MANAGEMENT OF EPILEPSY IN DRUG-RESISTANT PATIENTS

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Case Presentation

A 34-year-old man had a history of complex partial seizures that began at 12 years of age. In the past, he had been treated with phenytoin, valproate, and oxcarbazepine but had never achieved full control. Recently, he has been experiencing 3–4 seizures/month. One year earlier, he had been evaluated for epilepsy surgery, but scalp recording demonstrated clear evidence of independent bitemporal seizure foci. Recently, he felt less confident at work as an engineer due to seizures occurring while interacting with colleagues.

Introduction

Approximately two thirds of the 2.5 million Americans with epilepsy are expected to have acceptable seizure control with antiepileptic drug (AED) treatment. In an observational cohort study of newly diagnosed adults with epilepsy,[1] findings suggested that once a patient has failed trials of two appropriate AEDs, the probability of attaining seizure freedom is <3%. This study supported an operational definition of "medically refractory" or "intractable" epilepsy (failure of two to three AEDs) that epilepsy surgery centers had used for years. Interestingly, in a recent meta-analysis of patients with drug-resistant epilepsy who continued with AED therapy versus surgical intervention, 12% of patients had a seizure-free outcome.[2] In an attempt to improve patient care and facilitate clinical research, an ad hoc Task Force of the International League Against Epilepsy Commission on Therapeutic Strategies has provided a consensus definition of drug resistant epilepsy to improve patient care and facilitate clinical research. Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.[3]

Typically, a clinician determines drug failure when a dose is reached that is not providing adequate seizure control and the patient reports unacceptable side effects. It is important that the clinician verify this has occurred as studies have documented cases in which patients have been determined refractory, but review of the specific agents attempted and the patient's clinical course do not support that conclusion. A typical example is the patient who reports failing or being "allergic" to carbamazepine, when the actual cause for drug failure was that carbamazepine was initiated or escalated too rapidly before hepatic induction.

Despite attempts to obtain acceptable seizure control, the case patient has failed three appropriate AEDs and was referred for presurgical evaluation. Should this patient have been referred for presurgical evaluation earlier in light of the refractory course? Earlier referral for surgical intervention is encouraged and is believed to be beneficial in preventing the irreversible disabling psychological and social consequences of epilepsy.[4] A previous multicenter epilepsy surgery study tabulated that appropriate candidates for epilepsy surgery are not referred until an average of 22 years after onset.[5] Some clinicians and researchers believe that recurrent seizures may have detrimental effects on the brain similar to kindling and secondary epileptogenesis noted in animal studies.[6] The clinical implications for human epilepsy remain controversial.[7]

Unfortunately, with evidence obtained by noninvasive testing suggesting independent bitemporal epileptogenicity, the option of surgical intervention (eg, anterior mesial temporal resection), would leave this patient at high risk for continued seizures and probable significant deterioration in memory function. Thus, how should the neurologist in clinical practice approach the patient who appears to be pharmacoresistant to AED therapy, and not a candidate for focal resection? Due to the fact that this patient continues to have frequent seizures, difficulties in the work place, and limitations because of seizure restrictions, further options should be discussed in a timely manner. Depending on the nature of the neurology practice managing his condition, this discussion may be limited to recommending follow-up with the comprehensive epilepsy center for review of further options. However, a neurologist with significant experience managing drug resistant epilepsy patients may be interested in attempting AEDs the patient has not yet taken, or consider the option of vagus nerve stimulation (VNS).

