ABSTRACT

This article reviews the most recent findings regarding the physiological and psychological consequences of epilepsy, apart from the actual seizures. The issues discussed include higher risk for poor altered functioning of the nervous system, suboptimal reproductive health, the effect of antiepileptic drugs (AEDs) on pregnancy outcomes, and the prejudice and stigma that comes largely from ignorance and misinformation in the media. A discussion of the hormonal changes associated with epilepsy and AED use is provided. In addition, resources that address patient concerns about the limitations in their personal lives are provided for clinicians to use in their ongoing dialogue with epilepsy patients. This article concludes that the total cost of epilepsy extends far beyond the direct costs of medication, doctor visits, and neurologic tests.

THE RELATIONSHIP BETWEEN EPILEPSY AND SLEEP DISORDERS

Daytime drowsiness and poor concentration are frequent complaints of people with epilepsy and have typically been attributed to AED therapy. This assumed association is reasonable in many cases, but often, poor sleep quality may underlie some of the daytime symptoms. Two recent studies have shown that epilepsy is associated with prolonged sleep latency, increased frequency and number of awakenings, poor sleep efficiency, and a disruption in rapid eye movement (REM) sleep. In the first study, patients with intractable temporal lobe epilepsy underwent all-night polyvagography, as well as continuous video electroencephalography monitoring in order to identify seizures. As shown in Figure 1, patients with seizure disorders have significantly increased length of stage 1...
sleep, particularly if the seizures occur before REM sleep. In addition, REM sleep is decreased in these patients, with the reduction most pronounced if the nocturnal seizure occurs before REM sleep. These sleep disruptions persist as long as 2 nights after a single seizure, so the effects of seizure on sleep quality are long lasting.1

In the second study, researchers reported that one third of the 39 patients being evaluated for epilepsy surgery had obstructive sleep apnea (OSA). As shown in Table 1, OSA patients tended to be male, older, louder snorers, and of heavier weight, and they have more seizures during sleep.4 The prevalence of OSA in this cohort was 50% for men and 19% for women, which is significantly higher than the prevalence reported in a population-based study of adult state workers (24% of men, 9% of women).4 Previous studies show that treatment of OSA in epilepsy patients results in improved daytime seizure control, daytime sleepiness, or both.4

Clearly, patients with epilepsy and poor sleep are caught in a cycle where the poorer the sleep quality, the higher the likelihood of seizures, and the more frequent the occurrence of seizures, the poorer the sleep quality. The further corollary is that with good sleep quality, including treatment of sleep apnea, seizure control may improve independently of any other alterations in therapy.

People with epilepsy appear to be at higher risk for sleep disorders, and having seizures can disrupt sleep, both acutely and over the long term. Medication in epilepsy and the disease process itself can also interfere with good sleep practices. As the relationship between specific AEDs and sleep quality becomes better understood, it may become one of the variables in the choice of AEDs for individual patients. For new neurologists and epileptologists, it should be more sensitive to the increased risk for sleep disturbances in epilepsy patients. Daytime complaints of poor neurocognitive function may be a symptom of sleep disruption. Neurologists should consider referring these patients for sleep studies with polysomnography.

Sudden Unexplained Death in Epilepsy

Epilepsy puts individuals at risk for autonomic nervous system disturbances. Many of the areas most often involved with the epileptic focus, such as the limbic cortex, have extensive interconnections with regions of the brain controlling the autonomic nervous system, which is believed to increase the risk for SUDEP. During SUDEP interictal and ictal discharges appear to provoke cardiac and pulmonary abnormalities. Seizures are associated with sinus arrest, bradycardia, changes in blood pressure, hypoxemia, and cyanosis.4

Even more worrisome is the recurrent observation that ictal ventilatory dysfunction could play a role in certain cases of SUDEP in adults with partial seizures, as measured by oxygen desaturations, probably because seizure causes abnormalities in cardiovascular regulation.4 Finally, status epilepticus causes abnormalities in myocardial conduction. The net effect appears to be cardiac and pulmonary dysfunction.5

