Management of Refractory Epilepsy

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Abstract

Drug refractory epilepsy, defined as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used antiepileptic drug (AED) regimens (whether administered as monotherapies or in combination) to achieve freedom from seizures, affects approximately 30% of patients with new-onset epilepsy. Persistent epileptic seizures in these patients, in addition to having deleterious effects on health, are also associated with psychosocial, behavioral, cognitive, and financial consequences. Despite availability of several new drugs, response to therapy remains poor in most of drug refractory cases. Also despite several ongoing treatment trials, ideal combination of AEDs remains to be identified. Careful attention to ruling out alternative diagnoses, optimal selection of AEDs, rational use of combination therapy, as well as attention to patient-specific factors, such as poor compliance and drug abuse, remain cornerstone of therapy. In view of poor response to polytherapy, if possible, surgical intervention should be contemplated early. In future, development of new drugs with better efficacy and tolerability and minimal drug interactions, as well as better nonpharmacological therapeutic techniques, will help in managing these patients better.

Keywords
► refractory epilepsy
► rational polytherapy
► antiepileptic drug

Introduction

About 50 million people in the world suffer from epilepsy and every year 16 to 51 new-onset epilepsy cases occur per 100,000 people.1 In majority of patients, a single antiepileptic drug (AED) suffices to control epileptic seizures, which may be withdrawn after a seizure-free period of 2 years.2 Some patients, however, do not become completely free of seizures despite adequate compliance.3,4 Persistent epileptic seizures in these patients, in addition to having deleterious effects on health including sudden death, are also associated with psychosocial, behavioral, cognitive, and financial consequences.3-7

Definition of Drug Refractory Epilepsy

From a practical point of view, epilepsy can be considered refractory when seizures are too frequent or severe to allow the patient to live life as per his or her wishes or when they require drugs that, although effective, produce adverse effects. Although this concept of drug-resistant epilepsy appears self-explanatory and intuitive, a precise definition has remained elusive. This has resulted in diverse criteria used by different clinicians and researchers, rendering it difficult to compare findings across studies and to make practice recommendations. Recently, International League against Epilepsy formulated a consensus definition of drug-resistant epilepsy.8 The overall framework of this definition comprises two hierarchical levels. Level 1 defines the outcome of each therapeutic intervention as either freedom from seizures or treatment failure on the basis of standard criteria. When a patient has had a trial of an AED that is inadequate for determining efficacy (such as early discontinuation at a low dosage), the treatment trial is reported to have an undetermined outcome. This level-1 assessment forms basis of level-2 determination, which defines drug-resistant epilepsy as a failure of adequate trials of two (or more) tolerated, appropriately chosen, and appropriately used AED regimens (whether administered as monotherapies or in combination).
combination) to achieve freedom from seizures. Seizure freedom is defined as freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer. This is based on the observation that inability to achieve complete seizure control with two appropriate AEDs, markedly reduces likelihood of success with subsequent regimens.\(^5\)\(^6\)\(^7\) Although drug resistance may "remit" over time (at a rate of 4% per year among adults and even higher among children), seizure relapse is common, suggesting a fluctuating course.\(^5\)\(^6\)\(^7\)\(^8\) Other consistent clinical predictors of drug resistance (other than failure of therapeutic regimen) include a high frequency of seizures in the early phase of the disorder and the presence of a known, often structural cause of epilepsy, especially hippocampal sclerosis.\(^9\)\(^1\)\(^4\)

Paradoxically, an AED may aggravate epilepsy, giving rise to false impression of drug-resistant epilepsy. Idiopathic generalized epilepsies are particularly prone to pharmacodynamic aggravation; typical absences are constantly increased by carbamazepine (CBZ), vigabatrin, tiagabine, gabapentin. Juvenile myoclonic epilepsy is often aggravated by CBZ. In symptomatic generalized epilepsies myoclonus are generally aggravated by the same drugs that aggravated idiopathic generalized epilepsy; tonic seizures in the Lennox–Gastaut syndrome respond to CBZ, which may however aggravate atypical absences.\(^1\)\(^5\) Overall approximately 20% of patients with primary generalized epilepsy and 35% of those with partial epilepsy will fall into category of drug refractory epilepsy.\(^1\)\(^6\)\(^1\)\(^7\)

**Proposed Mechanisms of Drug Resistance**

The development of drug resistance is likely to be multifactorial according to the underlying cause and to the drug's site of action. Age also affects treatment outcome, with elderly people doing better than younger ones.\(^1\)\(^8\)\(^1\)\(^9\) Major hypotheses of cellular mechanisms responsible for drug resistance can be broadly categorized into four groups (Table 1).

