noted in animal and human studies. Levels of these hormones fluctuate throughout the menstrual cycle, and in some women with epilepsy, these fluctuations may be related to the occurrence of seizures around the time of menses or an increase in seizures in relation to the menstrual cycle, also known as catamenial epilepsy.[15]

Across the menstrual cycle, estradiol is elevated in the second half of the follicular phase and increases to a peak at midcycle, while progesterone is primarily elevated during the luteal phase and declines before menstruation begins. The contrasting effects of these hormones in activating or depressing central nervous system (CNS) function, respectively, may have implications for behavior or perhaps even epilepsy across the cycle.[15,16]

Estrogen

Estrogen has been shown to lower the seizure threshold in laboratory animals by altering calcium influx at the cell membrane, reducing chloride influx at the $GABA_A$ receptor, and acting as an agonist at glutamate receptors in regions of the hippocampus.[12] There are three biologically active forms of estrogen i.e., (i) 17B-estradiol, dominant in pre-menopausal women, (ii) estriol, the major form of estrogen during pregnancy, and (iii) estrone, which is prevalent after menopause. Estradiol has been shown in many studies to have significant proconvulsant effect. It facilitates various forms of induced seizures and has been shown to worsen seizures in women with epilepsy. On a cellular level, estradiol, aside from its normal reproductive effects, enhances neural excitation and suppresses inhibition. It also creates changes in the physical properties of some neurons (increase in excitatory dendritic spine density in the hippocampus), resulting in increased potential for seizures. It has been observed that there is a relationship between the ratio of estrogen to progesterone and the level of seizure occurrence. An increase in this ratio during certain periods in the menstrual cycle could create the increase in seizure susceptibility observed in catamenial epilepsy.[17]

Epilepsy, especially temporal lobe epilepsy (TLE), adversely affects testicular endocrine

function. The mechanism by which a brain disorder causes a testicular disorder is inexplicable. One mechanism by which this may occur is that subtle derangements in hypothalamic in pituitary function, caused by nearby epileptic discharges, produces elevation in circulating hormones, such as estrogen or prolactin. Estrogen can induce sex-hormone-binding globulin production in the liver, and thus, reduce free fraction of testosterone. On the other hand, carbamazepine may increase the negative effects of epilepsy on serum level of reproductive hormones.[18]

Progesterone

In contrast to estrogen, several studies have confirmed the anticonvulsive effect of progesterone and its metabolite. Progesterone enhances chloride influx at the $GABA_A$ receptor and reduces glutamate-mediated excitation, thereby increasing the seizure threshold. It also enhances the synthesis of GABA and of the $GABA_A$ receptor subunit. The clinical sequelae of these findings are seen most often during the menstrual cycle.[14]

Progesterone possesses anticonvulsive properties. The level of this hormone drops near the end of the menstrual cycle, leaving women more vulnerable to catamenial epilepsy. Recent studies have shown how progesterone protects women against seizures. Progesterone plays two roles in the brain. First, it binds to progesterone receptors in the brain, which help regulate the reproductive functions. Second, progesterone gets metabolized to allopregnanolone in the brain called a neurosteroid. Allopregnanolone plays a crucial role in seizure protection. The withdrawal from this neurosteroid, which occurs during the menstrual cycle, could provoke seizures. Consequently, neurosteroid replacement could be a novel therapeutic approach for catamenial epilepsy.[17]

The oral progestogen-only contraceptive pill should not be used in women taking enzyme-inducing AEDs because effective levels of progestogen cannot be guaranteed. However, the progestogen depot injection medroxyprogesterone acetate (Depo-Provera) does not undergo first pass metabolism and is a very useful contraceptive in these circumstances. There has been disagreement about the frequency of administration but most guidance now suggests shortening the usual 12 weeks to 10 weeks in women on enzyme-inducing anti-epileptic medication. Long duration implants of the progestogen etonogestrel or levonorgestrel are not thought to be reliable in conjunction with enzyme-inducing drugs on the basis of case reports of contraceptive failure. Intrauterine devices with progestogen levonorgestrel are effective because their action is primarily via a direct effect on the endometrium.[3]

