Epilepsy – Dilemmas in Management

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General Concepts
Therapy in epilepsy is determined almost entirely by accurate diagnosis.¹ The two broad classes of epileptic disorders, primary (or idiopathic) and secondary (or symptomatic), are becoming blurred, as we realize the genetic determinants for both, but the distinction is still useful for syndromic categorization and prognostic determination. It is, however, the classification of seizure types specifically that allows proper drug selection. It also allows a frame of reference from which to establish diagnosis of other disorders that may simulate recurrent seizures.² Within the two broad categories of generalized and partial seizure types are further nuances which pertain to therapeutic decision-making. Partial onset seizures may be without (simple partial) or with (complex partial) altered consciousness, or secondary generalization, but the pharmacotherapeutic selections are the same for all seizures in this group. Within the generalized onset seizures, however, individual types (myoclonic, tonic-clonic, atonic, tonic, absence) have differential pharmacologic responses. The syndromic “epilepsy” categorization combines the specific seizure types and other characteristics including age, family history, results of neurologic examination and imaging and EEG, and provides information on prognosis and responsiveness to the otherwise appropriately selected drug therapy.³ Careful history supplemented by observations of others, along with the results of EEG, imaging studies, and neurologic examination, are successful in achieving a correct diagnosis of the seizures and the epilepsy type in most situations. If not, video/EEG and more sophisticated studies are used.¹,⁴

Initiation of Treatment
The first decision after diagnosis is whether to treat at all, even with a firm diagnosis of the type of recurrent seizures and a classification of the epilepsy syndrome. This question arises in several specific situations, including: initial treatment after a first seizure; benign epilepsy syndromes; and seizures in acute medical settings. Berg and Shinnar concluded from a meta-analysis of 16 published studies that the overall risk of recurrence after a first unprovoked seizure (over 2 years) is 42%;⁵ the First Seizure Trial group found the risk to be 51% in untreated patients.⁶ Because of this, many physicians do not initiate antiepileptic drug therapy after an initial, unprovoked seizure in a child or an adult unless certain factors known to increase the risk are present. These include partial onset, abnormal neurological exam,
abnormal EEG with epileptiform features. In some settings, patient circumstances, including the need to drive or continue specific occupations, contribute to the decision. After a second unprovoked seizure occurs, however, the risk of recurrence rises to 74%, and is usually a clear indication to initiate therapy. Some pediatric neurologists also do not treat certain groups of patients, with recurrent seizures, when they are part of benign syndromes, such as benign rolandic epilepsy. This decision may also be modified by specific circumstances including the frequency and severity of individual seizures, or other concomitant diagnoses or medications. In patients with recurrent seizures due to acute medical situations (DTs or other drug withdrawal, intracerebral hemorrhage, trauma, among others), antiepileptic drugs are used for a limited interval, if at all, and are successful in preventing seizures in that setting. The selection of an individual drug is then made based on the kind of seizure, and is influenced to a large degree by the mechanistic considerations attendant upon individual drugs and classes of drugs. If successful treatment is achieved without unacceptable side effects with a single drug, perhaps the initially chosen one, then there is no need to consider further interventions, and decisions will subsequently rest upon how long a patient remains seizure-free. If an initial drug is unsuccessful, it may be switched to a different drug (also “appropriate” for the individual patient and seizure diagnosis). If multiple, individual drugs fail because of therapeutic inadequacy, two drugs may be combined. Drug therapy in epilepsy aims to stop seizures entirely, and is the first and only therapy utilized in the majority of patients.

Selection of Antiepileptic Drugs
There are three broad classes are based on mechanisms of action. The first class affects sustained repetitive firing by delaying the recovery from inactivation of sodium channels. This class of drugs is most effective in the treatment of partial onset seizures with or without secondary generalization. Sustained repetitive firing can also be reduced by glutamate receptor antagonists that block the AMPA or NMDA subtypes of the glutamate receptor, as well as by drugs that block voltage-gated calcium channels. The second main class of antiepileptic drugs includes those which enhance GABA-mediated neurotransmission. These include drugs that act on the GABA-A or GABA-B receptor. It is somewhat difficult to determine the type of seizures upon which these drugs act without knowledge of the specific brain locations in which they act; these drugs may be effective against any kind of seizure. The final class of antiepileptic drugs blocks T-type calcium channels in thalamocortical relay cells, and is effective in treating generalized, absence seizures. This broad classification of actions of the antiepileptic drugs does not explain all observed phenomena, so it is clear that our knowledge of all the ways in which our available antiepileptic drugs act is limited. Thus, carbamazepine, phenytoin, and lamotrigine are drugs which fit into the first class, acting on sodium channels to reduce sustained repetitive firing, and appropriate for partial onset seizures. However, the patients who respond to carbamazepine and phenytoin are not identical, and certain individuals benefit from one while failing the other. Another example is lamotrigine, which appears to be a very broad spectrum drug, i.e. effective against all seizure types including generalized onset and partial onset seizures inclusive of absence events.