Medical Therapy

Although the expected likelihood of obtaining a seizure-free state is low (3% to 12%) in patients with drug resistant epilepsy, there are still a number of AEDs the case patient has not yet taken that may provide a significant reduction in seizure frequency. Previous trials[8,9] demonstrated refractory patients initially on ≥2 drugs had better seizure control and fewer side effects when converted from polytherapy to monotherapy. These studies ushered in the concept that sequential monotherapy was the most effective treatment paradigm, but this occurred when most available AEDs were considered sodium channel blocking agents.[10] When newer agents became available in the 1990s with novel mechanisms of action—invoking the possibility of additive or possibly supra-additive enhancement of efficacy along with fewer pharmacokinetic interactions and less central nervous system side effects—the concept of rational polytherapy emerged.[11]

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Disclosures: Dr. Smith is a consultant to Lundbeck, NeuroPace, Pfizer, and UCB Pharma; has received honoraria from Lundbeck, Pfizer, and UCB Pharma; and receives research support from NeuroPace and Pfizer. Dr. Smith discusses unapproved/experimental uses of brain stimulation, brivaracetam, carisbamate, clobazam, eslicarbazepine acetate, marijuana, a modified Atkins diet, and retigabine for the treatment of epilepsy. Dr. Cole is a consultant to and has received honoraria from GlaxoSmithKline and UCB Pharma.

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Although seizure freedom without side effects is the ultimate treatment goal, the percentage of drug resistant patients who become seizure-free in placebo-controlled trials with available agents has been very low.[12] Nevertheless, these patients tend to tolerate AED side effects better than newly diagnosed patients.[13]

For the case patient, trials including second generation AEDs that are well known to the clinician including levetiracetam, lamotrigine, topiramate, zonisamide, felbamate, and pregabalin could be attempted. AED selection may be decided in part based on the patient's wishes (after review of side effect profile and tolerability), along with the physician weighing proposed mechanism(s) of action, drug interactions, patient age and sex, and existing comorbidities. With the failure of three agents, considering a drug with a different mechanism of action than the patient is presently on or previously attempted may be beneficial. Most AEDs are reported to have multiple potential mechanisms of action based on animal studies; how relevant each of these are in humans is unclear or unknown.[14] Nevertheless, there is the general idea that using two agents with different mechanisms may have complementary effects.[10] Many clinicians utilize certain AED combinations and avoid others based on their own personal experience with previous patients. Although there may be combinations that are more effective, no specific clinical trials have been designed to address this question. Despite limited data guiding selection of drug combinations, there is some evidence for synergy with the lamotrigine-valproate combination in humans. Although this can be a very effective combination, it needs to be monitored closely due to the significant interaction between these two AEDs. Drugs metabolized through the cytochrome P450 system[15] including phenobarbital, phenytoin, carbamazepine, primidone, and valproate, and to a lesser extent, topiramate and oxcarbazepine have the most risk for drug interactions. Drugs with least interactions because they are not metabolized by the liver include gabapentin, levetiracetam, pregabalin, and vigabatrin.[10]

Drug selection based on efficacy alone is determined mainly by the personal experience of the treating physician as there are few available studies comparing new AEDs with each other or with older AEDs in drug resistant epilepsy patients.[13] No new AED has proven more efficacious than carbamazepine, valproate, or phenytoin for partial onset seizure control in adults with drug resistant epilepsy. With the case patient's relatively high seizure frequency (3–4 per month), an ideal treatment would provide improvement fairly rapidly. Certain drugs may require more time to adequately test because of the length of time needed for drug escalation due to the risk of a hypersensitivity reaction (eg, lamotrigine).

In the past year, two new AEDs—lacosamide and vigabatrin—have been United States Food and Drug Administration-approved for use as adjunctive therapy in adults with drug resistant, partial epilepsy. Lacosamide, formerly known as harkoseride, selectively enhances slow inactivation of voltage-gated sodium channels, a presumed novel method of action.[16] Lacosamide exhibited a synergistic anticonvulsant effect in combination with topiramate, gabapentin, lamotrigine, levetiracetam, and carbamazepine in the 6 Hz seizure model in mice. Therapeutic dose ranges from 200–400 mg/day, and an intravenous formulation is available.[17]