The annual incidence of SUDEP is 1.23 per 1000 person-years in patients with epilepsy, being slightly higher in females, with a standardized mortality rate of about 24, although the risk is not the same for all patients with epilepsy. Mortality rates in seizure-free patients are not elevated, and patients who are successfully treated (ie, seizure free) with epilepsy surgery have lower mortality rates than those with persistent seizures. Overall, SUDEP is responsible for 2% to 7% of all deaths in patients with epilepsy. Risk factors for SUDEP appear to be poorly controlled seizures, early onset of epilepsy, and generalized tonic-clonic seizures.6,7 The incidence and mortality rate with SUDEP underscore the seriousness of epilepsy as a possible life-threatening neurological disorder. Similarly, these data also reveal that seizure freedom is associated with a greater life expectancy, an important observation when considering a patient as a candidate for epilepsy surgery. Often the risk of surgery is deemed too high, but with modern neurosurgery, the risk for a serious adverse outcome is less than 1%. Based on these recent studies, the risk of a premature death may be even higher.

Should neurologists discuss the risk of SUDEP with their patients? The Epilepsy Foundation has recently indicated that patients with epilepsy should be aware of this phenomenon, even though it is rare, and it provides information about SUDEP on the Epilepsy Foundation website. As clinicians, the goal is to identify persons at risk, with the understanding that seizure freedom is the only intervention that entirely protects patients from SUDEP. Perhaps in the future, therapies that suppress seizures, stabilize autonomic function, and provide some type of cardiopulmonary protection will be available.

Reproductive Dysfunction

Men and women with epilepsy are 30% to 60% less likely to have a child than their siblings who do not have epilepsy.8 Several potential mechanisms for infertility are relevant to the entire population of persons with epilepsy. First, to be discussed in greater detail later, marriage rates remain somewhat lower for people with epilepsy. Some individuals with epilepsy may choose not to become parents because of concerns about having a child while dealing with a seizure disorder and AEDs. Individuals with epilepsy are more likely to have sexual dysfunction, including disorders of sexual desire, disorders of sexual arousal, erectile dysfunction in men, and difficulty with intercourse in women because of lack of lubrication or dyspareunia.1

Women with epilepsy are at risk for reproductive endocrine disorders and ovarian dysfunction and are 3 to 5 times more likely to lose a pregnancy in the first trimester.10 While the reasons for this are not entirely clear, they may be related to reproductive endocrine abnormalities. The remainder of this discussion will focus on women with epilepsy.

Anovulatory Cycles

Women with epilepsy are more likely to have anovulatory cycles, affecting 30% or more of women with epilepsy, compared with 10% of the general population.11 The basis for this ovulatory failure is probably multifactorial. Women with epilepsy seem to have disrupted hypothalamic-pituitary-adrenal axis functioning and may have ovulatory failure associated with altered secretion of gonadotropin-releasing hormone (GnRH).

OSA and SUDEP: A New and Important Link

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Table 1. Epilepsy Patients with Obstructive Sleep Apnea (OSA) Have Significant Demographic Differences from Those Without OSA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OSA</th>
<th>No OSA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAS/DQ SCORE, mean ± SD</td>
<td>28.0 ± 7.2</td>
<td>23.3 ± 5.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Loud snoring or witnessed apnea, N (%)</td>
<td>8 (62)</td>
<td>6 (23)</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, mean ± SD (kg/m²)</td>
<td>28.6 ± 7.1</td>
<td>24.3 ± 4.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>39.9 ± 9.2</td>
<td>32.9 ± 9.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex, N (%)</td>
<td>9 (69)</td>
<td>9 (59)</td>
<td>0.04</td>
</tr>
<tr>
<td>Seizures during sleep, N (%)</td>
<td>10 (77)</td>
<td>11 (82)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Defined as occasionally, often, or almost always.