Identify Seizure Type and Tailor Therapy the Biggest Challenge
Generalized Seizures
Multiple types of generalized onset seizures are known (tonic, atonic, absence, tonic-clonic, myoclonic). Most of these respond to valproic acid, and valproic acid monotherapy is the usual standard for treatment of generalized onset seizures. A single published, randomized, double-blind, placebo-controlled trial found a significant reduction in generalized tonic-clonic seizures with topiramate. Lamotrigine resulted in significantly more absence-free patients than placebo according to another study. Lamotrigine was also found to be effective as add-on therapy in patients with refractory generalized epilepsy, including many with Lennox-Gastaut syndrome.
not used much now, also demonstrated efficacy for pharmacoresistant, symptomatic generalized seizures. Finally, zonisamide, a relative of piracetam, may have efficacy in various generalized seizure types, although it was approved as adjunctive therapy of partial onset seizures. So far, experience and evidence do not provide a rationale for the use of most other new or older antiepileptic drugs in generalized onset seizures, save for the specific use of ethosuximide in generalized absence, and benzodiazepine derivatives in myoclonic and other generalized seizures. The single caveat to these comments is the patient with only generalized tonic-clonic seizures; these may respond to many of the older and newer antiepileptic drugs, including all of those effective in partial onset seizures. These comments can be summarized by saying that valproate is the most universally accepted and broad spectrum of the choices for treatment of generalized seizures; lamotrigine monotherapy for absence seizures with or without generalized tonic-clonic seizures, in situations where valproate is inadequate or not tolerated, is a good choice as well; topiramate and zonisamide are potentially useful, although not as well established for this indication; and felbamate, though effective, is reserved for patients that do not respond to the others. When control of generalized seizures is not possible with a single drug, combinations of these drugs can be used to true advantage. Such combinations might include valproate and ethosuximide (where available) in refractory absence; and valproate plus clonazepam, felbamate, or lamotrigine in other refractory generalized seizures. Of all the generalized seizure types, myoclonic seizures have the least responsiveness and tend to respond best to valproic acid, benzodiazepines, or zonisamide.

**Partial Onset Seizures**

Institution of treatment for partial-onset seizures is more challenging because of the multiple options that now exist. Besides phenytoin, phenobarbital, and carbamazepine of the older armamentarium (of which carbamazepine was usually favored secondary to its combined profile of high efficacy and low side effects), all the newly marketed antiepileptic drugs (gabapentin, tiagabine, lamotrigine, topiramate, zonisamide, levetiracetam, and oxcarbazepine), were approved for, and are efficacious for, partial onset seizures (at least in add-on studies). Few comparative studies provide much basis to choose between them. In some published work, specific studies found the “new drugs” equivalent in efficacy to the “older” ones. Comparison meta-analyses of the newer agents to one another suggested higher efficacy for topiramate, oxcarbazepine, and levetiracetam, and more side effects for topiramate, lamotrigine, and oxcarbazepine. The balance of side effects, individual tolerability, ease of use, and experience suggest carbamazepine is still a “first” choice, although oxcarbazepine is equivalent in efficacy and has certain advantages. These include its relative lack of enzyme induction as well as its lack of hepatic and hematologic toxicity.

**Success of Drug Treatment**

In both generalized and partial onset seizures, the reported success rate in monotherapy (with switch to an alternative drug if the first one fails) is not much better now than it was 10 years ago, indicating that the new additions to our therapeutic choices, although providing more options and better quality of life for many patients, have not diminished the ranks of medically refractory pharmacoresistant) epilepsy patients. In generalized epilepsies, monotherapy produces freedom from absence seizures in 60 – 90% of patients, from myoclonic seizures in 70 – 90% of patients, and from generalized tonic-clonic seizures in 80 - 90% of patients. In partial onset seizures, the level of control with any agent in monotherapy is lower. Schmidt found no more than 50% of patients with previously untreated partial epilepsy responded to monotherapy, and alternative monotherapy resulted in 75% seizure reduction in only an additional 30%. Mattson and colleagues found minimal differences between carbamazepine, phenytoin, phenobarbital, and valproate in control of partial seizures. Although comparisons of older versus newer drugs are not extensive, one study found only a small percentage of patients refractory to older drugs became seizure free with newer ones. Some investigators did report

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improved efficacy with new agents. Wada and colleagues showed that, of a group of patients who were uncontrolled with “conventional” antiepileptic drugs, half showed significant improvement when a newer agent was added. Those who did not respond were more likely to have neuropsychiatric complications, multiple seizure types, and/or abnormal imaging studies. Cramer and colleagues (1999) reviewed and analyzed reported response rates to new antiepileptic drugs. Improvement rate (patients with more than 50% seizure frequency reduction) ranged from 10 – 15% (compared with placebo) for gabapentin, lamotrigine, and tiagabine, to 28 – 30% for vigabatrin and topiramate. (These studies were done before the release of levetiracetam and zonisamide.)

