NEW-ONSET EPILEPSY IN WOMEN: AN INDICATION FOR A NEWER ANTIEPILEPTIC DRUG?

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ABSTRACT

Seizure 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 an early accurate diagnosis and initiating appropriate medical treatment may decrease seizure recurrence, reduce the number of antiepileptic drug (AED) trials, and minimize the impact of seizures on the patient's quality of life. Epilepsy and the use of AEDs affect endocrine, sexual, and reproductive function. The newer AEDs, which have been associated with fewer drug interactions than the older AEDs, may be better tolerated in women. Patients with a first seizure are often seen in the emergency department or in an urgent-care setting, where a medication is often chosen based on protocols and what is available. Follow-up evaluation after an initial episode may reveal the need to change medication. Treatment strategies are likely to evolve as additional data regarding the AEDs become available.


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Although the prevalence of epilepsy and approaches to treatment are similar for men and women, women often have seizure patterns related to their reproductive cycles. Some health issues that women with epilepsy are likely to face include menstrual cycle influences on seizure activity, interactions of oral contraceptives and antiepileptic drugs (AEDs), pharmacokinetic changes of AEDs during pregnancy, teratogenicity of AEDs, and the safety of breast-feeding while taking AEDs. Special considerations regarding treatment decisions are required at various stages of a woman's life and during the reproductive cycle. This article reviews the epidemiology and etiology of new-onset seizures in women and the factors that influence diagnosis and treatment. Current treatment strategies for new-onset epilepsy also are discussed, with an emphasis on issues specific to women.

NEW-ONSET EPILEPSY IN WOMEN: EPIDEMIOLOGY AND ETIOLOGY

Approximately 2.5 million people in the United States have epilepsy. More than 1.1 million of these people are women of childbearing age. Although the incidence of epilepsy is slightly higher in men compared to women, the incidence may be higher in women during the first 5 years of life. Seizures are influenced by variations in the levels of sex hormones during the menstrual cycle and throughout the reproductive life of women with epilepsy. The steroid hormones estrogen and progesterone affect the excitability of neurons of the central nervous system and exert significant effects on the seizure threshold.
Estrogen has proconvulsant effects, while progesterone has the opposite effect. Changes in estrogen and progesterone levels at puberty, menarche, menses, and menopause may cause women with epilepsy to experience changes in their seizure patterns.

Some epilepsy syndromes, such as childhood absence (petit mal) and benign partial epilepsy with centrotemporal spikes (Rolandic epilepsy), often remit at puberty. However, other epilepsies may worsen, especially those involving partial seizures. Juvenile myoclonic epilepsy and juvenile absence epilepsy occur in women primarily at puberty. Approximately 33% of women experience improved seizure control after menopause. Another 33% of women describe a worsening in seizure control after menopause, often after beginning hormone replacement therapy with unopposed estrogen.

As high as 75% of women with epilepsy may have catamenial epilepsy, or the occurrence of seizures around menses or in relation to the menstrual cycle. Seizures may be more likely to occur around the time of menstrual flow because of a decrease in progesterone and a surge in estrogen at ovulation. Women who have anovulatory cycles are more likely to have seizures that are random and severe because the ratio of estrogen to progesterone remains high. Catamenial epilepsy often improves during menopause, when estrogen concentrations decline.

**IMPORTANCE OF ESTABLISHING A DIAGNOSIS**

Establishing an accurate diagnosis is a critical component in determining the appropriate treatment for a person who has had a suspected seizure. In addition, an early accurate diagnosis and optimal medical treatment may decrease seizure recurrence, reduce the number of AED trials, and minimize the impact of seizures on the patient’s quality of life.

The first step in evaluating a suspected seizure is to determine whether the event was actually an epileptic seizure. Epileptic seizures are behavioral changes caused by paroxysmal, excessive electrical discharges from the brain. Jerks, shakes, and episodic behaviors are not always indicative of epileptic seizures. For example, increased muscle tone after a stroke can cause sustained clonus of the extremity, which could be mistaken for a partial motor seizure. Several disorders can have features that mimic epileptic seizures. Table 1 lists some nonepileptic paroxysmal disorders that can mimic epileptic seizures.

Routine electroencephalogram (EEG) may be useful in supporting a clinical diagnosis of epilepsy by showing epileptiform discharges, or spikes or sharp waves, although the first EEG has a sensitivity of only 50%. Prolonged EEG-video monitoring allows a more thorough analysis of the EEG and is enhanced by the use of video monitoring to record the actual events around the occurrence of a seizure.