SA/DQ = Sleep Apnea Scale of Sleep Disorders Questionnaire.

from the hypothalamus or luteinizing hormone from the pituitary (which is affected by GnRH release), or by altered steroid metabolism from enzyme-inducing AEDs (Figure 2).24-26

AEDs also have significant effects on steroid hormone levels and their biological activity in both men and women. Women with epilepsy receiving the enzyme-inducing AEDs carbamazepine, phenobarbital, or phenytoin have significant reductions in levels of estradiol and adrenal and gonadal androgens. As a result, the brain experiences substantial reductions in concentrations of these steroid hormones.27-29 Legrand et al have reported increases in sex hormone binding globulin in male and female epilepsy patients, rendering the steroid hormones testosterone and estrogen biologically inactive.30 These effects on steroid hormones could affect hormonally mediated behaviors such as sexuality and further disrupt feedback to the hypothalamic pituitary axis (Figure 2). However, women receiving valproate, a cytochrome P-450 enzyme inhibitor, have elevated levels of ovarian and adrenal androgens.31 Another study showed that women receiving gabapentin or lamotrigine, which do not affect cytochrome P-450 enzymes, had no alterations in levels of any steroid hormone compared with age-matched non epileptic controls.32

**POLYCYSTIC Ovary SYNDROME**

Polycystic ovary syndrome (POS) has also received considerable attention because of recent data suggesting that this syndrome may occur in women with epilepsy. POS, also known as Stein-Leventhal syndrome, is the leading cause of infertility in the developed world. It affects about 24% of reproductive-aged women, but it is thought to be underdiagnosed.33-35 POS is defined by several characteristics, the most common being either hirsutism or hair loss on the head or both. The hairloss may appear as...36

...an interaction between the syndrome and the treatment appears to be present and it may promote reproductive disturbance.

Figure 3. Women with Epilepsy Have a Higher Occurrence of Polycystic Ovaries and Elevated Serum Testosterone Levels*

- GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.

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According to the age at which treatment with valproate (N=31) or other antiepileptic drugs (N=67) was begun.

**REGNANCY COMPLICATIONS**

These effects on steroid hormones could affect hormonally mediated behaviors such as sexuality and further disrupt feedback to the hypothalamic pituitary axis (Figure 2). However, women receiving valproate, a cytochrome P-450 enzyme inhibitor, have elevated levels of ovarian and adrenal androgens. As these studies show, an interaction between the disease and of the therapy has been observed in patients with epilepsy. Abnormalities in luteinizing hormone levels associated with anovulatory cycles and polycystic ovaries and appear to be a function of epileptiform discharges in the brain, altering hypothalamic and pituitary axis function. On the other hand, valproate appears to further promote polycystic-appearing ovaries and to be associated with anovulatory cycles and obesity, one sign of a metabolic disruption. Thus, an interaction between the syndrome and the treatment appears to be present and it may promote reproductive disturbance.

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exposed to an AED and born to a mother with no history of seizures: 20.6% versus 8.5%; odds ratio (OR) 2.8. The frequency increased to 28% (OR 4.2) for infants exposed to 2 or more AEDs and to higher doses of an individual AED. Infants of mothers with epilepsy who did not use AEDs during the pregnancy did not have a higher frequency of abnormalities than those in the control group.11,12,41,42

Another concern is that AEDs may cause minor variations in facial and digit appearance. The risk may be as high as 20% for women with epilepsy, which represents a 2-fold increase from the healthy population. However, the mechanisms of AED-mediated teratogenicity are not known but several mechanisms appear to be important, including toxic intermediates formed during metabolism, such as acrylamide and epoxide metabolites, and folate acid deficiency. The observation of toxic intermediates is relevant because carboxyamidine is a chemical cousin to carbaneprine but does not generate the episodic intermediate, suggesting that carbaneprine may be preferred in women of reproductive age. However, no controlled studies are available to support this theory. Folic acid deficiency is a known cause of teratogenicity in non-epileptic women and is specifically associated with neural tube defects. Phenobarbital, phenytoin, carbamazepine, and valproate can interfere with folic acid absorption, so it is assumed that folic acid deficiency may be a mechanism for teratogenicity in children born to mothers with epilepsy. Because of this, in 1998 the American Academy of Neurology (AAN) recommended prophylactic supplementation with folic acid for all women of childbearing potential receiving AEDs.43 However, in the last year, there has been reported a child born with major malformations to a mother receiving AEDs who was vigorously supplemented with folic acid.44 While the neurology community still supports the recommendations of the AAN, the recognition is being made that folic acid supplementation may not be absolutely protective. The AAN also recommends several additional steps for women of childbearing age to avoid major malformations in their infants, as outlined in Table 2. Further resources are available for women with epilepsy (please see Useful Resources).

