

Issues in the Treatment of Epilepsy

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Epilepsy is one of the most common neurologic conditions with an incidence of about 80 per 100,000 cases per year. Another 20 per 100,000 cases per year may have a single isolated seizure. Seizures can be classified as either partial or generalized. Differential diagnosis is critical as different treatments are available for the different seizure types and other conditions are frequently mistaken for seizures.



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Introduction. Epilepsy is one of the most common neurologic conditions with an incidence of about 80 per 100,000 cases per year. Another 20 per 100,000 cases per year may have a single isolated seizure. Seizures can be classified as either partial or generalized. Differential diagnosis is critical as different treatments are available for the different seizure types and other conditions are frequently mistaken for seizures.

Temporal Lobe Epilepsy. Temporal lobe epilepsy is the most common type of localization-related epilepsy in adults, accounting for up to 80 percent of cases. Clinically, the condition is characterized by simple and/or partial complex seizures, often with secondary generalization. The simple partial seizure, often called an aura, is characterized by symptoms, such as a sensation of déjà vu or out of body experience or may involve a strange but consistent smell. There is also sometimes a rising sensation within the body, an abdominal aura. This type of seizure may remain sensory or may involve jerking of one part of the body. During simple partial seizures, there is no confusion or loss of consciousness. The patient is aware of the symptoms, but cannot control them. Complex partial seizures, by definition, do involve altered consciousness. This type of seizure may begin as a simple partial and progress to involve cognition or begin with altered consciousness with no

prior warning or symptoms. Patients may or may not be aware of their confusion. During this time, the patient may begin to show automatisms, which are characteristic of complex partial seizures and patients often have variable recollection of these as well.

The most common abnormality found in temporal lobe epilepsy is mesial temporal sclerosis (MTS). There are characteristic pathological findings in the hippocampus, gradually developing scarring and atrophy. It is frequently seen in patients with a history of febrile seizures. Complex partial seizures can develop later in life, sometimes after many years of seizure freedom.¹

Scientific Basis of Treatment. Ever since the serendipitous discovery that bromides can reduce seizures in epileptic patients, scientists have been trying to find ways to prevent seizures medically. For many years it has been known that the drugs found to prevent seizures affect sodium and other ion channels, but whether those were the physiological effects that produced seizure reduction was not clear. Today, much is known about the mechanisms of antiepileptic drugs but, until recently, there was no solid evidence that these effects were responsible for their clinical actions.

Over the past few years, the genetics of several epilepsies have been defined and are providing insight into the pathogenesis and treatment of these diseases. The syndromes

about which the most is known so far, however, are those with simple, easily studied inheritance patterns.

An epilepsy syndrome, which has been shown to be a channelopathy, is the syndrome of benign familial neonatal convulsions. Seizures begin between ages of 3 days and 3 months, and then typically remit with no chronic neurologic complications. Gene abnormalities have been identified in sodium, SCN2A (2q24), and potassium, KCNQ2 (20q13), and KCNQ3 (8q24) channels.²

In contrast, autosomal dominant partial epilepsy with auditory features (ADPEAF) is a rare, idiopathic temporal lobe epilepsy. It invariably involves auditory symptoms, usually hallucinations, which range from simple sounds to voices or music. Only 2 families have been studied and the abnormality was in a protein sequence on chromosome 10. So far, it is the only gene found in the temporal lobe epilepsies which does not code for an ion channel abnormality.

For the first time, there is evidence that at least some of the epileptic syndromes have genetically determined ion channel abnormalities and that drug effects on those channels can reasonably be expected to affect seizure frequency. Obviously, these are complex disorders and not all seizure disorders respond to ion channel modification. Most epilepsies show complex inheritance including febrile seizures, idiopathic generalized epilepsy, and benign Rolandic epilepsy (epilepsy with centrottemporal spikes). Hopefully, as more research is done, treatment will become more targeted and effective.