When a diagnosis of seizure or epilepsy has been made, the likelihood of seizure recurrence should be assessed and treatment benefits versus risks should be addressed. Many patients do not experience additional seizures after a single seizure. The cause of the seizure plays an important role in determining a patient’s risk for relapse. Patients who have had a single seizure and have a history of neurologic abnormality or injury are almost 2 times more likely to have a recurrent seizure compared to patients with an idiopathic first seizure. Patients who experience a generalized seizure are at lower risk for recurrent seizures compared to patients who have had a partial seizure, especially a complex partial seizure. A family history of epilepsy, abnormal EEG patterns, such as a generalized spike-and-wave pattern, or abnormal neurologic findings increase risk for recurrent seizures.

Deciding whether to treat a first seizure depends on the individual patient. Not all patients require treatment upon initial presentation. The risks of treating

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<thead>
<tr>
<th>Table 1. Neurologic, Psychiatric, and Medical Disorders that Can Mimic Epileptic Seizure</th>
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<tr>
<td>• Syncope</td>
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<td>• Migraine</td>
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<td>• Cerebrovascular event</td>
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<td>• Periodic paralysis</td>
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<td>• Sleep disorders</td>
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<td>• Gastrointestinal disorders</td>
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<td>• Drug toxicity and substance abuse</td>
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<td>• Breath-holding spells</td>
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Data from Prego-Lopez and Devinsky.
must be weighed against the risks of not treating. Lifestyle restrictions, such as limitations on driving and work activities, financial and insurance issues, the likelihood of medication compliance, and various social and cultural restrictions should all be considered. Treatment may be necessary if the patient runs the risk of injury if she has a seizure at work. However, the potential adverse effects of medication may be more troublesome than the seizure for a patient who has had a seizure in her sleep.

Distinguishing between partial and generalized seizures can help identify patients who need treatment and guide selection of AEDs. Medication should be initiated gradually, if possible. In addition to seizure type, AED selection also is based on findings on the EEG, concomitant medications, past medical history, and hematologic, hepatic, and renal functions. Adverse effects of medications can include sedation, psychomotor slowing, and gastrointestinal upset. Although rare, life-threatening adverse effects include Stevens-Johnson syndrome, liver or bone marrow failure, and pancreatitis.

EXAMINATION OF CURRENT TREATMENT STRATEGIES FOR NEW-ONSET EPILEPSY

Efficacy and Safety Profiles of the Antiepileptic Drugs: Issues Specific to Women

Epilepsy and its treatments affect pituitary, adrenal, thyroid, bone, and sexual function. Data regarding the effects of the newer AEDs on endocrine disorders and sexual or reproductive function are limited. However, the newer AEDs are less likely to cause drug interactions compared to older AEDs, suggesting that the newer AEDs may be better tolerated.

A study by Isojarvi et al reported an increased incidence of polycystic ovarian syndrome (PCOS) and hyperandrogenism with menstrual disturbances in women taking valproate compared to women taking other AEDs. In another study, Isojarvi et al found that the number of PCOS cases, body mass index, fasting serum insulin level, and testosterone level decreased significantly when women with PCOS or hyperandrogenism had their medication switched from valproate to lamotrigine. However, these studies have not been reproduced. There is no consistent evidence to link a specific AED to PCOS. Any increase in weight in women with epilepsy should be closely monitored because obesity may be a trigger for PCOS.

Smaller body size and the effects of estrogen loss during menopause put women at high risk of bone disease. Women with epilepsy are at even greater risk because of the danger of falls during seizures and the effects of some of the AEDs on bone health. Phenobarbital, phenytoin, and primidone, which are inducers of the cytochrome P450 (CYP450) enzyme system, are most commonly associated with altered bone metabolism and decreased bone density. Other CYP450 inducers, such as carbamazepine and CYP450 inhibitors (eg, valproate), also may have negative effects on bone health. A limited number of studies have evaluated the effects of the newer AEDs on bone health. One study that examined the effect of lamotrigine, topiramate, vigabatrin, and gabapentin on bone mineral metabolism and bone mineral density found no significant abnormalities. However, many of the patients in the study were taking a newer AED in combination with other AEDs. A study by Pack et al found no significant reductions in calcium or markers of bone resorption and bone formation in young women treated with lamotrigine (monotherapy).

