

EPILEPSY, ANTIEPILEPTIC DRUGS, AND NEUROENDOCRINE EFFECTS

Alison Pack

Key points

- Estrogen in clinical and animal studies has proconvulsant properties.
- Progesterone mediated through its metabolite, allopregnanolone, has antiepileptic properties.
- Women with epilepsy who have a catamenial pattern have increased seizure susceptibility secondary to fluctuations in reproductive hormones.
- Women and men with epilepsy treated with antiepileptic drugs are at increased risk for reproductive dysfunction.
- Contraceptive choice should consider potential bidirectional effects between hormonal contraception and antiepileptic drugs.
- Thyroid abnormalities are reported in association with cytochrome P450 enzyme inducing antiepileptic medications.
- Abnormalities in bone health including poor bone quality, low bone mineral density, and fractures are increased in persons with epilepsy treated with antiepileptic drugs, particularly cytochrome P450 enzyme inducing antiepileptic drugs.

Relationship between Epilepsy and Hormones

Hormones, specifically female reproductive hormones, can through mechanisms that affect brain excitability influence the presentation of seizures and epilepsy. Estrogen in animal and clinical studies has proconvulsant properties whereas, progesterone and its metabolites have antiepileptic properties. The clinical model that nicely demonstrates this relationship is catamenial epilepsy which is defined by seizure frequency variability related to fluctuations in estrogen and progesterone during the menstrual cycle. Three patterns have been described: 1) C1, the most common pattern, occurs during the perimenstrual phase of the menstrual cycle when there is a rapid decrease in progesterone, 2) C2 occurs during ovulation when there is a rapid increase in estrogen, and 3) C3 occurs in inadequate luteal phase cycles secondary to elevated estrogen/progesterone levels. In general, seizure vulnerability occurs during periods where the estrogen/progesterone ratios are high.

The clinical direct excitatory effect of estrogen was demonstrated when after receiving intravenous injections of the estrogen, Premarin, 11 of 16 women with epilepsy had increased epileptogenic activity on EEG recordings and four experienced seizures. In contrast, progesterone infusions in women with epilepsy reduce seizure susceptibility as evidenced by significant decreases in spike frequency in four of seven women who received two hour intravenous infusions of progesterone during the first week of their menstrual cycles.

In animal models, estrogen increases neuronal excitability through multiple mechanisms. Estradiol, the main estrogen in reproductive aged non-pregnant women, increases the production and density of NMDA receptors on the dendritic spines of hippocampal CA1 pyramidal neurons and in cerebellar Purkinje neurons. Increased NMDA receptors leads to increased intracellular calcium entry resulting in more excitatory inputs to pyramidal cells. Estrogens also suppress GABA-ergic inhibition of hippocampal neurons.

The antiepileptic activity of progesterone is mediated through its metabolite, allopregnanolone which enhances the postsynaptic GABAergic effect. Allopregnanolone is a positive allosteric modulator of GABA_A conductance and it increases inward chloride current induced by GABA.

Reproductive Function in Women and Men with Epilepsy

Reproductive dysfunction has been reported in women and men with epilepsy. Antiepileptic drugs (AEDs) can affect reproductive function and notably in women can influence contraceptive efficacy. In women, reported symptoms of reproductive dysfunction include hyperandrogenism, menstrual disorders with ovulatory failure, polycystic ovary syndrome and hyperinsulinemia. In men, effects on sperm quality and motility, delayed sexual development and small testicular size have been described.

Enzyme-inducing AEDs alter hepatic metabolism and decrease concentrations of endogenous and exogenous reproductive hormones. This decrease in reproductive hormones results in decreased efficacy of hormonal contraception. Women should be counseled about this effect and if using enzyme inducing AEDs should consider

other types of contraception such as an intrauterine device. In addition, enzyme inducing AEDs increase production of sex hormone binding globulin (SHBG), which reduces serum concentrations of free reproductive hormones. Men with epilepsy taking carbamazepine or oxcarbazepine have been reported to have low total testosterone concentrations and free androgen indices which may result in decreased sex drive.

Valproate has multiple reported effects on hormones and reproductive function. It can induce ovarian androgen synthesis and is associated with increased testosterone concentrations, anovulation, and polycystic ovarian syndrome.

