One Size Does Not Fit All: Personalized Treatment of Patients with Epilepsy

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Abstract Epilepsy is a common neurologic disorder that often requires chronic medical therapy to suppress seizures. As the number of available antiepileptic drugs (AEDs) has grown in recent years, so has the challenge of selecting the correct dose of the correct drug for the correct patient. Advances in genetic technology have enhanced our understanding of individual variation in drug response, underscoring that one size does not fit all when AEDs are considered. At a symposium held during the 67th Annual Meeting of the American Epilepsy Society, speakers discussed personalization of AED therapy based on available genetic information; the logistics of formulation and dosing; and the risk of adverse reactions, gender, and comorbidities.

Epilepsy is a complex spectrum disorder characterized by an enduring tendency to have recurrent seizures.1,2 In the United States, only three neurologic disorders—migraine, stroke, and Alzheimer’s disease—are more common than epilepsy, and an estimated 1 in 26 individuals will develop epilepsy at some point.3 People with epilepsy are at increased risk of physical injuries, psychiatric comorbidities, negative socioeconomic consequences, and premature mortality.4 The prevalence and severity of epilepsy have motivated the development of many new therapies, including over 15 second- and third-generation antiepileptic drugs (AEDs), which have been introduced since the 1980s.5

This rapid growth of the neurologist’s armamentarium has raised significant clinical challenges. Evidence of AED superiority often is lacking,6 and prudent drug selection necessitates consideration of patient-specific factors, including genetic information, physical characteristics, comorbid conditions, and concurrent medications.7 Thirty percent of patients never achieve good seizure control despite multiple trials of AED therapy,8 yet the stakes remain high—the first AED chosen offers the highest chance of seizure remission,9 and patients may remain on this drug for long periods.

At a symposium held during the 67th Annual Meeting of the American Epilepsy Society, experts emphasized the importance of individualizing AED treatment to maximize tolerability, adherence, and efficacy.

Pharmacogenomics refers to the use of genomic biomarkers, including genetic sequences and expression patterns, to guide drug therapy, with the goal of predicting the optimal drug and the dose for each patient.10 Recent advances in genetic sequencing technology have made pharmacogenomics a reality for the practicing clinician.11

Recognizing the Risk of Drug Reactions

The first application of pharmacogenomics to treat patients with epilepsy followed the discovery that the HLA-B*1502 allele predicts carbamazepine-induced Stevens-Johnson syndrome (SJS) in patients of Han Chinese and South Asian ancestry.12 Testing for HLA-B*1502 in at-risk ethnic populations is now recommended in several countries, including the United States.

More recently, genome-wide association studies (GWAS), which apply a tagging approach to provide information on hundreds of thousands of SNPs per patient, have revealed that analysis of the HLA-A*3101 allele is helpful in predicting adverse drug reactions to carbamazepine in other patient populations.13,16 A patient

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testing positive for HLA-A*3101 has an increased baseline risk of experiencing a carbamazepine-induced cutaneous drug reaction from 5% to 26%, whereas this risk in patients testing negative for HLA-A*3101 is just 3.8%. These findings should provide useful information for improving the personalized treatment of epilepsy with carbamazepine.17

Adverse reactions to AEDs are common and often are more bothersome to patients than are the seizures themselves.18 A tantalizing prospect is the use of genetic testing to mitigate or avoid such reactions. In some cases, knowledge of a specific disease-associated gene mutation can lead a clinician to avoid entire classes of AEDs. For example, sodium-channel blockers such as lamotrigine should be avoided in patients with epilepsy syndromes caused by SCN1A mutations, including Dravet syndrome. In other cases, however, elucidation of genetic markers with predictive potential has been more challenging. For example, weight gain during treatment with valproic acid is common and a major cause of treatment discontinuation.19 At present, however, the genetic underpinnings of this susceptibility remain unclear. Similarly, vigabatrin-associated retinopathy causes irreversible peripheral visual field loss in 20%–40% of patients, but precise genotypes that identify at-risk individuals have not been clearly defined.20

These current limitations may soon be overcome because pharmacogenomics remains one of the most rapidly growing fields in translational biomedical research. Indeed, candidate genes and SNPs have been reported for adverse reactions related to several AEDs, including lamotrigine, oxcarbazepine, phenytoin, and vigabatrin.13