Vigabatrin was synthesized in an attempt to find a molecule that would increase CNS levels of γ-aminobutyric acid (GABA). The method of action of this drug is believed to be the result of action as an irreversible inhibitor of GABA-T, the principle enzyme responsible for metabolism of GABA.[18] This results in increased GABA levels in the CNS. Vigabatrin was FDA-approved for adjunctive therapy in adult patients with refractory complex partial seizures (CPS) who have inadequately responded to several alternative treatments, and for whom the potential benefits outweigh the risk of vision loss. Its approval and use in the US is closely monitored as visual field defects may occur in ≥30% of patients and these changes may be irreversible and unpredictable. Use of vigabatrin requires specific documentation (FDA-approved risk evaluation and management program) and periodic formal visual testing. The recommended maintenance dose is 1.5 g BID.[19]

Although not FDA-approved or available in the US, there have been anecdotal reports of patients with drug resistant epilepsy secondary to independent bitemporal foci becoming seizure-free with the addition of clobazam, a benzodiazepine that can be utilized for chronic therapy. One review of data found that clobazam, as an add-on treatment, may reduce seizure frequency and be most effective in partial onset seizures.[18] However, it is not clear the type of patient who will best benefit from clobazam and over what time period. Two of the studies reported a ≥50% seizure reduction compared to placebo; 57.7% and 52.4%. Side effects were described in two of the studies, reportedly present in 36% and 85% of patients.[20]

Enrollment into a research trial attempting to determine the efficacy and tolerability of new agents may be an option for some patients, although there are many approved AEDs that the case patient has not yet received (Slide 1). Brivaracetam, carisbamate, eslicarbazepine acetate, and retigabine are some of the agents undergoing further clinical trials, and are not yet FDA-approved for epilepsy treatment.[21]

Alternative Medical Therapies

Although less commonly considered, there are some alternative therapies (eg, a modified Atkins diet, marijuana) that have been examined as options in this refractory population.[22-25] A modified Atkins diet has been used in adults in place of the ketogenic diet because of its perceived inefficacy and restrictiveness. A prospective trial utilizing the modified Atkins diet in 30 adult patients with drug resistant epilepsy was completed by Kossoff and colleagues.[22] Using an intent-to-treat analysis, 47% had a >50 seizure reduction after 1 and 3 months on the diet; 33% of patients reached this threshold after 6 months. The median time to improvement was 2 weeks (range 1–8 weeks), and the median weight loss was 6.8 kg ($P<.001$).

SLIDE 1
Other Medical Treatment Options

Available AEDs

Carbamazepine	Phenobarbital
Clobazam*	Primidone
Felbamate	Tiagabine
Gabapentin	Topiramate
Lacosamide	Vigabatrin
Lamotrigine	Zonisamide
Levetiracetam	

AED Research Trials†

Brivaracetam	Eslicarbazepine acetate
Carisbamate	Retigabine

Dietary: Modified Atkins diet†

Other: Marijuana†

* Not FDA-approved or available in the United States
† Not FDA-approved

AED=antiepileptic drug; FDA=Food and Drug Administration.

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Side effects included increased cholesterol, blood urea nitrogen, and urine calcium to creatinine ratio.[22]

Despite the fact that there is limited scientific evidence regarding the efficacy of marijuana for the management of epilepsy (not an FDA-approved treatment option), it continues to receive more attention as more states in the US allow an exemption from criminal penalties for defined patients who possess and use medical marijuana under physician supervision.[23] Some evidence suggests that marijuana and its active cannabinoids have antiepileptic effects, and these may be specific to partial or tonic-clonic seizures.[24] In a telephone survey by a tertiary care epilepsy center, 21% of subjects had used marijuana in the past year with the majority of active users reporting beneficial effects on seizures.[25]

Alternative Surgical Therapies

VNS is currently the only FDA-approved neurostimulation treatment strategy for patients who are not considered candidates for epilepsy surgery. VNS has been shown to decrease seizure frequency by ~50% in 30% to 40% of implanted patients[26] and provided long-term seizure freedom in 5% to 10% of patients.[27] Although patients who appreciate an aura at onset of a typical event have the advantage of self stimulation using the provided magnet, many patients without an aura benefit from the effects of chronic stimulation. The ability to control a part of their treatment (ie, magnet stimulation) has had a positive effect in most patients. Implantation of the device is a fairly simple procedure that can be done on an outpatient basis, with the patient returning to clinic at regular intervals for parameter adjustments. Surgical complications and perioperative morbidity are low. Alsaadi and colleagues[28] reported that six out of 10 patients with documented bilateral independent temporal lobe epilepsy had a >50% reduction in their seizure frequency, which persisted to >1 year follow-up.