Water balance and hormones

In 1931 McQuarrie & Peeler reported their observations on water balance in epileptic patients.[19] Early observations of an association between cerebral edema and convulsions led to a series of experiments in the early 20th century investigating the effects of water ingestion on seizures. Excessive water ingestion and the antidiuretic hormone vasopressin provoked seizures in patients with epilepsy, while negative water balance produced by fluid restriction had the opposite effect. These findings suggested that neuronal cell membrane permeability was defective in epilepsy and that water imbalance may underlie catamenial epilepsy. However, the study by Ansel & Clarke revealed no significant difference in body weight, sodium metabolism, or total body water was found between women with perimenstrual seizures and healthy controls or between epileptic women with and without catamenial tendencies.[20]

HORMONAL THERAPY

Oral contraceptives

Isolated cases of improved seizure control have been reported in women taking oral contraceptives. In the only double-blind, placebo-control study, the oral synthetic progestin norethisterone was ineffective in nine women with perimenstrual seizures.[15]

Medroxyprogesterone acetate (MPA)

MPA has been shown to reduce seizures in small numbers of women with epilepsy. Some women experience an increase in seizures during the interval between discontinuation of MPA and resumption of regular ovulatory cycles. This may be related to unopposed estrogen exposure during anovulatory cycles.[15]

Natural progesterone

In contrast to oral synthetic progestin, which has been shown to be ineffective, Herzog has found natural progesterone to be effective in women with focal epilepsy and catamenial tendencies. Average monthly seizure frequency declined by 54% to 68% during the 3-month treatment periods and by 62% to 74% after 3 years. Adverse effects, including transient fatigue and depression, resolved within 48 hours of dose reduction.[15,21]

Neurosteroids

Neurosteroids are steroids that are synthesized locally in the brain and have a strong and rapid effect on neural excitability. Ganaxolone, 3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one, is a neuroactive steroid, or neurosteroid, that modulates the $GABA_A$ receptor complex. It is a synthetic analogue of allopregnanolone, a progesterone metabolite, which has been shown to possess broad-spectrum anticonvulsant properties. Recently it has been discovered that allopregnanolone is a positive modulator of $GABA_A$ receptors. GABA is the primary inhibitory neurotransmitter in the brain. Allopregnanolone has specific, distinct binding sites on $GABA_A$ receptors that are separate from those for GABA, benzodiazepines, and barbiturates. At normal physiological levels, it is sufficient to activate these receptors. This suggests that an abrupt "withdrawal" of allopregnanolone at the onset of menstruation could decrease the inhibitory effect and possibly exacerbate seizures.[22-24]

Thyrotropine-releasing hormone

Thyrotropine-releasing hormone (TRH) has been successfully used for treating children with neurologic disorders including epilepsy. The effectiveness of TRH and a TRH analog has been reported in West syndrome, Lennox-Gastaut syndrome, and early infantile epileptic encephalopathy that were intractable to anticonvulsants and adrenocorticotropic hormone (ACTH). However, the peptide has not been widely studied as a treatment of intractable epilepsy outside Japan. TRH is safe for children and effective in some cases of West syndrome and Lennox-Gastaut syndrome. TRH is considered as a possible new strategy fro treating West syndrome and Lennox-Gastaut syndrome prior to ACTH therapy, especially for the patient with an infection, immunosuppression, or severe organic lesions in the brain. The mechanism of anti-epileptic action may differ from those of other anti-epileptic drugs (AEDs). One possibility is that TRH may act as an anti-epileptic through a kynurenine mechanism, considering that kynurenic acid acts as an antagonist on the N-methyl-D-aspartate receptor complex. The adverse affects of TRH therapy are transient urinary retention, irritability, sleepiness, worsening of involuntary movements, tremor, tachycardia or bradycardia, appetite loss, nausea, and vomiting. However, the adverse effects are infrequent and minimal.[25]

Other hormonal agents

The anti-estrogen clomiphene citrate, the synthetic androgen danazol, and the synthetic gonadotropin agonists triptorelin and goserelin have been effective in reducing seizure in small series. However, the use of these agents is limited because of the potential for significant adverse effects, and consultation with a reproductive endocrinologist or gynecologist is suggested before their use.[15]