**Transporter Hypothesis: Failure of Drugs to Reach Their Targets**

This hypothesis proposes that drug resistance results from increased expression of multidrug efflux transporters (ATP-binding cassette [ABC] transmembrane proteins) at the epileptic focus. These transporters push substrates from the cell against the concentration gradient. The most well-known efflux transporter is P-glycoprotein. It is expressed in capillary endothelial cells in the brain and it pumps xenobiotics from intracellular space back to the capillary lumen, thereby reducing their cerebral accumulation. Upregulation of P-glycoprotein and other efflux transporters has been demonstrated in capillaries of surgically resected brain specimens from drug refractory patients. In addition, in same specimens, aberrant expression of P-glycoproteins in glial and neuronal cells has also been demonstrated.\(^2\)\(^0\)\(^2\)\(^1\)\(^2\) However, this is still unclear as to if polymorphisms of the gene encoding P-glycoprotein (ABCB1) are actually associated with a poor response to AED therapy and in addition, extent to which human P-glycoprotein transports AEDs remains undetermined.\(^2\)\(^3\)\(^2\)\(^5\)

**Target Hypothesis: Alteration of Drug Targets**

The “target hypothesis” proposes that drug resistance results from alteration in cellular targets of AEDs resulting in reduction in their sensitivity to treatment.\(^2\)\(^0\)\(^2\)\(^6\) There are several reports in literature supporting this hypothesis. Remy et al\(^2\)\(^7\) studied hippocampi resected from patients with carbamazepine-resistant temporal-lobe epilepsy and found that use-dependent blockade of the fast sodium current in dentate granule cells by carbamazepine was lost in these patients. However, this finding did not extend to lamotrigine, which has a pharmacologic action similar to that of carbamazepine. Kwan et al found polymorphisms of the SCN2A gene (which encodes α-2 subunit of neuronal sodium channels) to be associated with resistance to AEDs, while Loup et al observed altered expression of subtypes of the γ-aminobutyric acid type-A receptor in drug-resistant temporal lobe epilepsy.\(^2\)\(^8\)\(^2\)\(^9\) However, actual significance of these changes remains unknown. The main weakness of target hypothesis is its presumption of knowledge of the mechanisms of action of AEDs, which remain incompletely understood. This hypothesis also does not account for the observation that is why patients often have resistance to multiple drugs with different modes of action, although it cannot be ruled out that alteration in drug targets may play a contributory role.

**Drugs Missing the Real Targets**

Current AEDs are primarily meant for preventing seizures and thus, they may not be targeting the actual pathogenic processes. For example, autoantibodies against ion channels (voltage-gated potassium and calcium channels, glutamate N-methyl-d-aspartate [NMDA] and γ-aminobutyric acid type B [GABAB] receptors) involved in neuronal excitation and inhibition have been found in patients with seizures of otherwise unknown cause, particularly in encephalitis and in patients with occult cancer.\(^3\)\(^0\)\(^3\)\(^1\) These patients often do not respond to conventional AEDs and may require immunotherapy. Other relevant mechanisms of epileptogenesis, which remain unaffected by conventional AEDs, include mitochondrial oxidative stress and dysfunction\(^3\)\(^4\) and abnormal electrical coupling through gap junctions in neurons or even glial cells.\(^3\)\(^5\)

**Alteration in Drug Metabolizing Enzymes**

The main candidate genes in this category are cytochrome P450 (CYP450), superfamily encoding genes. There are four main enzyme families (CYP1–4), encoded by at least
25 different genes. Around eight isoenzymes are known to be involved in the metabolism of AEDs. CYP2D6, CYP2C9, CYP3A4, and CYP2D19 are involved in the metabolism of most AEDs. Low-activity alleles of CYP2C9, which accounts maximum metabolism of commonly used phenytoin, are associated with decreased phenytoin clearance, higher plasma levels and increased toxicity. Similarly, genetic influences on phenobarbital metabolism relate mostly to CYP2C19 polymorphism. Individuals with defective allelic variants have been reported to show a mean reduction in phenobarbital clearance by approximately 20 to 50% compared with fast metabolizers. Little data are available on genetic factors influencing the metabolism of second-generation AEDs. All these mechanisms represent potential novel targets for future drug development.