Building on the success of indirect brain stimulation (VNS trials) and utilizing specific neuroanatomical sites which effect epileptic seizures, pilot studies of deep brain stimulation (DBS) in various thalamic nuclei and medial temporal lobe structures have shown to be efficacious.[27] Two multicenter trials addressing the efficacy of intracranial brain stimulation have now been completed in the US and await FDA review and approval (Slide 2).

The first study completed was a prospective, randomized, double-blind pivotal study to evaluate the use of DBS in patients with drug resistant partial epilepsy. The study, known as the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy study, collected data from 110 patients enrolled at 17 US centers who were implanted with a DBS system and were monitored for a minimum of 13 months following implant.[29] Study participants had partial-onset epilepsy, had failed to see benefit from at least three AEDs, and had an average of ≥6 seizures per month. Data showed that stimulating the left and right anterior nucleus of the thalamus in conjunction with epilepsy medications produced a statistically significant median percent reduction in seizures compared to a no stimulation control group at the end of the blinded phase of the study (38% in the treatment groups vs. 14.5% in the control group with both groups continuing on their epilepsy medications without change during this phase). The results from long-term follow up during the trial show greater reductions in seizures for the majority of patients. The types of adverse events reported in the study were consistent with known adverse events associated with epilepsy and implanted DBS systems.[29]

SLIDE 2
Other Surgical Treatment Options

Surgery: Vagus nerve stimulation

Surgery Research Trials*

Intracranial stimulation

- Anterior nucleus of the thalamus
- Neocortical/hippocampal

Radiosurgery

* Not Food and Drug Administration-approved

Another intracranial stimulation trial, the Responsive Neurostimulator (RNS) System Pivotal Clinical Investigation was just recently completed in the US.[30] In this study, each patient had implantation of either subdural or depth electrodes (or a combination) directly to the presumed area of ictal onset localized by previous testing, instead of a predetermined neuroanatomical target. The responsive neurostimulation device (ie, RNS System) was designed to detect abnormal electrical activity in the brain via intracranial electrodes and then deliver small amounts of electrical stimulation to suppress the abnormal activity before any seizure symptoms occur (closed loop design). This type of treatment that delivers stimulation on seizure detection differs from DBS, which delivers stimulation continuously or on a pre-set schedule (open loop design). With the RNS System, physicians had the ability to non-invasively program the detection and stimulation parameters of an implanted RNS neurostimulator specifically for individual patients. The RNS System Pivotal Clinical Investigation was a randomized, double-blind, placebo stimulation controlled investigation that included 191 patients implanted with the RNS System across 31 sites. All subjects in the study were required to be ≥18 years of age and have partial onset epilepsy, with seizures that start from one or two areas of the brain, which have not been effectively treated with >2 AEDs alone or in combination.

The trial demonstrated a statistically significant reduction in seizure frequency in the treatment group (responsive stimulation active) as compared to the placebo stimulation group (responsive stimulation inactive).[30] During the last 2 months of the 3-month blinded evaluation period of the study, patients in the treatment group experienced a mean percentage reduction of 29% in their disabling seizures compared to a 14% reduction for those in the placebo stimulation group.[30] In the long term, open label period of the trial, at least 12 weeks of data were available for 171 study participants; 47% of these subjects experienced a ≥50% reduction in their seizure frequency based on their most recent 12 weeks of data, as compared to their baseline.[30]