ANTI-EPILEPTIC DRUGS

AEDs are used to prevent or interrupt seizures. They act via three mechanisms i.e., (i) limitation of sustained repetitive neuronal firing via blockade of voltage-dependent sodium channels, (ii) enhancement of GABA-mediated inhibition, and (iii) blockade of glutamatergic excitatory neurotransmission.[26] Several AEDs target aspects of the inhibitory system. Phenobarbital and benzodiazepines bind to different sites on the $GABA_A$ receptor. These drugs enhance inhibition by allowing increased chloride influx through the GABA receptor; Phenobarbital by increasing the duration of chloride channel openings and benzodiazepine increasing the frequency of openings. Vigabatrin is an example of a "designer drug" that was created to target a specific pathophysiologic mechanism. Vigabatrin inhibits the GABA degradatory enzyme, GABA transaminase, thereby increasing the amount of GABA available to partake in inhibitory neurotransmission.[6]

Other AEDs affect aspects of neuronal excitation. Phenytoin, carbamazepine, and lamotrigine block voltage-dependent sodium channels and reduce the ability of neurons to fire repetitively. Ethosuximide, used primarily for absence seizures, blocks a unique calcium current that is present only in thalamic neurons, preventing them from firing in an oscillatory fashion and recruiting neocortical neurons into spike-wave patterns. Several new AEDs are said to alter the function of N-methyl-D-aspartate (NMDA) receptors (lamotrgine and felbamate) or non NMDA receptors (topiramate).[6]

Effects of AEDs on male sexual hormones and function

Medications might have a direct effect on gonadal function. For example, spermatogenesis sensitive to a variety of factors (temperature, diet, alcohol, stress) including drugs. AEDs such as carbamazepine and phenytoin have been shown to directly inhibit testosterone production by the Leydig cells in vitro. These studies demonstrated a differential effect by each of the AEDs on the metabolic pathway of sex steroid hormones.[27]

Herzog et al[28] reported their study on differential effects of AED on sexual function and hormones in men with epilepsy. They compared sexual function and reproductive hormone levels among 85 men with localization-related epilepsy who took carbamazepine (25 patients), phenytoin (25 patients), lamotrigine (25 patients), 10 untreated patients for at least 6 months (no AED) and 25 controls. Sexual function scores (S-scores), hormone levels (bioactive testosterone, estradiol), hormone ratios (bioactive testosterone/bioactive estradiol), and gonadal efficiency (bioactive testosterone/luteinizing hormone) were compared among the five groups. The conclusions were that sexual function, bioavailable testosterone levels, and gonadal efficiency in men with epilepsy who took lamotrigine were comparable to control and untreated values and significantly greater than with carbamazepine or phenytoin treatment.[28]

Carbamazepine, oxcarbazepine, and valproate are associated with sperm abnormalities in men with epilepsy. In addition, valproate-treated men with generalized epilepsy who have abnormal sperm may have reduced

testicular volume. However, no specific AED can be solely implicated as causing reproductive abnormalities; the common features of the subjects was that they had epilepsy, and the AEDs produced further variations (or correction) in parameter. In addition, there is no specific reason readily used to advise individual male patients about the risk of impotence or infertility.[29]

Herzog et al[28] found total and non-sex hormone-binding globulin (SHBG)-bound serum estradiol levels to be significantly higher among phenytoin-treated men with epilepsy than among untreated epileptic men or normal control subjects. A significant linear correlation between serum concentrations of biologically active estradiol and phenytoin, but not albumin or hepatic enzymes, suggests a direct medication effects rather than an indirect cause mediated via drug-induced hepatic dysfunction. Estradiol exerts a potent inhibitory influence on luteinizing hormone secretion and plays a major role in negative feedback in men as well as women. Suppression of luteinizing hormone secretion results in hypogonadotropic hypogonadism. Chronically low free testosterone leads to testicular failure and hypergonadotropic hypogonadism. This may explain the frequent occurrence of both of these reproductive endocrine disorders in men with epilepsy.[21,30]

