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Optimizing Antiepileptic Drug Therapy in Refractory Epilepsy

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Introduction: When are patients "refractory"?

Establishing whether your patient has refractory epilepsy is a topic well covered in Chapter 14. In general, epilepsy patients fall into two categories in terms of the ease of treatment: those for whom nearly anything will work and those for whom seemingly nothing will work. This bimodal distribution of patient characteristics was established clearly by a retrospective study by Kwan and Brodie of all patients presenting with a first seizure; about two-thirds of patients were rendered seizure-free with trials of the first one or two medications. Notably, the likelihood of successful treatment did not differ between newer-generation antiepileptic drugs (AEDs) and older drugs. Also, patients who achieve seizure freedom with initial monotherapy often do so at AED dosage below "standard" levels, for example, using carbamazepine at 600 mg/day. Thus, the majority of new-onset patients can be successfully treated with moderate doses of whichever AED presents the most favorable tolerability profile, assuming it is indicated for their seizure type. Although there is no sharp boundary between patients whose seizures will remit with treatment and those that will be refractory, it is clear that the odds of achieving seizure freedom drop off with each successive drug failure. Thus, many epileptologists consider refractoriness to be the failure of two or three appropriate drug trials, in either monotherapy or polytherapy.

Before declaring a treatment regimen a failure, it is important to avoid some dangerous pitfalls. The most notable of these is the possibility that the patient does not in fact have epilepsy. Patients with nonepileptic, psychogenic spells constitute a sizable fraction of the inpatient video–EEG monitoring service of any tertiary care epilepsy center, and these patients have often undergone several – sometimes many – fruitless AED trials. Identifying these patients after just one or two failed AED trials can spare years of needless AED exposure and open the possibility of successful psychiatric treatment. A more difficult problem is that of noncompliance. Missing even one dose of AEDs may be sufficient to provoke a seizure in some patients. It is hard for the epilepsy practitioner to know just how often this happens and how much it is a factor in apparent refractoriness to treatment. Subtherapeutic AED levels obtained at the time of emergency department visits are sometimes the only clear evidence of noncompliance, so I always ask ED providers to obtain these if they call for one of my patients, even for "sendout" levels of newer AEDs. Diabetes doctors have the benefit of tracking hemoglobin A1C levels and daily finger-stick

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glucose levels in their most difficult patients in order to assess compliance. Epilepsy doctors have no such luxury. Thus, I continually preach the importance of the low-tech pill container (subdivided into day of the week compartments) as the best way to assure compliance. Another provoker of refractory seizures, especially in some forms of generalized epilepsy, is alcohol abuse. I've stumbled on the source of a few patients' refractoriness when a loved one tipped me off to their alcoholism – and witnessed a remarkable improvement when they cut down their drinking.

☆ TIPS AND TRICKS

The low-tech pill box is the clinician's best friend in improving treatment compliance.

More antiepileptic drug trials versus surgery

For some refractory localization-related epilepsy patients, epilepsy surgery is a viable option. Knowing when to quit further AED trials and when to offer surgical referral is a judgment call that has to be considered carefully since the surgical evaluation process is time-consuming, is expensive, and sometimes takes on a life of its own. I find it helpful to present the possible outcomes in rough probability terms that even unsophisticated patients can understand. For those who have gone through at least three AED trials and for whom the epilepsy diagnosis is secure, I suggest that the likelihood of seizure freedom with further AED trials is about 1 in 10, with temporal lobe resection about 6 in 10, and with extratemporal resection less than half. Many patients prioritize the possibility of discontinuing all AEDs as a reason for surgery. It's important to emphasize from the beginning that AEDs may only be reduced not discontinued altogether post-surgery, since only about half of patients successfully discontinue all AEDs after temporal lobectomy. Conversely, although some studies have shown that overall quality of life is most meaningfully increased if surgery results in seizure freedom, it is important to consider that a significant decrease in seizure frequency from "unsuccessful" surgery does mean a decreased risk of injury or sudden death from seizures. Presenting all of these contingencies to the patient contemplating surgery versus further medication trials may take multiple clinic visits in order to let him or her fully digest the risks and benefits.

General approach to the refractory patient

For those patients for whom further AED trials are warranted, there are some general principles to consider. First off, the statistical likelihood of success with further medical treatment applies to a population, but every individual is different. So it is important not to deprive the patient of hope or of motivation for going forward. Refractory does not equate to impossible. (And for this reason I avoid the word "intractable" that I think has a more negative connotation.) Even in refractory patients exposed to multiple prior medications, success can be achieved if one tries enough different combinations of medications.