Anticonvulsant Drug Treatment. The anticonvulsants in use today are categorized as old or new. The older drugs are those

which were developed and came into general use before 1978. In this category are phenytoin, phenobarbital, valproic acid, and carbamazepine, all of which are still useful and relatively inexpensive. Ethosuximide falls into this category, but is useful exclusively for absence epilepsy and will not be discussed here. Most physicians are familiar with their indications and side effects.

Phenytoin, phenobarbital, and carbamazepine all affect voltage-gated sodium channels and this is considered to be their primary mode of action. However, each has other biochemical effects as well. Phenytoin and phenobarbital also affect chloride and calcium conductance. Phenobarbital increases GABA_A receptor activity and decreases glutamate and carbamazepine affects NMDA receptors. Valproic acid has several biochemical effects on GABA function and metabolism and inhibits excitatory neurotransmission by glutamate and aspartate. It also affects calcium and potassium conductance.

Phenytoin and phenobarbital have been used for primary generalized seizures as well. While valproic acid is primarily used for primary generalized seizures, it has been used successfully in partial seizures, especially those which tend to generalize. Carbamazepine has efficacy for partial seizures.

Side effects, especially long-term effects, must be considered and each has its own specific problems to consider. Lethargy is common to all of them, but is most problematic with phenobarbital use. Phenytoin typically causes gum hypertrophy requiring meticulous dental hygiene. Its use requires monitoring for potential liver toxicity and, over the long term, contributes to osteoporosis. Carbamazepine must be monitored for bone marrow and liver toxicity and may also contribute to bone loss over the long term.

Phenobarbital accelerates osteoporosis and rarely causes connective tissue abnormalities that can be disabling. All of these induce the liver, making their metabolism more efficient over time. The patient may require increased drug over time to achieve the same drug level and effect. Patients taking valproate often exhibit weight gain and hair loss. Other potentially serious complications include osteoporosis, hyperammonemia, liver toxicity, pancreatitis, polycystic ovaries, and clotting abnormalities.

Next Generation of Anticonvulsants.

Over the last 25 years, a number of new anticonvulsants have been developed and come onto the market. Some of the mechanisms of action of the new drugs overlap with the older ones, but a few have unique effects. Many have a better side effect profile. They have all been tested and were approved in partial seizures. Clinically, some have shown efficacy in the primary generalized epilepsies as well. Felbamate, lamotrigine, gabapentin, topiramate, oxcarbazepine, zonisamide, tiagabine, and levetiracetam are all currently available in the United States.

Almost all of the new agents also affect sodium channel conductance. Many have effects on calcium channels, chloride conductance, and GABA modulation. Unlike the older agents, they do not induce the liver and have lower protein binding giving them better side effect and safety profiles and fewer drug-drug interactions. Because several have efficacy in headache or neuropathic pain, other beneficial effects can be taken into account when making a choice of anticonvulsant.

Oxcarbazepine is used for partial seizures and is approved for monotherapy. It has shown efficacy in patients who are difficult to control and has helped a few to

avoid surgery. However, it can cause sedation and hyponatremia. Using a slower than recommended titration may help. Sodium levels should be checked within 3 months of initiation of treatment. A mild reduction in sodium is common and infrequently requires treatment.

Lamotrigine has the best side effect profile with few patients complaining of cognitive problems or sedation. However, about 10 percent of patients will develop an allergic reaction, usually manifested by a rash. Severe reactions, such as Stevens-Johnson syndrome, are rare, but if any rash, which appears drug-related occurs, the drug should be stopped. Slow titration and avoidance of large bolus doses help prevent reactions.

Topiramate is another powerful anticonvulsant. It has multiple mechanisms of action and is efficacious for both partial and generalized epilepsies. Side effects often limit upward titration of the dose. The dose should be titrated slowly. Patients may experience sedation and some develop cognitive issues, especially slowed thought processes and difficulty expressing themselves verbally. Dose reduction often helps, but some require discontinuation. Rarely, kidney stones have developed.

Zonisamide also has numerous actions. It is efficacious against partial seizures and has been particularly useful clinically in some patients with primary generalized epilepsy (PGE). One advantage of this drug is its once a day dosing. Side effects tend to be mild and are similar to topiramate.