Drug Resistant Epilepsy
Some authors think that “drug-resistant seizures” belong to a different class, and have entirely different basic mechanisms. Recent teaching extends the use of polypharmacy in this group, a reversal of the previously negative attitude towards simultaneous use of multiple agents. The record of response to rational (complementary mechanisms of actions) drug combinations after failed monotherapy trials of at least 2 drugs is variable. According to the literature addressing the older drugs, 37 – 47% of patients not adequately controlled with single drug therapy have remission of seizures with a combination of 2 agents. Bauer, however, reported only about 12% of patients achieved seizure control with polytherapy after failure of several agents in monotherapy. Kwan and Brodie also found an unimpressive response to combination therapy when single drugs failed, and reported a relatively low response to changes in monotherapy agents as well. Some investigators proposed that broad spectrum drugs like valproic acid and lamotrigine are an excellent choice for polytherapy. Willmore and colleagues found that adding valproate to a regimen produced additional control in almost 40% of patients who failed monotherapy with phenytoin or carbamazepine. This suggests that one approach to polytherapy might be the combination of a more specific and a more broad spectrum agent. Recent publications suggest, based on careful review of published literature, that AED combinations that appear to be associated with improved effectiveness are phenobarbital and phenytoin, phenytoin and valproate, carbamazepine and valproate, valproate and ethosuximide, and valproate and lamotrigine. Other suggested combinations were phenytoin and clonazepam, phenobarbital and topiramate, carbamazepine and topiramate, and lamotrigine and topiramate. Although standard teaching is that additive toxicity is observed using polytherapy, at least some studies indicate that increased effectiveness might be associated with improved tolerability with polytherapy in certain situations. Further, some authors reported that combining a glutamate receptor antagonist and a drug which enhances GABAergic inhibition, the previously recommended approach to polytherapy, may not necessarily produce incremental efficacy, and that combining two glutamate antagonists or two GABAergic drugs may produce increased efficacy. On the basis of this published data and our present knowledge of these drugs, combinations that might be recommended include the use of a sodium channel blocker with a drug that enhances GABAergic inhibition; the use of two drugs both of which enhance GABAergic inhibition; or the use of two drugs that target glutamate receptors by combining an AMPA antagonist with an NMDA antagonist. Combining two sodium channel blockers seems less promising. Even when the appropriate agent or agents are utilized, refractory seizures may continue because of inadequate dosing. Schmidt found that fully 30% of patients referred for inadequate seizure control had remission of seizures after raising their daily dose of phenytoin or primidone, without any change, addition, or reduction in numbers of medications. In my experience, supratherapeutic doses and levels of certain drugs produce incremental efficacy, for example in frontal lobe seizures with serum concentrations of phenytoin over 30, and can be well tolerated. When the appropriate antiepileptic drugs are used to best advantage and seizures remain uncontrolled, one must also consider other factors in modifying patient response. Foremost among these is compliance. Despite an understanding of the importance of medication, simplification of schedule, and reduction in number of pills, it is difficult to achieve full patient compliance. Probably the best mechanism is a pill box
that enables arranging doses for an entire week. Patients who experience significant toxicity are likely to self-adjust medications or not take them, and a physician should be careful to consider toxicity in the design of the medical regimen. Intrinsic hormonal variations as well as extrinsic hormone therapy can impact seizure control. Catamenial seizure exacerbation is difficult to manage even by changing doses at a particular time of month. Hormonal replacement therapy, particularly with unopposed estrogen, may cause seizure exacerbation. Pregnancy can result in an exacerbation of seizures, an amelioration, or no change, all in approximately equal numbers of patients. Sleep deprivation is a powerful factor in lowering seizure threshold, as is fasting. Bulimic and anorexic patients can be difficult to manage, although the exact reasons have not been systematically explored. These factors are often hidden from the physician. Anecdotal reports associate excessive use of aspartame and caffeine with seizure exacerbation. Another precipitant of seizure activity is a rise in body temperature, whether due to illness, high ambient temperatures, exercise, or immersion in hot tubs. Stress and anxiety exacerbate seizures. Photic-sensitive individuals with generalized seizures may be sensitive to video games, computer monitors, sunlight, and flashing lights at discos. Photic sensitivity is most common in primary generalized epilepsy but also occurs in partial onset seizures of occipital lobe origin. Metabolic derangements, extrinsic or intrinsic, commonly exacerbate seizures and may be unrecognized. Hypoglycemia associated with insulin-dependent diabetes is the most common. It can be extremely difficult to control seizures in individuals with brittle insulin-dependent diabetes. Hyponatremia, hypocalcemia, and hypophosphosphatemia can exacerbate epilepsy. Illicit drug use is a serious difficulty: the most common cause of seizures in the emergency room is cocaine. Alcohol and benzodiazepine withdrawal are also common culprits. Rarely will individuals volunteer their use of these agents. Other medications prescribed for common medical conditions can exacerbate seizures by causing pharmacokinetic interactions and enhanced metabolism, or can lower the seizure threshold. Drugs in the latter category include theophylline, penicillin and its derivatives, and antihistamines. Antidepressants and antipsychotic agents lower the seizure threshold, particularly the older generation ones, but also some of the newer alternatives including bupropion. It is illogical and usually ineffective to consistently change antiepileptic drug selections or even pursue polytherapy because mitigating factors are causing breakthrough seizures. These general comments cannot stand without more specific discussion of the available and currently used antiepileptic drugs. As stated earlier, the vagaries of drug selection include individual sensitivity to side effects. Individual drugs also have variable kinetic profiles which allow more ease of use in certain situations than in others. Side effects occur variably in individual patients. Effects on weight, appetite, fluid retention, sodium levels, insomnia, sedation, and concentration, may all appear, and impact individual selections of antiepileptic drugs.