Establishing the epilepsy diagnosis is vital, and for most refractory epilepsy patients should involve long-term video–EEG monitoring to capture typical seizures. The utility of this test stems from multiple considerations: weeding out patients with nonepileptic spells (even patients with interictal abnormalities on routine EEG can have superimposed nonepileptic spells), establishing which localization-related epilepsy patients may be surgical candidates, and discriminating generalized from localization-related epilepsies so as to better refine AED choice (more on this in the succeeding text).

Once the epilepsy diagnosis is secure and the question of surgery settled, it is important to guide AED therapy on the basis of data. This means asking patients or their caregivers to keep a seizure diary. Most people would know without a diary whether they were seizure-free or not, but otherwise can lose track of how frequently seizures are occurring. Without this information, it is difficult to tell whether progress is being made as medication regimens are altered. Likewise, following occasional AED serum levels will confirm compliance and provide some guidance as to whether reasonably therapeutic drug levels are being reached. While obtaining drug levels is not recommended as a substitute for decision making based on asking patients how they are doing, they sometimes reveal pharmacokinetic surprises (e.g., low levels of lamotrigine while on oral contraceptives or when pregnant, low levels of P450-metabolized drugs in combination with hepatic inducers like carbamazepine).

On the topic of pharmacokinetics, it would seem that drugs with relatively long serum elimination half-lives might be more effective than those with

greater diurnal variations in their serum concentrations. Unfortunately, there is little empiric evidence for this idea, but given the choice it is reasonable to opt for extended-release versions of drugs, or drugs with intrinsically long half-lives (zonisamide, perampanel, lamotrigine in combination with valproate). In the USA extended-release versions of second-generation AEDs (lamotrigine, levetiracetam) are now available in generic versions. Conversely, drugs with shorter half-lives may need to be dosed three times daily (pregabalin, levetiracetam).

Most patients will have arrived at the refractory treatment pathway by virtue of having failed at least two drugs in monotherapy. The practice especially in the USA has been to titrate each drug in monotherapy to its limits of tolerability before declaring it a failure. It is typical at that point to begin treating with combinations of drugs, and it is safe to say that the majority of refractory patients will be treated with combinations of AEDs. It is reasonable to wonder what to expect from adding a second or third drug to a patient's regimen: is there an added benefit in reduction in seizure frequency that is the sum of each drug's effect when used in monotherapy? Does adding three drugs produce more benefit than two? What about four or more AEDs at a time?

EVIDENCE AT A GLANCE

A retrospective study (Poolos et al., 2012) examined the benefits of combination therapy in a developmentally disabled population and found that adding a second agent to monotherapy in a highly refractory population produced a 19% decrease in seizure frequency; surprisingly, adding a third agent to a two-drug regimen produced no added benefit. These results suggest that there may be diminishing returns from adding successive numbers of concurrent AEDs. Possible reasons for this may be increased pharmacokinetic interactions as drug number increases, poorer overall tolerability due to increased side effects, or even adverse pharmacodynamic (drug effects based on mechanisms of action) interactions. This study also demonstrated superior efficacy of the combination of lamotrigine and valproate against convulsive seizures. This was the only statistically superior AED combination out of 32 tested.

CAUTION!

More concurrent AEDs may not equal better efficacy, just increased adverse effects.

There is only a small amount of data addressing answers to these basic questions. Clinical trials of new AEDs typically occur in refractory patient populations where the new agent is added to existing regimens of one or two other drugs. These studies have typically shown a 15–30% (corrected for placebo) maximum improvement in seizure frequency from adding what is in essence a second or third agent. In practice, I would suggest that two-drug combinations in refractory epilepsy provide an efficacy benefit over a single agent; three-drug regimens should be attempted with caution; and four or more concurrent AEDs probably should not be used at all.

While it would appear that adding successive numbers of concurrent AEDs produces a benefit that it is less than the sum of their individual actions in monotherapy, much has been said over the years on the opposite idea that some combination of AEDs may exhibit "synergy" or actions together that exceed the sum of the parts. As can be imagined, this is an exceedingly difficult question to study considering the myriad possible combinations of the 20 or some AEDs in clinical use today. A study of the older agents phenytoin and carbamazepine suggested that either of these drugs in combination with phenobarbital worked better than when phenytoin and carbamazepine were paired with each other, supporting the idea that combining drugs with differing theoretical mechanisms of action was beneficial. Several prospective studies have suggested a benefit to combination therapy with lamotrigine and valproate compared either to agent alone or to lamotrigine in combination with phenytoin or carbamazepine. Whether the actions of lamotrigine and valproate together represent a pharmacokinetic or pharmacodynamic interaction is unclear; thus, the search for the holy grail of AED synergy goes on. One practical consideration of combining AEDs is the difficulty of ascertaining which drug is producing adverse effects if both have similar side effect profiles. This would suggest it is wise to avoid combinations of drugs with similar mechanisms: phenytoin with carbamazepine or lacosamide; topiramate with zonisamide; or two benzodiazepines together.