Effects of AEDs on female sexual hormones

Anticonvulsants that induce hepatic cytochrome (CY) P450 enzymes can increase the metabolism of sex hormones and make hormonal contraception ineffective. Anticonvulsant drugs in this category include carbamazepine, phenobarbital, phenytoin, and primidone. Two of the newer anticonvulsant also may interfere with contraceptive efficacy. Oxcarbazepine at doses in excess of 1,200 mg/day and topiramate at doses above 200 mg/day can induce CYP450 enzymes. Women receiving these anticonvulsants and oral contraceptives should consider taking higher dosage formulations of oral contraceptives. Women receiving a CYP450 enzyme-inducing anticonvulsant have at least a 6% failure rate per year for oral hormonal contraceptive pills. Gabapentin, lamotrigine, levetiracetam, and tiagabine do not reduce sex-steroid hormone levels and should not reduce contraceptive efficacy.[31]

Women wishing to take an enzyme-inducing AED with the combined oral contraceptive should be advised to take at least 50 ug of ethinylestradiol and to report any breakthrough bleeding. If it occurs the dose of estrogen should be increased to 75 or 100 ug. “Tricycling” the oral contraceptive – that is, taking three months consecutively followed by a four day break, is also advised if the woman wishes to continue with the combined oral contraceptive, although there is no good evidence to back this up. Absence of breakthrough bleeding does not necessarily mean that the contraception is effective. If maximum protection against pregnancy is desired barrier methods (for example, condom or diaphragm), should be used in addition to the oral contraceptive pill, or the type of contraception changed to one unaffected by enzyme induction.[3]

Previous observations have indicated that reproductive endocrine disorders are common among patients with epilepsy. Valproate treatment is associated with hyperandrogenism, polycystic ovaries, and obesity in women. Carbamazepine may also induce endocrine disorders, while the hormonal effects of oxcarbazepine are poorly known.[32]

Drugs that stimulate hepatic metabolism may directly affect the serum concentration of endogenous sex steroids and vice versa. Fluctuations of AED concentrations across the menstrual cycle have been reported. Women with catamenial seizures taking phenytoin or phenytoin and phenobarbital were found to have

lower AED concentrations despite taking higher doses of the drugs. The phenytoin concentration was significantly lower during menses in women with perimenstrual seizures compared with women who had seizures unrelated to menses, and levels were lower and clearance was greater during menses than during the periovulatory period in women with perimenstrual seizures.[16]

Paradox effects of AEDs

AEDs may even increase seizure frequency or severity or change the seizure type (Table 1). It may be difficult to be certain that an AED exacerbates or worsens a seizure type, particularly with partial seizures, but accurate counts of seizures preceding the introduction of a new AED may help the clinician identify this adverse effect. AEDs that increase GABA levels may worsen or exacerbate some generalized seizures. Toxic levels of some AEDs, such as phenytoin, can increase seizures that were controlled initially. Because AEDs may worsen seizures, one of the first considerations in choosing an AED is the efficacy for patient's type of seizure or epilepsy.[33]

SUMMARY

Threshold can be defined as lowest point at which a stimulus begins to produce a sensation, or a minimal stimulus that produces excitation of any structure, eliciting a motor response. A low seizure threshold makes it easier for epilepsy to develop and easier for someone to elicit single seizure.

The ovarian sex steroid hormones such as estradiol, progestin, and androgen modulate the seizure threshold. Estradiol decreases seizure threshold; progestin and androgen genetically increase seizure threshold. The effect of estrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold have been noted in animal and human studies. Adult women with epilepsy face additional issues stemming from seizures and AEDs that require neurologists to be well versed in medical specialties outside of epileptology, in particular gynecology. The opposing effects of estrogen (proconvulsant) and progesterone (anticonvulsant) on seizure threshold have been noted in animal and human. Level of these hormones fluctuates throughout the menstrual cycle. In some women with epilepsy these fluctuations may be related to the occurrence of seizures around the time of menstruation or an increase in seizures in relation to the menstrual cycle.

In prescribing AEDs, it is important to be aware of potential drug-to-drug anddrug-to-hormone interactions, especially in women taking hormonal contraceptives. Hormone therapy may be associated with an increase in seizure frequency in menopausal women with epilepsy, and women who have had a catamenial seizure pattern may have increased seizure frequency during perimenopause.

Table 1. AEDs reported to increase seizures[34,35]

Antiepileptic drugs	Seizure type that increases
Carbamazepine, phenobarbital, vigabatrin, gabapentin	Absence
Carbamazepine, vigabatrin, gabapentin, lamotrigine	Myoclonic
Carbamazepine, phenytoin, vigabatrin	Complex partial
Carbamazepine	Tonic-clonic

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