All women with epilepsy must be advised regarding contraception choices as they approach childbearing age. Some of the AEDs may increase the risk for hormonal contraceptive failure. CYP450 enzyme-inducing drugs, such as phenobarbital, primidone, phenytoin, and carbamazepine, enhance the hepatic metabolism of contraceptive steroids and increase the binding of steroids to serum proteins, which reduces the concentration of biologically active steroid hormone and may result in contraceptive failure. Topiramate in doses over 200 mg daily and oxcarbazepine may also lower the effectiveness of oral contraceptives. The oral contraceptive dosage must be adjusted when a woman is taking any of these drugs or an alternative or additional birth control method should be recommended. Oral contraceptives can lower lamotrigine concentration and may require adjustments in lamotrigine dosage.

The pharmacokinetics of the AEDs may be altered by physiologic changes in pregnant women. The absorption of AEDs does not seem to be affected by the decreased gastric tone and motility in pregnancy. However, nausea and vomiting experienced by some women in early pregnancy may interfere with the ability to ingest medications. In some studies, rectal administration of phenytoin, carbamazepine, valproate, and lamotrigine has provided adequate
bioavailability.\textsuperscript{18} Hepatic metabolism of phenytoin increases during pregnancy, and total and unbound total plasma concentrations of phenytoin and phenobarbital decrease in the third trimester.\textsuperscript{18} Of the newer AEDs, total lamotrigine plasma concentrations have been reported to decrease.\textsuperscript{18} Renal clearance increases during pregnancy, but none of the drugs that are renally excreted (ie, gabapentin, levetiracetam, vigabatrin) are significantly protein bound.\textsuperscript{18} However, those drugs that are renally excreted demonstrate lowering of levels during pregnancy. Therefore, total concentration is equivalent to unbound concentration.

According the American Academy of Neurology, there is no strong consensus or epidemiologic evidence that supports a specific frequency for clinical or AED monitoring of pregnant women with epilepsy.\textsuperscript{19} Total AED levels fall throughout pregnancy, but nonprotein-bound (free) levels remain more constant. For women with good control of seizures, a baseline, preconception, nonprotein-bound AED level should be repeated at the beginning of each trimester and in the last 4 weeks of pregnancy.\textsuperscript{19} Lamotrigine levels decline during pregnancy, especially during the first 2 trimesters. Many epileptologists recommend frequent monitoring of blood levels (as often as monthly). More frequent measurements should be taken if seizure frequency increases or adverse effects occur, or if noncompliance is an issue. Drug dosages should be adjusted based on clinical need. The teratogenicity of the older AEDs is well documented, but data regarding the effects of the newer AEDs are limited.\textsuperscript{18} Women with epilepsy should be reminded that they have a greater than 90% chance of having a healthy baby.\textsuperscript{18} The use of phenytoin, carbamazepine, phenobarbital, and valproate have been associated with fetal anticonvulsant syndrome, which includes lip and palatal malformation, congenital heart disease, and facial and digital anomalies.\textsuperscript{18} Exposure to valproate and carbamazepine in the first trimester has been associated with neural tube defects, such as spina bifida.\textsuperscript{18} Women of childbearing age who are taking AEDs should be advised to take supplemental folic acid (1–4 mg/day),\textsuperscript{19} which is thought to lower the risk of neural tube and other congenital defects.

**Emergency Department Management of Patients with Seizures**

Patients with a first seizure are often seen in the emergency department (ED) or in an urgent-care setting.\textsuperscript{8} In a study published in 2001, Huff et al examined the frequency of patients with seizure disorders seen in 12 EDs over 18.25 days and determined seizure etiologies, characteristics of diagnostic tests, treatment, and dispositions.\textsuperscript{20} The study was a retrospective chart review of ED records for all patients with seizures or a presenting complaint related to seizures. Each site used a standard template form for data collection. A total of 31 508 patient visits in the participating EDs during the study period was recorded. Of this total, 368 (1.2%) visits were related to a seizure or seizure disorder; 362 of these charts were available for review. Laboratory studies were performed in 299 patients. Diagnostic studies included cranial computed tomography ($n$ = 126), cranial magnetic resonance imaging ($n$ = 3), lumbar puncture ($n$ = 22), and EEG ($n$ = 11).