☆ TIPS AND TRICKS

The combination of lamotrigine plus valproate may be more effective than either drug alone.

Antiepileptic drugs in refractory generalized versus localization-related epilepsy

The most rationally based guidance for treating refractory epilepsy derives from observations of seizure exacerbation in generalized epilepsy. The utility of knowing whether the refractory patient has a generalized syndrome (often requiring long-term video–EEG monitoring) comes from avoiding those AEDs known to exacerbate generalized seizures. In mechanistic terms, the AEDs with theoretical mechanisms of action against voltage-gated Na^+ channels (principally phenytoin and carbamazepine) can worsen absence, myoclonic, and tonic–clonic seizures that are generalized from onset. Although lamotrigine is effective in absence epilepsy, it can occasionally provoke myoclonic seizures. Lacosamide and rufinamide have theoretical actions on Na^+ channels, and although lacosamide appears to have some efficacy in convulsions in primary generalized epilepsy and rufinamide is approved for Lennox–Gastaut syndrome, these drugs should be used with caution in generalized epilepsy. Drugs that indiscriminately act on GABA receptors (vigabatrin, tiagabine, pregabalin, and gabapentin) can have similar effects. However, $GABA_A$ receptor-selective drugs, such as benzodiazepines or phenobarbital, are effective in generalized epilepsy.

CAUTION!

Some AEDs may exacerbate generalized epilepsy syndromes and produce the appearance of refractoriness

Sometimes the effect of these drugs contraindicated in generalized epilepsy is not observed as outright seizure provocation, but as rendering a patient refractory to drug regimens that include other more appropriate agents. Patients admitted for video–EEG monitoring and diagnosed with refractory epilepsy of unknown type are often ultimately found to have generalized epilepsy, often on contraindicated AEDs; once their regimens were rationalized to appropriate medications, a large proportion become seizure-free. A not uncommon scenario is the refractory patient whose only seizure type is a generalized convulsion, who has been on phenytoin all their life, sometimes in conjunction with other AEDs, and whose routine EEGs are nonepileptiform. When video–EEG monitoring discloses the generalized onsets of their convulsions, phenytoin can be replaced with a more appropriate AED (see Table 11.1), and their seizures often come under much better control.

Aside from the avoidance of seizure-exacerbating AEDs, there is little evidence-based guidance on the choice of drugs in generalized epilepsy. Several large prospective studies in nonrefractory, new-onset epilepsy have demonstrated valproate as the gold standard of efficacy in generalized epilepsy. This drug has serious dose-dependent and idiosyncratic toxicities, especially on the fetus in pregnant women with epilepsy, and so must be used with caution. Clonazepam is often helpful where myoclonus is predominant, such as in juvenile myoclonic epilepsy, whereas lamotrigine sometimes worsens seizures in this condition. This is also true in the relatively rare syndrome of severe myoclonic epilepsy of infancy (SMEI or Dravet), where drugs with Na^+ channel antagonism markedly worsen seizures, whereas benzodiazepines are helpful.

In focal-onset, localization-related refractory epilepsy, there is even less rational guidance for AED choice. Analogous to valproate in generalized epilepsy, carbamazepine has been the gold standard for efficacy (if not necessarily tolerability) in focal epilepsy, stemming from its modest superiority in new-onset epilepsy demonstrated in the VA Cooperative trials. However, a later prospective trial failed to show much efficacy difference between carbamazepine, oxcarbazepine, lamotrigine, and topiramate. Nonetheless, refractory patients should probably be exposed to carbamazepine at some point in their treatment course. Many clinicians feel that topiramate has comparable efficacy to carbamazepine, albeit with a number of dose-dependent cognitive adverse effects.

Two drugs are occasionally employed as "last-ditch" agents in refractory epilepsy: felbamate and vigabatrin. The experience with both of these drugs is that they are relatively effective but at their use comes with either a tiny but finite risk of death (felbamate) or a frequent, irreversible risk of vision loss (vigabatrin). My feeling is that neither of these drugs

provides a sufficiently high chance of seizure freedom in refractory epilepsy to justify starting them in patients not already exposed, except in the most severely affected for whom there are no other options. The chance of seizure freedom with other less dangerous AEDs remains comparable given enough medication trials.

Summary

Refractory epilepsy affects about one-third of all epilepsy patients, yet significant advances in treatment remain elusive. The likelihood of treatment success is increased by definitively establishing the epilepsy diagnosis through video–EEG monitoring, emphasizing compliance with treatment, avoiding AEDs that exacerbate seizures, and persistently varying the drug regimen in the hopes of arriving at the correct concoction of medications that works for the individual patient.

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