**Principles in Management of Refractory Epilepsy**

**Ruling Out Pseudoresistance—Is the Epilepsy Truly Intractable?**

The first and foremost step in management of refractory epilepsy is ruling out pseudoresistance, that is, persistence of seizures due to inadequate/inappropriate treatment of the underlying disorder. It must be carefully ruled out before considering failure of drug treatment. This phenomenon may occur in several situations (misdiagnosis of epilepsy, administration of wrong drug, administration of wrong dosage, or lifestyle such as poor compliance) of which misdiagnosis of epilepsy is most common. Causes of pseudoresistance are enumerated in – Table 2. Each of these causes must be carefully ruled out before a label of drug-resistant epilepsy is given. Following stepwise approach is suggested to avoid missing pseudoresistance as a cause of drug unresponsiveness.

**Identification of the Correct Diagnosis**

The accuracy of diagnosis should be carefully reviewed as approximately 20 to 30% of patients referred for management of intractable epilepsy do not have epilepsy. Conditions that frequently mimic epileptic seizures include nonepileptic attack disorder, asystolic syncpe, cardiac arrhythmias, metabolic disturbances, and other neurologic disorders with episodic manifestations (e.g., transient ischemic attacks and migraine). Patients with nonepileptic attacks (pseudoseizures) can usually be diagnosed clinically. Psychiatric comorbidity is almost universal. Chronic depression, dissociative states consequent upon physical, sexual, or emotional abuse, and previously unexplained physical symptoms (somatization) are common findings. Frequent hospitalizations, in apparent status epilepticus, are also common. Videotelemetry helps to confirm the diagnosis to identify seizures of frontal origin and to identify patients with coexistent epilepsy and pseudoseizures. When the diagnosis of nonepileptic attack disorder is made, drugs are stopped and further treatment is tailored as per patient's needs. Certain rare vitamin-responsive inborn errors of metabolism may present as early encephalopathy with anticonvulsant-resistant seizures in pediatric age group. These include pyridoxine-dependent seizures, pyridoxal-phosphate-dependent seizures, folic acid–responsive seizures, and biotinidase deficiency. Management of this heterogeneous group of patients requires involvement of both the neuropsychiatrist and the neuropsychologist.

**Review the Classification of Epilepsy**

An attempt should be made to syndromically classify each patient’s epilepsy. A common cause of treatment failure or even seizure aggravation is incorrect classification of the syndrome or seizure type, with previously unrecognized juvenile myoclonic epilepsy not treated with valproate being the most common example of suboptimal treatment. Phenytoin, carbamazepine, gabapentin, oxcarbazepine, vigabatrin, tiagabine, and pregabalin can worsen absence epilepsy and myoclonic seizures. Lamotrigine can also exacerbate some myoclonic epilepsy syndromes. If one cannot reach at correct classification clinically, further investigation should be carried. Clinically, the distinction between IGE, unresponsive to valproate, and frontal lobe epilepsies, can be difficult. Tonic–clonic and complex partial seizures of frontal lobe origin often occur without warning. Seizures, indistinguishable from typical absences, can arise from the mesial frontal lobe. Similarly brief, asymmetric tonic seizures, and bilateral clonic movements of upper limbs, without loss of consciousness, arising from the supplementary motor area, can be mistaken for generalized myoclonus. In such instances, a videotelemetry may be of immense help in classifying the disorder. In patients with partial seizures, high-resolution magnetic resonance imaging (MRI) may reveal structural pathology amenable to surgery.

**Prescribe Proper Dosage of Drug**

An AED may fail to control seizures satisfactorily because it is not prescribed at the optimal dosage. This may result from an injudicious reliance on monitoring of serum drug concentrations; a “therapeutic range” can be interpreted as dictating dosage adjustment without adequate clinical correlation.