Identification of specific genetic signatures that underlie the predisposition to unwanted drug reactions raises the possibility that genetic information also could help predict favorable treatment responses, which can be equally idiosyncratic. For instance, a subset of patients previously refractory to many AEDs can achieve seizure freedom upon exposure to levetiracetam.21 A candidate gene-association study of these "dramatic responders" examined 279 genes, including levetiracetam's target gene, SV2A, along with SV2B and SV2C; however, the results were negative for clinically relevant effects.22 Another study similarly concluded that a rare variation in SV2A did not affect response to levetiracetam.23

Future work in this area must account for the confounding effect of polytherapy, which could blur the association between a specific drug and the gene(s) conferring clinical responsiveness.

Mapping Genetic Variations
The pharmacogenomics community has made significant progress in mapping the influence of genetic variation on optimal AED dose. Functional variants of cytochrome P-450 enzymes, particularly when considering phenytoin metabolism, have been among the most well characterized,24,25 but other genes are being investigated as well.

An intronic splice-site polymorphism of SCN1A has been linked to maximum doses of phenytoin and carbamazepine.26 SCN1A polymorphisms also reportedly correlate with serum levels of phenytoin at maintenance dosage levels27; however, similar associations have not been reported with carbamazepine.28

Applications for Genetic Data
Could genetic information collected at birth serve as a health repository that guides medical therapy for the remainder of that person’s life? Many challenging ethical, financial, and legal issues surround the application of genetic analysis to routine clinical care. For now, traditional pharmacokinetic factors, such as body mass index, gender, and renal/hepatic function, likely will remain primary considerations in determining medical therapy in epilepsy. Nevertheless, researchers are employing increasingly sophisticated technologies in large, collaborative cohort studies.13,29 The day when patient genomic analysis is performed before a first AED and dose are selected may not be far off.

PERSONALIZING AED DELIVERY
Based on a presentation by Emilio Perucca, MD, PhD, Clinical Pharmacology Unit, University of Pavia and C. Mondino National Neurological Institute, Pavia, Italy.

Personalizing treatment for patients with epilepsy does not end with selection of an optimal AED. What is the best formulation for the patient in his or her current state? How should the dose be divided, and what is the most appropriate route of delivery?

It is often inappropriate to extrapolate dosing information from animals to humans or from children to adults. Furthermore, drug dosing schedules may affect adherence rates.30 Even the most thoughtfully chosen AED can be ineffective if administered suboptimally.

Advantages and Disadvantages of Extended-Release Formulations
Several widely used AEDs are available in extended-release formulations, which allow more gradual systemic drug absorption than do immediate-release formulations. In principle, an extended-release formulation offers several advantages,31 including decreased fluctuation of serum drug levels and a lower incidence of peak-dose toxicity.32 In addition, increased patient convenience related to use of these formulations probably translates into greater compliance (however, see Bautista and Rundle-Gonzalez30).

There is a paucity of studies specifically evaluating the impact of drug formulation. However, evidence on the benefit of extended-release formulations comes from two studies that compared carbamazepine with lamotrigine head-to-head. In a double-blind trial performed in an elderly population, Brodie and colleagues33 found that lamotrigine led to greater patient retention on drug—presumably reflecting a combination of efficacy and

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tolerability—than did treatment with standard (immediate-release) carbamazepine. However, a follow-up study employing identical dosing and titration schemes found that treatment retention was similar if lamotrigine therapy was compared with extended-release carbamazepine use.34

Still, extended-release formulations may not be superior in all situations. Cost must be a factor, and it may be difficult to justify added expense for drugs that have wider therapeutic windows and allow less control of peak-dose toxicity. In other situations, higher peak doses achievable with immediate-release formulations may be advantageous, such as when seizures occur with predictable diurnal variation.35

In addition, patients on extended-release formulations may have a shorter “forgiveness period,” meaning that a missed dose of one of these agents may leave the patient without AED coverage for a longer time than would occur with a missed dose of an immediate-release formulation.31

**Efficacy Differences with Administration Route**

Insight into the importance of administration route is provided by studies on acute seizure treatment. The finding thatrectal diazepam in solution led to a more rapid increase in plasma drug levels when compared with rectal suppositories36 provided the foundation for the current widespread use of rectal diazepam gel in the home treatment of children with acute repetitive seizures.37

