ABSTRACT

Making an accurate diagnosis and correctly classifying seizure types are instrumental processes in placing patients on the correct path to control of their epilepsy. Once the diagnosis is established through careful history taking supported by diagnostic testing, a medication regimen must be selected. Treatment decisions are a highly individualized matter based not only on efficacy, but also on tolerability, safety, drug interactions, and comorbid conditions. The nurse plays a vital role in obtaining a thorough history from patients and witnesses, and is also a key member of the health management team, serving as an advocate for patients and families as they cope with the lifestyle issues that accompany a new diagnosis of epilepsy. (Adv Stud Nurs. 2005;3(3):72-78)

THERAPEUTIC OPTIONS IN NEW-ONSET EPILEPSY

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The primary goal for the neurologist when evaluating a patient with new-onset seizures is to make an accurate diagnosis and, if indeed the diagnosis is epilepsy, to classify the seizure type accordingly. Both of these factors play an important role in treatment decisions and successful outcomes for the patient. Epilepsy is defined as the presence of recurrent, unprovoked seizures. Excluded from this definition, and from discussion here, are seizures provoked by acute systemic factors (eg, fever, infection, drugs, toxins, electrolyte abnormalities, hypoglycemia). Though simply defined, epilepsy is not always simply diagnosed. Like a headache or chest pain, a seizure is more a symptom than a disease, indicating that abnormal electrical discharges are occurring in one or more regions of the brain. Determining the underlying etiologies for these aberrant discharges is not always a straightforward process because epilepsy can be caused by a variety of pathophysiologic changes. Obtaining an accurate and thorough history is the key to distinguishing seizures from other events that may resemble epilepsy and also to determining the type of seizure.

DISTINGUISHING SEIZURES FROM OTHER EVENTS

Nurses are particularly capable of obtaining useful and objective information from patients, family members, and witnesses to seizures. It is important to ask open-ended questions to allow the patient and any witnesses to describe what happened during the seizure or what they can remember about the event. Patients may describe an aura, which represents the beginning of a partial onset seizure and generally is a reflection of where in the brain the abnormal activity begins. Patients may experience somatosensory phe-
nomena, visual phenomena, auditory, olfactory, or gustatory phenomena. If seizures originate in the limbic system, patients may experience fear or a feeling of impending doom. Some of the feelings expressed by patients may sound psychiatric in nature (eg, so-called “out of body” experiences), but are in fact a consequence of abnormal electrical activity in this region of the brain. Witnesses may describe automatisms, or repetitive behaviors (eg, chewing or swallowing out of context) performed in a stereotyped fashion. Auras, automatisms, and localized central nervous system dysfunction during a seizure and postictal paralysis are more characteristic of partial onset versus generalized onset seizures.

Again, the history is vital, because the neurologic examination is usually normal in people with epilepsy. The electroencephalogram (EEG) may or may not contribute to the diagnosis, as a single EEG will only be abnormal in 50% of patients. The diagnostic yield is enhanced significantly by sleep deprivation and also by obtaining repeated tracings. Three or more sleep-deprived EEGs increase the chance of detecting an abnormality to 80%. Depending on the information obtained in the history, other ancillary tests may be needed. For example, if syncope or cardiac events are suspected an electrocardiogram and a cardiac event monitor may be appropriate.

The etiology of seizures may be genetic, secondary to brain injury (from trauma, infection, fever, tumor), or undetermined (idiopathic). Determining the underlying etiology is only possible in 50% of cases. However, if successful, it allows the patient and clinician to make important decisions regarding treatment (eg, medical vs surgical interventions), and also to have a sense of the prognosis; in other words, whether seizure activity will be able to be controlled.

**Making an Etiologic Diagnosis**

The first step in making an etiologic diagnosis is seizure classification. There are 2 broad categories: (1) generalized-onset seizures, which begin with abnormal electrical discharges that appear simultaneously in both hemispheres of the brain; and (2) partial-onset seizures, which begin with abnormal electrical discharges confined to one part of the brain. Within the category of partial-onset seizures, there are 3 subtypes: (1) simple partial, (2) complex partial, and (3) secondarily generalized. Individuals with simple partial seizures experience no alteration in consciousness or amnesia for the event. By contrast, those experiencing complex partial seizures will have some loss of awareness and will not be able to recall the events that transpired during the seizure, because the brain is incapable of forming new memories during these seizures. If the seizure begins in one region of the brain and then spreads to diffuse areas in both hemispheres, these are considered to be partial seizures that secondarily generalize. Within the category of generalized-onset seizures, several seizure types are recognized, including: (1) tonic-clonic seizures; (2) absence seizures; (3) myoclonic seizures; (4) clonic seizures; (5) tonic seizures; and (6) atonic seizures. The first 3 are generally hereditary or primary (idiopathic) forms of epilepsy in which the individual is otherwise neurologically and intellectually normal, and are usually fairly easy to treat. By contrast, clonic, tonic, or atonic seizures are usually secondary (symptomatic) forms of generalized epilepsy whereby the seizures are symptoms of a diffuse underlying brain abnormality. These seizures are often associated with brain malformations, inborn errors of metabolism, or neurodegenerative diseases that cause some degree of intellectual impairment and are very difficult to treat.