**The Burden of Epilepsy**

Society has made tremendous advances in welcoming persons with disabilities into the broader community, but people with epilepsy face prejudice and stigma worldwide as well as in the United States. This stigma comes largely from ignorance and misinformation.

### Table 2: AAN Practice Parameters for Women with Epilepsy

<table>
<thead>
<tr>
<th>Strong evidence is available in support of:</th>
</tr>
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<tbody>
<tr>
<td>Optimizing AED therapy before conception</td>
</tr>
<tr>
<td>Completing AED therapy changes at least 6 months before planned conception, if possible</td>
</tr>
<tr>
<td>Not changing or alternating AED during pregnancy for the sole purpose of reducing teratogenic risk</td>
</tr>
<tr>
<td>Offering additional tests to patients being treated with carbamazepine, divalprox sodium, or valproic acid</td>
</tr>
<tr>
<td>Measurement of alpha-fetoprotein levels at 14 to 16 weeks’ gestation</td>
</tr>
<tr>
<td>Level II (structural) ultrasound examining the fetal microcephaly</td>
</tr>
<tr>
<td>Encouraging breastfeeding monitoring the neonate for sedation or feeding difficulties</td>
</tr>
</tbody>
</table>

A recent survey shows some disheartening statistics about the quality of life for people with epilepsy. Marriages rates for men and women with epilepsy are lower than for men and women without epilepsy (51% vs 63% for men; 48% vs 59% for women). The occupational and economic disabilities are also significant. The household income was 93% that of the median US family income, and the respondents were less likely to have graduated from high school (64% vs 81.7%), and even less likely to graduate from college (20% vs 23%). The US unemployment rate is 5%, but 25% of people with epilepsy in the United States are unemployed. The majority of the respondents (69%) attributed their unemployment to having epilepsy.

The estimated annual cost of epilepsy in the United States in 1995 was $12.5 billion, amounting 2.3 million present cases and taking into account the indirect costs.45 Importantly, medications, doctor visits, and tests are only a fraction of the total cost of epilepsy. Other factors causing the high cost of epilepsy include housing, employment, and personal opportunities. When last wages of caretakers of persons with epilepsy is factored in, the total cost is even greater.

A recent study of English-language print media found that misinformation surrounding epilepsy is conveyed in the media. The misinformation usually stems from relying on information from the medical community and, to a lesser extent, from people with epilepsy. Any third parties included inaccuracies as well as severe exaggeration of treatment benefits and risks of seizures (e.g., life and death, life hanging in the balance). As a result, the concept of epilepsy as being possessive, demonic, frightening or out-of-control is reinforced—epilepsy becomes “The Scarlet E”46. However, epilepsy associations were shown to be the most accurate source of information in the survey. When an Epilepsy Foundation source was used in the article, the information was balanced and accurate. Physicians can make every effort to provide accurate information that neither embellishes nor belittles the risk and outcomes of epilepsy. Physicians must also realize that patients are obtaining much of their medical information—worthy or fraudulent—from the Internet. This can be used to the neurologist’s advantage by steering patients towards reliable sources, such as the Epilepsy Foundation.

### Conclusion

Epilepsy continues to present numerous challenges to clinicians and patients. A new understanding is beginning to take place regarding the complex interdependent relationship between a patient’s seizure type and typical number of seizures and their related effects on sleep. Similarly, the effects seizures and AEDs have on the hypothalamic pituitary axis are complex and can significantly affect important aspects of quality of life, such as sexual function and reproductive ability. Astute neurologists can be aware of early hormonal dysfunction to limit the consequences of epilepsy and their toll on the personal lives of the patients. As recent studies of media information are showing us, a significant amount of misinformation is given to both epilepsy patients and the general public, which propages the stigma associated with this disease. However, the amount of information currently available can be used to the patients’ advantage, but neurologists must guide their patients to high quality information and provide realistic expectations of therapy and the risks associated with epilepsy, particularly SUDEP.

### REFERENCES