Another surgical option for drug resistant partial epilepsy which is undergoing further investigation is radiosurgery. Many clinicians have witnessed the improvement in seizure control in patients who have completed radiosurgical therapy for tumors and arteriovenous malformations, but it was not until Regis and colleagues[31] reported seizure reduction in a group of partial epilepsy patients receiving doses in excess of 20 Gy to the amygdala and hippocampus that it was considered a potential future epilepsy treatment option.[31] Barbaro and colleagues[32] subsequently reported the 3-year outcomes of a multicenter, prospective pilot study of radiosurgery completed in the US.[32] Sixty-seven percent of patients were free of seizures for the prior 12 months (76% receiving 24 Gy to the amygdale, hippocampus, and parahippocampal gyrus; 58.8% receiving 20 Gy to the same structures). The prevalence of verbal memory impairment was 15%, while the prevalence of significant verbal memory improvement was 12%. Gamma knife treatment has the advantage of being a noninvasive procedure which avoids the risk of major surgery and potential, significant neurological morbidity (1% to 3%) of permanent hemiparesis, language disturbance, memory decline, hemianopia, and increased mortality.[33] However,

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specialists in epilepsy remain apprehensive of what role this option will play in light of its disadvantages including delayed response (2–3 years), and absolute requirement for continued medications compared to anterior medial resection.[34]

Conclusion: *Case Discussion*

Although there are many potential treatment options for the case patient with independent bitemporal seizure foci, unfortunately, there is little data available at this time to suggest that the possibility of his obtaining a seizure-free outcome is >5% to 10%. Due to his seizure frequency, it would be relatively simple to attempt some sequential trials of adjunctive therapy while he considers the option of VNS. Care must be taken that multiple variables are not changed at once (ie, AED dosage change and VNS parameter changes), since it would be difficult to determine which variable resulted in improvement or deterioration of his clinical course. There is also hesitation after an additional AED is added to remove an AED that has been previously maintained. The patient may make this decision easily if he implies a certain AED provided no improvement. Otherwise, there is always the concern that an agent will be removed with a specific mechanism of action (ie, GABA agonist, Na channel blocker) that has provided some seizure control and its removal could result in a seizure exacerbation. The patient always needs to be forewarned of this possibility. Nevertheless, addition of agents without subtraction of others over time will result in an excess "drug load." With too many AEDs taken, agents will compete with each other, alter metabolism, and result in an increased side effect profile and decreased quality of life. As the patient attempts additional medications and considers VNS implantation, the hope is that further progress will be made in providing options that result in a higher percentage of seizure-free outcomes.

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QUESTION-AND-ANSWER SESSION

Q: When would it be appropriate to reconsider the idea of epilepsy surgery for the case patient? Is it possible additional evaluation may point to a single explanation for the apparent bitemporal onsets suggested by the scalp recording?

Dr. Smith: The patient may reconsider epilepsy surgery at anytime since he has already fulfilled the criteria for drug resistant epilepsy. Scalp ictal patterns suggesting independent bitemporal onset may be misleading and actually represent a single focus with extratemporal onset and independent bitemporal propagation. Intracranial implantation would be needed to determine ictal origin(s) and potential benefits and risks of focal resection. Some patients who are found to have independent temporal lobe foci may benefit from surgical resection, although which factors result in a positive outcome is still debatable.[1]

Q: Is there any scientific way to determine which combinations of medication have a high likelihood of having a synergistic effect?

Dr. Smith: Animal studies may be utilized to determine which combinations of antiepileptic drugs (AEDs) may have a synergistic effect when a second drug added lowers the effective-dose 50 (EC50). A more complex procedure is the isobolographic method, which combines two drugs in various proportional percentages of their EC50s.[2] If the combination is supra-additive (synergistic) in potency, then lower proportions of both drugs should be effective.[3] Of course, results obtained in animal studies may not correlate with subsequent human experience.

Q: Given the wide therapeutic window for some of the newer drugs, how high a dose should a clinician prescribe before ending the drug's use?

Dr. Smith: With some AEDs, the daily dosage can be increased to amounts higher than the United States Food and Drug Administration-approved maximum dosage with few side effects. Justification of these higher daily dosages will be determined by physician- and patient-based reports on tolerability and improvement with seizure control after

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