More recently, a double-blind, randomized clinical trial investigating prehospital treatment of patients with status epilepticus demonstrated that intramuscular (IM) midazolam is superior to intravenous (IV) lorazepam.38 Early administration of IV lorazepam is the preferred initial treatment of status epilepticus in the emergency department and other controlled clinical environments. However, the difficulties inherent in paramedics establishing IV access and lorazepam’s shorter shelf-life when unrefrigerated have favored IM midazolam in several clinical outcome measures (ie, seizure freedom on arrival to the emergency department and rates of admission to the hospital and intensive care unit).39 Ease of drug administration always must be weighed against efficacy; a recent study demonstrated that sublingual lorazepam, although easier to administer than rectal diazepam, was associated with higher rates of treatment failure.40

Taken together, these studies highlight several important considerations when determining the optimal drug-delivery route for an individual patient, including: (1) setting (prehospital vs hospital, household vs ambulance), (2) clinical urgency (status epilepticus vs self-limited seizure), (3) ease of obtaining parenteral access, (4) logistical considerations of particular medications and formulations (availability, storage conditions, cost), and (5) regulatory approval status and extent of data supporting clinical efficacy. Several innovative strategies on the horizon may enhance a clinician’s ability to deliver personalized anti-epileptic therapy, including multifunctionalized nanoparticles,41 lipid-based exosome formulations,42 imaging-guided drug-delivery systems,43 and convection-enhanced drug delivery.44

**CUTANEOUS DRUG REACTIONS**

Based on a presentation by Bernard A. Cohen, MD, Director of Pediatric Dermatology and Professor of Dermatology, Johns Hopkins Children’s Center, Baltimore, Maryland.

Perhaps the most useful metric of successful personalization of AED therapy is treatment retention rate, which reflects the efficacy and tolerability of a medication in the context of a patient’s preferences. Among treatment-related side effects that can underlie AED intolerance, rash is one of the most common.45 and neurologists frequently are asked to evaluate cutaneous manifestations that may be related to AED therapy.

**Adverse Cutaneous Drug Reactions (ACDRs)**

ACDRs can affect over 2% of hospitalized patients46,47 and are the source of significant morbidity and potential mortality. Risk factors for ACDRs include age, number of secondary diagnoses, polypharmacy, and immunosuppression.48,49 Female gender often is considered a risk factor, but evidence supporting this perception is mixed.48

AEDs are among the most common medications associated with ACDRs; up to 15% of patients receiving AEDs have cutaneous reactions within 4 weeks of drug initiation.50 These reactions often manifest as mild, diffuse, self-limited morbilliform eruptions, but AED-induced ACDRs also can be life-threatening emergencies requiring early clinical recognition and urgent treatment. Initial evaluation of a cutaneous reaction should include assessment of the chronicity, distribution, pattern, organization, morphology, and probable anatomic depth of the lesion, with particular attention paid to involvement of mucosal membranes.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

DRESS, also referred to as drug-induced hypersensitivity syndrome, manifests in children and adults as a morbilliform cutaneous eruption involving the face, trunk, and limbs, along with fever, lymphadenopathy, hematologic abnormalities, and organ dysfunction, particularly of the liver.51 Despite lack of significant epidermal sloughing, multi-system involvement can be profound, and mortality approaches 10%.

Aromatic AEDs (particularly carbamazepine) and sulfonamides are the most common inciting agents, and DRESS is typically seen 2–6 weeks after treatment initiation. However, this reaction occurs more rapidly upon re-exposure to the culprit drug. Several formal diagnostic criteria have been advanced,52–54 all based on clinical presentation and laboratory studies.

**Potentially Fatal Reactions**

SJS and toxic epidermal necrolysis (TEN) represent a spectrum of severe, potentially fatal drug reactions characterized by widespread epidermal necrosis and mucosal involvement.55 Most experts consider SJS and TEN as different only in severity.55 In essence, SJS involves < 10% of body surface area (BSA) skin detachment, whereas TEN involves higher mortality and > 30% of BSA skin detachment.