The age of onset, detailed history of seizures, neurologic and general medical status, EEG, family history, and imaging studies are all used to make an etiologic diagnosis. Once the diagnosis of epilepsy has been established, how then does one determine the proper course of treatment?

**Treatment Decisions**

The first consideration in selecting an antiepileptic drug (AED) is seizure type/epilepsy syndrome. Traditionally, for generalized-onset seizures, valproate has been the drug of choice, and ethosuximide has been used exclusively for absence epilepsy. For partial-onset events, phenytoin and carbamazepine have been the established AEDs. However, in recent years, a host of new AEDs have entered the armamentarium, particularly for use in partial-onset epilepsy (Figure 1). Now that there are many more drugs, treatment decisions need not be so limited. Selecting the correct AED can be based on several considerations, with the goal of attaining the best outcome for the patient both in terms of minimizing seizures and maximizing quality of life. These treatment considerations include efficacy, tolerability, safety, cost, interactions with other medications...
the patient may be taking, and/or other comorbid conditions that the patient may have (see Sidebar).

**Efficacy**

In 1985, Mattson et al conducted a 10-center, double-blind trial to compare the efficacy and toxicity of 4 commonly used AEDs available at the time for the treatment of partial and secondarily generalized tonic-clonic seizures. Over 600 patients were randomly assigned to treatment with carbamazepine, phenobarbital, phenytoin, or primidone and were followed for 2 years or until the drug failed to control seizures or caused unacceptable side effects. Overall treatment success was highest with carbamazepine or phenytoin, intermediate with phenobarbital, and lowest with primidone (P < .002). Differences in failure rates of the drugs were explained primarily by the fact that primidone caused more adverse effects. The investigators found that control of tonic-clonic seizures did not differ significantly with the various drugs. However, carbamazepine provided complete control of partial seizures more often than primidone or phenobarbital (P < .03). Overall success rate was 47%.

Fifteen years later, Kwan and Brodie published a similar study looking at the success rate of initial treatment with several older and newer agents (mostly carbamazepine, valproate, or lamotrigine). Among 470 previously untreated patients, 222 (47%) became seizure-free during treatment with their first AED, regardless of which drug they were taking. The findings were very similar in yet another study comparing carbamazepine, valproate, and topiramate. No statistically significant differences between fixed doses of these drugs were observed in efficacy measures: time to exit, time to first seizure, and the proportion of patients seizure-free during the last 6 months of treatment—success rates ranged from 44% to 49%. Even with newer agents, clinicians are still only able to control seizures with initial monotherapy in slightly less than 50% of patients. Therefore, in terms of efficacy, there does not seem to be a difference between older AEDs versus newer agents. However, efficacy is not the only consideration. Looking at tolerability of established versus newer medications, distinct differences begin to emerge. This is an important issue for nurses in counseling patients, because nurses can serve as educators and advocates for patients who may be struggling with compliance and other issues if their medications are giving them unacceptable side effects.

**Tolerability**

Carbamazepine and valproate have long been considered the treatments of choice for partial- and generalized-onset seizures, respectively. These medications are typically regarded as being well tolerated, however a prospective double-blind study of carbamazepine and valproate revealed that adverse effects are common. High percentages of individuals experienced adverse effects, especially sedation (42%), nystagmus (about 28%), dizziness (about 26%), gait disturbances (about 24%), mood changes (25%), and cognitive dysfunction (18%). Because there is a significant relationship between adverse events from AEDs and overall quality of life, it is essential that nurses and other healthcare providers assess adverse effects and seek to minimize them. The nature of the side effects varies according to medication type. For example, in one study by Privitera et al of approximately 400 subjects, topiramate (at doses of 100 mg once daily) caused paresthesias, appetite decrease, and weight loss most commonly while carbamazepine (600 mg once daily) was linked to more so-called neurotoxic side effects, such as headache, fatigue, nausea, dizziness, and som-
nolence. Valproate (1250 mg once daily) caused more tremor, alopecia, and weight gain. Although no prospective head-to-head trials have been reported, several studies suggest that at least some of the newer medications are better tolerated than the older medications. Knowing the specific adverse effect one is most likely to experience may help patients and clinicians to tailor therapy. This is also important information for nurses to convey to patients, who may be better able to tolerate adverse effects if they know what to expect and how to cope with these effects. Closely related to adverse effects are safety issues.