Approximately 25% of the patients ($n$ = 87) had new-onset seizures, including 17 children with febrile seizures. The other patients seen in the ED during the study had previous seizure histories. Of the patients with new-onset seizures (but not including children with febrile seizures), 63% were admitted to the hospital. The final diagnoses for patients admitted to the hospital and for those patients discharged from the ED included CNS tumor, meningitis, hyponatremia, ethanol-related seizures, acute stroke, subarachnoid hemorrhage, and presumptive idiopathic seizures. Most of the patients (81%) who were discharged from the ED underwent neuroimaging studies; 42% of discharged patients were started on anticonvulsants.

| Table 2. Antiepileptic Medications Administered to Emergency Department Patients with Seizures |
|---------------------------------|-------------------|
| **AED** | **Patients, n** |
| Lorazepam | 66 (33%) |
| Diazepam | 23 (12%) |
| Midazolam | 2 (1%) |
| Phenytoin | 85 (42%) |
| Fosphenytoin | 27 (14%) |
| Phenobarbital | 15 (8%) |
| Carbamazepine | 21 (11%) |
| Valproate | 13 (7%) |

AED = antiepileptic drug.

Data from Huff et al.\textsuperscript{20}
A total of 199 patients received antiepileptic medications (Table 2). Although AEDs, such as phenytoin and valproate, are administered in the ED solely for their antiepileptic effects, drugs such as midazolam and lorazepam may be used for other effects. For example, midazolam was administered as an adjunct for rapid-sequence intubation in 2 patients in the study by Huff et al.20 In addition, lorazepam was administered to some patients with alcohol-related seizures to blunt alcohol withdrawal symptoms.20

Patients with seizures and complaints related to seizures are frequently seen in EDs. The study by Huff et al showed that most patients received some advanced clinical care and more than 50% of the patients received antiepileptic medications.20 Many of the interventions reported in the study appeared to be protocol-driven.20 Although an appropriate medication is often selected by an emergency physician on the basis of the available parenteral medications, the choice can be re-evaluated at a later time.8 Approaches to the treatment of seizure disorders may undergo changes as additional data on the AEDs are published.

**FOLLOW-UP CARE IN THE COMMUNITY: AN IDEAL TREATMENT STRATEGY**

Patients and their families must work in collaboration with their physicians, nurses, and other healthcare providers. After an initial episode, patients may be referred to a general neurologist or an epileptologist at a specialized epilepsy center for further evaluation. Cooperative relationships between healthcare providers can help to ensure that the needs of patients are met.

In an ideal situation, education should be provided when the patient receives a diagnosis and should continue as the patient encounters new problems or enters new life stages.21 Referral to community support organizations also may be helpful for some patients.21 Patients and their families should be taught to observe and to record seizures, manage adverse drug effects, identify and manage stress and other triggers, and maintain personal safety.22 Medication management issues are especially important for women with epilepsy because their general health and needs will change throughout their life span.

**CONCLUSIONS**

Epilepsy is not a gender-specific disease and prevalence is similar for men and women. However, women with epilepsy are more likely to have seizures that are influenced by variations in the levels of steroid hormones throughout their reproductive years. Some types of epilepsy remit at puberty, whereas other types of epilepsy occur primarily at that time. Many women have seizures that occur around menses or in relation to their menstrual cycle. Seizure patterns may change after menopause.

Establishing an accurate diagnosis can help to ensure optimal treatment and can help patients achieve the goal of no seizures, no adverse effects. An appropriate medication should be chosen based on the patient’s seizure type and the AED’s side-effect profile, in addition to the patient’s lifestyle, medication cost, and potential compliance issues.

Women with epilepsy must deal with the effects of epilepsy and treatments on reproductive function, bone health, contraception, and pregnancy. Valproate may increase risk for developing PCOS. CYP450 enzyme-inducing drugs, such as phenobarbital, phenytoin, primidone, carbamazepine, and valproate, may alter bone metabolism and decrease bone density. Some of the CYP450 enzyme inducers also increase the risk for hormonal contraceptive failure. In addition, physiologic changes in pregnancy may affect the pharmacokinetics of AEDs. Although a woman with epilepsy has a high chance of having a healthy baby, the use of phenytoin, carbamazepine, phenobarbital, and valproate has been associated with congenital malformations and diseases. All women of childbearing age taking AEDs should take supplemental folic acid to lower the risk of birth defects.

Many patients who experience an initial seizure seek treatment in an ED or urgent-care setting. Although patients are often administered an antiepileptic medication in the ED, follow-up care may reveal that another medication is more appropriate. In addition, changes in general health and needs throughout the patient’s life span may warrant revisions to the treatment plan. A comprehensive treatment team helps to ensure that all of the patient’s concerns and needs are addressed.

**REFERENCES**