**Ensure Compliance**

Noncompliance or partial compliance with the medication regimen frequently contributes to recurrence of seizures. Compliance can be monitored by determining plasma drug levels. Noncompliance results from many factors, such as missed medication, failure to refill the prescription, a complicated regimen, problems with memory or vision, postictal confusion, denial of epilepsy and need for medication, fear of teratogenicity, concern about adverse effects of drugs, and cost of drugs. In dealing with problem of noncompliance,
the main reason for noncompliance should be enquired and the education about the importance of compliance should be tailored to each patient’s specific problems.

Lifestyle Modification
Lifestyle factors can trigger recurrent seizures, particularly in adolescents and young adults. Examples include emotional stress, sleep deprivation, menstrual cycle (usually premenstrual and ovulatory phases), flickering lights and other sensory stimuli, alcohol use or withdrawal, and illness. An attempt should be made to identify these factors and correct them wherever possible.

Identification/Exclusion of Structural Pathology
Refractory partial epilepsy demands exclusion of structural pathology. It is worthwhile to relook at previous neuroimaging findings. MRI has a higher diagnostic yield. Some findings (for example, diffuse low-grade glioma, multifocal malformation of cortical development) may have no therapeutic implications, but explain the refractory nature of epilepsy. Occasionally unexpected vascular disease prompts a search for a treatable underlying cause, for example, antiphospholipid syndrome.

Optimal Use of Antiepileptic Drugs
The most important factor in choice of an AED is type of the seizure and, wherever possible, the epileptic syndrome. Other important factors in choosing the drug include profiles of its efficacy and tolerability, half-life, potential for drug interactions, its effect on coexisting disorders, and its cost. An adequate trial of an AED consists of a systematic increase in the dosage and plasma drug levels until the seizures are controlled or intolerable adverse effects appear. The adequacy of the trial as per ILAE guidelines is defined by the frequency of seizures and not by time but the more frequent the seizures, the less time is required for determining the efficacy of a drug. One should begin treatment with a single drug and then increase to two or more drugs in combination, if required. Therapy should begin with a first-line AED (Table 3). If the seizures remain uncontrolled, or intolerable side effects appear, one should consider factors such as selection of an inappropriate drug, lack of administration of maximally tolerated dosages, poor timing of doses, too rapid introduction of medication, or inadequate control of seizure-provoking events. These factors must be ruled out before the first drug is withdrawn and another one is tried. If seizures persist despite high-therapeutic plasma levels of second drug, a trial of two drugs in combination is reasonable.

Evidence Favoring Polytherapy
Initial AED monotherapy is effective in approximately 60% of epilepsy patients. The remainders are candidates for polytherapy, surgery, or vagus nerve stimulation (VNS). As per Mattson et al., in patients who fail monotherapy, a combination of two drugs results in cessation of seizures in 10% and improved control of seizures in approximately 40%. The guidelines of American Academy of Neurology/American Epilepsy Society (AAN/AES) support second generation AEDs for adjunctive treatment of refractory partial onset seizures in adults. Nearly all currently marketed AEDs are effective in adjunctive treatment of refractory partial seizures (except ethosuximide, which is effective only for generalized absence seizures). However, an ideal combination of AEDs is not yet identified. Veterans Affairs Status Epilepticus Cooperative Study Group VA I Cooperative Trial, 40% of patients failing phenytoin or carbamazepine monotherapy responded to polytherapy, with 11% of these becoming seizure free.

What is Rational Polytherapy?
The concept of “rational polytherapy” is based on the fact that AED combinations with differing mechanisms of action are more effective than combinations with similar mechanisms of action. It is expected, as pathophysiology of epilepsy relates to the following two opposing types of neural imbalances: (1) increased neuronal excitation (increased glutamate) or (2) a decreased neuronal inhibition (decreased GABA). AED combinations targeting both these are expected to be more efficacious, that is, while AED combinations with similar mechanisms of action, a synergistic effect would be expected to produce merely additive efficacy. However, other factors need to be considered. For example, combining AEDs with competitive hepatic enzymatic metabolism or protein binding may produce antagonism of each other’s efficacy or lead to heightened toxicity. AEDs with similar toxicity profiles could produce additive or synergistic pharmacodynamic adverse effects. Thus, while combination of sodium channel blocking AEDS with Y-aminobutyric acid (GABA) augmenting AEDs may produce synergistic efficacious effects, the combination of two GABA mimetic drugs may enhance efficacy but reduce tolerability. However, while it appears sensible, there is no evidence from clinical trials to support rational polytherapy. One previous trial demonstrated that combination of valproate and lamotrigine was more effective than other combinations suggesting potential synergy. Other combinations that are sometimes recommended, include valproate with ethosuximide for absence seizures and lamotrigine with topiramate for a range of seizure types.