SAFETY

One of the advantages of the newer agents appears to be better safety profiles compared with established drugs, such as phenytoin, carbamazepine, phenobarbital, and valproate. Even though concerns about serious rash have been raised in association with the newer agent lamotrigine, comparative studies with carbamazepine and phenytoin have not demonstrated substantial differences in the incidence of rash.

Bone health is a very important safety issue, which may have been neglected in the past for individuals on AEDs. Phenytoin, carbamazepine, phenobarbital, and valproate accelerate loss of bone mass. Although much attention has been focused on postmenopausal women, data reveal a significant loss associated with long-term treatment, even in otherwise healthy young men. Pack et al studied bone health in people with epilepsy under 50 years of age who were taking enzyme-inducing AEDs (phenytoin, phenobarbital, primidone, and carbamazepine), and found an increased fracture risk, which may be related to medication side effects and seizures themselves (see Sidebar). Only 57.4% of women with epilepsy on AEDs had normal bone mineral density compared with an expected 84.1% in a normal population of this age. Likewise, 31.9% of women had osteopenia and 10.6% osteoporosis compared with expected rates of 15.3% and 0.6%, respectively (Figure 2).

Bone density. The risk from enzyme-inducing AEDs appears to be the most substantial, although valproate has been implicated as well. Patients taking AEDs should have periodic bone density assessments. Because the predominant mechanism of bone loss involves effects on vitamin D metabolism, patients taking AEDs should receive supplemental vitamin D and calcium rather than bisphosphates. Significant improvement in bone density has been demonstrated with dietary supplementation in people with epilepsy. For patients with osteoporosis, referral to a rheumatologist or endocrinologist specializing in bone health is recommended.

Gingival hyperplasia is a well-known adverse effect of treatment with phenytoin. Although often regarded as a “cosmetic” side effect and acceptable in exchange for seizure control, the pain, bleeding, and loss of dentition that may ensue can have a substantial effect on quality of life. This is particularly tragic in developmentally disabled institutionalized patients in whom seizures are common and the ability to express discomfort may be limited. The availability of newer AEDs provides an opportunity to change therapy, resulting in significant improvements in oral health.
Cost

Unfortunately, living with epilepsy is costly not only in terms of lifestyle issues such as loss of employment, loss of driving privileges, and medical costs related to seizure-related accidents, but also in terms of drug costs. A monthly prescription for an AED may range from $20 or $30 for an older agent to over $200 for one of the newer agents, and sometimes patients require 2 or more drugs to control their symptoms. If monotherapy with an older agent can successfully control seizures without adverse effects, this is certainly the most cost-effective regimen for the patient.

Despite the availability of various patient assistance programs for newer medications, an older AED is sometimes the only option. However, “cost” becomes a complex issue, because one must factor in the costs of treatment for drug-induced adverse effects such as osteoporosis or gum disease, the costs related to even occasional seizures (inability to drive or find employment), the cost to the patient in terms of reduced quality of life, and the cost associated with drug interactions.

Interactions with Other Medications and Other Medical Conditions

Last but not least, selecting the AED best suited for a particular patient must take into consideration other medications that patient is taking. As our population ages, the number of medications taken for various problems increases substantially. In addition, some medical problems are known to occur more frequently in people with epilepsy than in the general population. Examples of these comorbid conditions include depression and headache. Unfortunately, especially for the older AEDs, the list of drug interactions is extensive (see Sidebar). By comparison, newer AEDs, including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide, have fewer interactions. Those interactions that do occur are often with older AEDs as opposed to medications taken for other conditions. One special area of concern for women of childbearing age is the use of oral contraceptive hormones. It has been noted that women with epilepsy who are taking older enzyme-inducing AEDs have a higher incidence of breakthrough bleeding and unplanned pregnancies.15 These women should use oral contraceptive pills that contain at least 50 mcg of estrogen, or if they are using medroxyprogesterone injections, take these every 10 versus 12 weeks.15 Newer agents, including lamotrigine, gabapentin, tiagabine, levetiracetam, topiramate (at doses less than 200 mg/day), and zonisamide, as well as ethosuximide, valproate, and benzodiazepines do not interact with hormonal contraceptives (Figure 3).15

If a patient is elderly or has other serious health considerations, choosing the appropriate AED becomes even more of a challenge and a concern. Aside from changes in bone mineral density, some AEDs have been linked to changes in weight (such as