Lamotrigine, a commonly used AED in women with epilepsy, is not associated with changes in sex steroid hormone concentrations. Its main metabolic pathway is through glucuronidation which is accelerated approximately 50% by treatment with estrogen containing hormonal formulations. If women are prescribed estrogen containing hormonal contraception, dose adjustments will need to be made. Although not to the same extent, clearance of valproate is also increased by estrogen containing hormonal contraception.

Thyroid Function in Women and Men with Epilepsy

Cross sectional and longitudinal studies have evaluated the effect of AEDs on thyroid function. Treatment with cytochrome P450 enzyme inducing AEDs including phenobarbital, phenytoin, carbamazepine, valproate and oxcarbazepine has resulted in subclinical hypothyroidism, reduced thyroxine, triiodothyronine, free thyroxine, free triiodothyronine and thyroid binding globulin concentrations. Studied patients were clinically euthyroid and hormonal changes were reversible after AED withdrawal. The mechanisms for AED mediated thyroid dysfunction include enhanced metabolism and/or altered protein binding or interference of hypothalamic–pituitary–thyroid axis function.

Bone Health in Women and Men with Epilepsy

Fractures are increased two to six fold in persons with epilepsy when compared to the general population. The increased risk is secondary to a combination of seizures, particularly generalized convulsive seizures and long term effects of AEDs on bone. AEDs can result in effects on bone quality, reduced bone mineral density, and biochemical abnormalities. AEDs can also result in poor coordination, another factor that increases fracture susceptibility. The principal mechanism reported to explain AED related changes in bone relates to cytochrome P450 enzyme induced increased vitamin D metabolism resulting in decreased active vitamin D metabolites, reduced gastrointestinal absorption of calcium, relative hypocalcemia, increased parathyroid hormone and decreased bone mineral density as a means of restoring serologic calcium concentrations. This mechanism does not explain all reported findings including abnormalities in bone among children and adults treated with valproate. Other reported mechanisms include impaired absorption of calcium, vitamin K deficiency, directs effects of AEDs to stimulate osteoclastic bone resorption, effects of reproductive hormones, genetic influence, and a potential role of epilepsy itself. No specific guidelines exist for screening for bone disease in persons with epilepsy. Routine screening of active vitamin D metabolites should be performed. Consider DXA screening for persons with prolonged treatment, particularly if the patient has another risk factor for low bone mineral density.

References

1. Davis AR, Pack AM, Dennis, A. Contraception for Women with Epilepsy. *Contraception for the Medically Challenging Patient*. Eds. Rebecca H. Allen, Carrie A. Cwiak. New York: Springer, 2014:135-146.
2. Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. *Expert Rev Clin Pharmacol* 2015;8(6):741-750.
3. Hamed SA. The effect of epilepsy and antiepileptic drugs on sexual, reproductive and gonadal health of adults with epilepsy. *Expert Rev Clin Pharmacol* 2016;9(6):807-819.
4. Herzog AG. Catamenial epilepsy: Update on prevalence, pathophysiology, and treatment from the findings of the NIH Progesterone Treatment Trial.
5. Pack, AM. Anticonvulsant-Related Bone Disease. Osteoporosis. Fourth Edition. Eds. Robert Marcus, David Feldman, David Dempster, Marjorie Luckey, Jane Cauley. New York: Elsevier, 2013:1225-1235.

6. Petty SJ, Wilding H, Wark JD. Osteoporosis associated with Epilepsy and antiepileptics – a review. *Curr Osteoporos Rep* 2016;14(2):54-65.
7. Reddy DS. Role of hormones and neurosteroids in epileptogenesis. *Front Cell Neurosci* 2013;7:1-20.
8. Reimers A, Brodtkorb, Sabers A. Interactions between hormonal contraception and antiepileptic drugs: Clinical and mechanistic considerations. *Seizure* 2015;28:66-70.
9. Velez-Ruiz NJ and Pennell PB. Issues for Women with Epilepsy. *Neurol Clin.* 2016;34(20):411-425.
10. Tauboll, E Sveberg L, Svalheim S. Interactions between hormones and epilepsy. *Seizure* 2015;28:3-11.