Drug-induced SJS/TEN usually occurs...
1–3 weeks after the start of therapy, with a prodromal phase of flu-like symptoms. Mucocutaneous involvement begins abruptly, with flat, irregular lesions that have central necrosis and tend to coalesce over time. Ocular involvement is common and can range from mild conjunctivitis to corneal ulceration. Early recognition and withdrawal of all possible causative drugs are imperative. Among the AEDs, phenytoin, phenobarbital, carbamazepine, and lamotrigine have the most well-known associations with SJS/TEN, with incidence estimates of 1–10 per 10,000 new users. However, case reports have implicated other AEDs as well.

### Production of ACDRs

The mechanisms by which AEDs produce ACDRs remain poorly understood, although chemical, genetic, and environmental factors have been suggested. The reactions have long been suspected to be immunologic; this notion is supported by detection of activated T lymphocytes and macrophages in areas of damaged skin. A genetic predisposition for drug rashes also is likely because of high monozygotic twin concordance rates. Hypersensitivity to AEDs in children treated with phenytoin was first described in 1934. These children recovered if the drug was immediately discontinued. Today, some 80 years later, prompt withdrawal of the offending agent and initiation of aggressive supportive care remain the mainstays of treating all severe ACDRs. Systemic corticosteroids and other forms of immunosuppressive therapy can be employed, but their use in treating ACDRs is controversial.

Management in an intensive care or burn unit is advisable to manage systemic complications and to optimize fluid status, nutrition, and pain and infection control.

### Antiepileptic Treatment in Women

Based on a presentation by Page B. Pennell, MD, Director of Research, Division of Epilepsy, Division of Women’s Health, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts.

Care for women with epilepsy presents a unique opportunity for personalizing AED selection in light of drug risks during planned or unplanned pregnancy and the complex interactions between AEDs and female steroid sex hormones.

### Effect of Hormones

About one third of women with focal epilepsy demonstrate a “catamenial” pattern, in which seizure frequency increases consistently during certain phases of the menstrual cycle. In line with animal studies showing that estrogen has proconvulsant effects and that progesterone and its metabolite allopregnanolone have neuroinhibitory properties, catamenial seizures most commonly worsen when estrogen levels are relatively higher than those of progesterone or when hormone levels change rapidly.

A recent (2012) double-blind, placebo-controlled, randomized clinical trial provided evidence that cyclic progesterone therapy may benefit a subset of women with perimenstrually exacerbated seizures. Less robust evidence exists for treatment with clobazam or acetazolamide during perimenstrual seizure exacerbation.

Effective contraception and pregnancy planning may facilitate implementation of measures known to improve pregnancy outcomes. However, the use of AEDs with hormonal contraceptives can be complex, as enzyme-inducing AEDs lead to increased clearance of steroid sex hormones and decreased contraceptive efficacy. Further, estrogen-containing contraceptives may decrease the concentration of AEDs like lamotrigine. In general, long-acting reversible contraceptives (eg, progesterin implants, intrauterine devices [IUDs]) are preferred options, because progesterin concentrations delivered by implants are sufficiently high to be compatible with enzyme-inducing AEDs, and the local action of IUDs is unlikely to be affected by systemic medications.

### Pregnancy and AED Therapy

An estimated 0.6% of births in the United States are to women with epilepsy, and up to 3.5% of women in their reproductive years may be taking an AED for epilepsy or for other indications (eg, headache, pain, mood disorders). The increased risk of major congenital malformations (MCMs) in the offspring of women taking AEDs is well known and, across all AEDs, varies between 3% and 9%, which is about two- to threefold higher than the risk of MCMs in the general population. Valproic acid is noteworthy among the AEDs for association with such complications. In addition to its well-known potential to cause neural tube defects, fetal exposure to valproic acid...
has been associated with dose-dependent impairment in cognitive abilities during childhood.75 Because seizures occurring during pregnancy are associated with many maternal and fetal risks,66 a clinical dilemma exists: How should we maintain maternal seizure control as we minimize teratogenic risk to the fetus?