<table>
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<th>Older AED Interactions</th>
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<tr>
<td>Carbamazepine—phenobarbital, lamotrigine, phenytoin, primidone, tiagabine, topiramate, valproate, antipsychotics, cimetidine, corticosteroids, erythromycin, SSRIs, tricyclics, theophylline, warfarin</td>
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<tr>
<td>Phenobarbital—benzodiazepines, carbamazepine, ethosuximide, lamotrigine, phenytoin, tiagabine, topiramate, valproate, antipsychotics, corticosteroids, theophylline, tricyclics, warfarin</td>
</tr>
<tr>
<td>Phenytoin—benzodiazepines, carbamazepine, ethosuximide, lamotrigine, phenobarbital, primidone, tiagabine, topiramate, valproate, antipsychotics, cimetidine, corticosteroids, digoxin, SSRIs, theophylline, tricyclics, warfarin</td>
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<tr>
<td>Valproate—benzodiazepines, carbamazepine, ethosuximide, lamotrigine, phenobarbital, phenytoin, primidone, zonisamide, antipsychotics, erythromycin, tricyclics, warfarin</td>
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AED = antiepileptic drug; SSRI = selective serotonin reuptake inhibitors.

Bone Health

- Phenytoin, carbamazepine, phenobarbital, and valproate accelerate loss of bone mass
  - Significant loss in 34% of patients under age 40 years
  - Recent data implicate carbamazepine in bone loss even in adolescents
- Screen all patients over age 12 years
  - If normal: Ca 1200 mg once daily, vit D 400 IU once daily
  - If osteopenia: Ca 600 mg 3 times daily, vit D 800 IU once daily
  - If osteoporosis: refer to rheumatologist or endocrinologist
valproate and carbamazepine), to hyperlipidemia and possible accelerated atherosclerosis (carbamazepine), kidney stones (topiramate, zonisamide), and behavioral side effects (levetiracetam). Conversely, certain AEDs may confer an added benefit in specific medical conditions. For example, topiramate may aid in weight loss for the obese patient with epilepsy, and is effective for treatment of migraine. In elderly patients, several newer AEDs appear to be effective and better tolerated than the older AEDs, probably because of fewer drug interactions, fewer age-related changes in metabolism, and linear pharmacokinetics.

CONCLUSION

Treatment of new-onset epilepsy is a challenge for both patient and healthcare provider, complicated by issues such as efficacy, tolerability, safety, cost, drug interactions, and comorbid diseases. Experience has taught us that monotherapy is preferable to combinations of AEDs. Increasing the number of medications in a patient’s regimen increases the risk of drug interactions and iatrogenic illness, increases cost, and reduces tolerability, which in turn decreases compliance. Furthermore, adding additional agents rarely improves seizure control.

The selection of an AED in patients with newly diagnosed epilepsy is a complex but critically important decision, which can have a profound impact on quality of life. For years, we have understood that medication selection should be based on epilepsy syndrome and seizure type. The availability of newer AEDs enhances our ability to improve outcomes by allowing us to consider additional factors such as drug interactions, specific adverse-effect profiles, and comorbid or coexisting conditions.

Recently, the American Academy of Neurology and the American Epilepsy Society reviewed the evidence of the efficacy, tolerability, and safety of 7 new AEDs, which have been approved by the US Food and Drug Administration in the past decade. Overall, efficacy was comparable to older agents, however there were significant differences in tolerability and cost. Gabapentin was found to be effective for the treatment of patients with newly diagnosed partial seizures; lamotrigine, topiramate, and oxcarbazepine were found to have efficacy as monotherapy in a mixed population of newly diagnosed adolescents and adults with either partial or generalized tonic-clonic seizure disorders, but the expert panel failed to support effectiveness of the newer agents with other generalized epilepsy syndromes.

Tolerability was better with the newer agents, which do not generally affect the hepatic enzyme induction system or the hormonal milieu, as do the older AEDs. Therefore, drug interactions and long-term side effects may not be as much of an issue for patients prescribed these agents. However, this comes at a higher monetary cost. Individual decisions must be made with each patient as to whether the potential benefits of monotherapy with the newer agents are worth the additional financial burden. However, it is not appropriate to deny people with epilepsy a normal quality of life simply on the basis of cost. People with other chronic medical conditions ranging from hypertension to schizophrenia have benefited from the availability of better tolerated, albeit more expensive, treatments. People with epilepsy deserve the same standard of care.

Overall, nurses are instrumental in educating patients and helping them to ask the right questions and assume an active role in collaboration with their physicians to make the correct decisions regarding management of their epilepsy within the context of their unique lifestyles.
REFERENCES