Levetiracetam is a unique anticonvulsant, quite different in action to the others previously described. It is primarily used for partial seizures and is occasionally used for PGE. There are no significant drug interactions and side effects are uncommon. If they

occur, patients most commonly complain of lethargy. There may be mood alterations and patients have developed depression.

Gabapentin is an extremely safe drug. It is useful adjunctively in partial seizures and has been found to relieve neuropathic pain. Side effects are rare, although occasionally sedation occurs. Rarely patients develop mild edema peripherally. If it occurs, the drug should be stopped and if the edema is persistent medical evaluation is required.

Felbatol is an exception. It is still quite useful and highly efficacious. Unfortunately, a small number of people developed serious hepatic and bone marrow complications. Because of the potentially fatal toxicity, use of this drug is now usually limited to patients with severely intractable seizures.

Surgical Treatment Options. The vagal nerve stimulator has become increasingly popular as an adjunctive treatment of epilepsy, especially in those patients who are not fully controlled with AEDs and are not candidates for resective surgery. It is approved for the adjunctive treatment of partial seizures and has been used in primary generalized epilepsies, as well with good effects. It is placed under the skin in the anterior left chest. A wire is attached to the vagus nerve in the neck and then threaded under the skin and inserted into the device, leaving the patient with 2 small scars.

The advantages are that there are no drug side effects, the stimulator gives a dose of electricity without the patient having to remember to use it and it can be activated with a swipe of the magnet when the patient feels a seizure coming to give an extra dose when needed. Giving an extra dose at the beginning of a seizure may shorten or even abort it. However, the patient may become hoarse or cough when the stimulation cycle

begins, especially when the dose of electricity is increased. There is little discomfort and this effect lessens over time. It takes much longer to show an effect than medications with only 31 percent showing more than a 50 percent decrease in seizures at 1 year. It took 18 months for over 50 percent of patients to have a 50 percent or more reduction in seizures.³ Patients must understand that this is a long-term process and results will not be seen quickly. Also, the chances of attaining seizure frequency is low and most patients remain on at least some of their anticonvulsants.

The mechanism of action is unknown. Stimulation has been shown to increase certain chemicals in the cerebrospinal fluid (CSF) and to reduce epileptic discharges on EEG. It appears to have effects on the dopaminergic and serotonergic systems⁴, in addition to increasing the blood flow to the thalamus.⁵

Resective surgery is a useful and underutilized treatment for intractable epilepsy.⁶ The average time from onset of seizures to epilepsy surgery is often over 20 years. For appropriate patients, temporal lobectomy has a success rate of over 70 percent. Temporal lobectomies are the most common operation. Other procedures include frontal lobectomy, lesionectomy, and corpus callosotomy. To be considered for surgery, patients must have had 18 months to 2 years of intractable epilepsy, failing at least 2 to 3 medications in therapeutic doses during that time. After failing multiple agents, chances of seizure control with medical therapy alone are less than 5 percent. Patients meeting these criteria have pre-surgical work-up including inpatient video/EEG monitoring, neuropsychological and intracarotid amytal testing (WADA test). Some patients will need PET scanning or intracranial monitoring. Risks of

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temporal lobectomy include memory or speech problems, mood disorders, and rare perioperative complications, such as stroke, infection, and bleeding.

These risks must be weighed against the long-term morbidity and mortality of uncontrolled seizures and chronic medication side effects.

Currently, an Early Randomized Surgical Epilepsy Trial (ERSET) is being conducted to assess the risks and benefits of early treatment. Some centers are conducting experimental trials of deep brain stimulation for epilepsy as well.⁸

Conclusion. Treatment options for people with epilepsy have increased significantly. Numerous medications have been developed, which are not only efficacious, but, in many cases, also have significantly fewer side effects. Surgical protocols have been standardized and are generally safe and effective. Improved imaging techniques and digital electroencephalographic equipment have reduced the need for invasive procedures further reducing the morbidity of epilepsy treatment. Increasingly, treatment options can be tailored to the individual patients' needs. For the future, research continues on many fronts and hopefully soon there will be even more and better therapies available.

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