Surgical Intervention

The use of surgery to treat epilepsy continues to find an increasingly important role in management of medically refractory patients, who comprise 30% or more of those with partial onset seizures. Localization of the region or regions of partial seizure onset determines the applicable surgical procedure. There are no surgical interventions currently described for treatment of primary generalized epilepsy. When a combination of structural, electrographic, and functional studies (including MRI, ictal and interictal EEG, PET, SPECT, neuropsychological evaluation) show that medically refractory seizures arise in a single cortical region, it is the possible functional impact of removing the area that determines whether resective surgery is possible. In the optimal situation, resective surgery can cure seizures with a success rate approximating 90%. The best situation is removal of anterior-medial temporal structures in the syndrome of medial temporal lobe epilepsy with mesial temporal sclerosis as its substrate. Demonstration of hippocampal atrophy on MRI is highly suggestive of that diagnosis, a pathologic entity of hippocampal neuronal loss, gliosis, and synaptic reorganization that is highly characteristic. Correlates of hippocampal atrophy include temporal lobe hypometabolism and hypoperfusion on PET and SPECT scans; neuropsychological profiles demonstrating significant loss of verbal
(dominant hemisphere) or visual (nondominant hemisphere) memory; scalp EEG with unilateral, anterior temporal interictal spikes and ictal, rhythmic theta discharge. In some situations, the localizing information is insufficient or discordant, in which case invasive EEG is needed. Invasive EEG, utilizing some combination of depth and subdural electrodes or implanted subdural grids, is always necessary for partial epilepsies that arise outside of medial temporal lobe structures when the MRI is normal. Regardless of the exact combination of diagnostic procedures used, localization of the region or regions of seizure onset is possible in up to 70% of patients with medically refractory, partial onset seizures. After mapping, when needed to define the function of the cortical epileptogenic zone, resection can be pursued. The success of resective surgery in medial temporal lobe epilepsy, or in epilepsy arising in any lobe when it is associated with MRI-demonstrated lesion (and when EEG is concordantly localized), is so high that these “lesional” substrates of epilepsy have come to be regarded as “surgically remediable syndromes”. Unfortunately, the same record of success is not achieved with resections when no MRI abnormality is present. In those situations, the success rate for cure of seizures is only about 50%. Until recently, there were no randomized studies of results in resective epilepsy surgery. Last year, because of the usual 1 year waiting period for surgery in Canada, Wiebe and colleagues were able to randomize candidates for medial temporal lobe resections into immediate surgery versus a 1 year delay. In this first-ever, randomized study of epilepsy surgery, they documented 58% remission of seizures in the surgical group compared to 8% in the non-surgically treated group. Quality of life was also improved in the surgical group. Unfortunately, follow-up was limited to 1 year, while some work suggests that there may be up to a 25% relapse rate in temporal lobe resective surgery. No randomized studies are available for extratemporal or neocortical resective epilepsy surgery.

Conclusion
The current dilemmas in managing patients with epilepsy mainly deal with the correct drugs to start for the particular type / syndrome of epilepsy. The issues about when to start and stop drugs, drugs to be used in pregnancy are more or less rationalized with experience in treating epileptics over the past decade. It is a must to recognize refractory cases and subject them to the work up of intractable seizures at centers equipped to do so.

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