In general, discontinuation of AEDs during pregnancy is not recommended. Approximately 20%–33% of pregnant women with epilepsy experience an increase in seizure frequency, 7%–25% experience a decrease in seizures, and 50%–83% have no significant change.76 Determination of AEDs that likely are safest during pregnancy has been aided by large pregnancy registries that prospectively correlate AED use with MCMs during pregnancy (Figure 1).74,77,78

Polytherapy with AEDs should be avoided whenever possible, because rates of MCMs are consistently higher in women using multiple AEDs than among those using a single AED. Optimization of a patient’s AED regimen before pregnancy is important for prognosis, because seizure freedom for at least 9 months prior to pregnancy is associated with a high likelihood (84%–92%) of remaining seizure-free during pregnancy.79 Changes in maternal physiology during pregnancy cause increased clearance (ie, a decrease in serum concentration) of lamotrigine, levetiracetam, phenytoin, and, probably, carbamazepine and the active monohydroxy derivative of oxcarbazepine. Among these AEDs, the most dramatic changes are seen with lamotrigine (≥ 94% increased clearance by hepatic glucuronidation)80 and levetiracetam (increased clearance may exceed 200%).81

Intrapartum decreases in serum AED levels may partially underlie the increased seizure frequency seen in some patients. Monthly therapeutic drug monitoring during pregnancy may be useful for compensatory dose adjustments, particularly when an effective baseline serum concentration has been established. Finally, folic acid supplementation at doses of 0.4–5 mg daily has been suggested to help prevent MCMs,82,83 but there is little evidence supporting the efficacy of folic acid, specifically in women with epilepsy.84

### TREATING EPILEPSY IN PATIENTS POSITIVE FOR HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Based on a presentation by Gretchen L. Birbeck, MD, MPH, Professor, Center of Human Experimental Therapeutic and Departments of Neurology–Epilepsy and Public Health Science, University of Rochester Medical Center, Rochester, New York.

The first widely used application of DNA sequencing in personalized medicine was in resistance testing for HIV.85 Large international repositories of HIV genotype response data have since been developed, employing sophisticated data-mining and machine-learning techniques to predict individual treatment response.86 The goal of these data-driven engines is to predict the most effective treatments for any patient and virus combination.

In addition to HIV genotype, selection of appropriate antiretroviral (ARV) medications must factor in a patient’s comorbidities, pregnancy potential, adherence potential, and interactions with other medications, including AEDs (Figure 2). Worldwide, the concurrent use of AEDs with ARVs is substantial, and the potential interactions between these types of medications are extensive.

Fortunately, evidence-based guidelines for AED selection in patients on ARVs,87,88 serve as a useful roadmap for avoiding potentially problematic drug combinations. For example, saquinavir should be avoided in patients at risk of cardiac arrhythmia, including those who are on AEDs that can impact cardiac conduction, such as ezogabine and lamotride. Rilpivirine and etravirine, members of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of ARVs, are contraindicated for use with carbamazepine, oxcarbazepine, phenobarbital, and phenytoin. Similarly, therapy with many ARVs inhibit hepatic drug metabolism and is therefore contraindicated with the use of benzodiazepines, due to the risk of prolonged sedation. It is important to avoid enzyme-inducing AEDs in patients taking protease inhibitors or NNRTIs, because pharmacokinetic interactions may result in virologic failure, which has clinical implications for both disease progression and development of ARV resistance.87

Seizure risk factors in HIV-positive patients include vulnerability to HIV-associated CNS diseases, medication effects (eg, efavirenz may lower the threshold for seizures89), and metabolic disturbances. Where available, the AED of choice in HIV-positive patients is levetiracetam, due to its broad-spectrum activity, ease of use, minimal drug interactions, and favorable side-effect profile. For similar reasons, lamotride, gabapentin, and pregabalin also are favored choices in patients with partial-onset seizures. Among older AEDs, valproic acid may be preferred, because it will not cause enzyme induction-associated ARV failure, although its side-effect profile is less favorable than that of the other AEDs mentioned.90

Except in resource-limited settings, treatment with ARVs is now recommended for all HIV-positive patients. Neurologists must assume that these patients with HIV are or soon will be taking ARVs. Given the complexities outlined here, close collaboration between neurologist and infectious disease special-
ist often is necessary to optimize patient management.

**CONCLUSION**

Epilepsy is a chronic condition that can require a lifetime of medical therapy. Genes are major determinants of medication efficacy, safety, and tolerability, and pharmacogenomics increasingly will be integrated into neurologists’ clinical practice. Optimal AED therapy must be personalized for each patient based on consideration of available genetic information, logistics of formulation and dosing, risk of adverse reactions, gender, and comorbidities.

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