Table 4 lists the proposed pharmacological targets of commonly used AEDs and serves as a reference for choosing

Table 3 First line antiepileptic drugs

<table>
<thead>
<tr>
<th>Primary generalized tonic–clonic</th>
<th>Partial</th>
<th>Absence</th>
<th>Atypical absence, myoclonic, atonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Carbamazepine</td>
<td>Valproic acid</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Phenytoin</td>
<td>Ethosuximide</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Oxcarbazepine</td>
<td>Valproic acid</td>
<td></td>
</tr>
</tbody>
</table>
combinations of AEDs with complementary mechanisms of action with respect to the practical principle of “rational polytherapy” and Table 5 lists some of the examples of desirable and undesirable drug combinations.

**Appropriate Polytherapy: A Practical Approach**

As polytherapy only modestly improves efficacy and causes increased adverse effects, one should try to avoid it. Most patients should receive two sequential trials of monotherapy.

### Table 4  Mechanisms of actions of antiepileptic drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Sodium channels</th>
<th>Calcium channels/currents</th>
<th>Effects on GABAergic transmission</th>
<th>Glutamate receptors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>c</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>c</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td>Bind to CRMP-2 receptor</td>
</tr>
<tr>
<td>Lacosamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>c</td>
<td>a</td>
<td></td>
<td></td>
<td>Modulates presynaptic neurotransmitter release by SV2A receptor binding.</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Modulates presynaptic neurotransmitter release by SV2A receptor binding.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>c</td>
<td>a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td></td>
<td>b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rufinamide</td>
<td>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>Weak carbonic anhydrase inhibitor</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>c</td>
<td>b</td>
<td></td>
<td></td>
<td>Weak carbonic anhydrase inhibitor</td>
</tr>
</tbody>
</table>

Abbreviations: GABA, gamma aminobutyric acid; Y-aminobutyric acid type B; SV2A, synaptic vesicle glycoprotein 2A.

| Possible target. |
| Probable target. |
| Primary target. |

### Table 5  Examples of beneficial/unbeneficial drug combinations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Benefit</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (CBZ) plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine (LTG)</td>
<td>–</td>
<td>CBZ increases LTG metabolism; There is higher incidence of neurotoxic side effects</td>
</tr>
<tr>
<td>Topiramate (TPM)</td>
<td>–</td>
<td>CBZ decreases TPM concentrations while TPM increases CBZ concentrations. Possible increase in side effects</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>a</td>
<td>Potential synergism with CBZ</td>
</tr>
<tr>
<td>Valproate (VPA) plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin (PHT)</td>
<td>±</td>
<td>VPA increases PHT levels and side effects; however retrospective case series do suggest some synergism</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>±</td>
<td>Same primary mechanism of action; VPA increases CBZ metabolite concentrations</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>±</td>
<td>Increased efficacy, but at increased risk of rash</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>b</td>
<td>Potential synergism</td>
</tr>
</tbody>
</table>

± Potentially beneficial.

Beneficial.

– Potentially unbeneficial

± Data conflicting.
utilizing AEDs with differing mechanisms of action, prior to attempting chronic polytherapy. Successful polytherapy requires selecting cotherapies that lack drug-drug interactions, do not amplify adverse effects, and actually minimize total drug load to achieve desired seizure control. For further study regarding desirable and undesirable AED combinations, readers can be referred to recently published article on rational polytherapy.31

Before Initiating Polytherapy
When utilizing polytherapy, the clinician must be aware of potential pharmacokinetic and pharmacodynamic interactions, which influence the risk of developing adverse effects. In general, the main pharmacokinetic interactions to consider are potential cytochrome P450 (CYP) metabolism competition and a high percentage of protein binding. Coadministration of the enzyme-inducing AEDs (EIAEDs; i.e., phenobarbital, phenytoin, or carbamazepine) with inducible AEDs (such as lamotrigine, oxcarbazepine, tiagabine, topiramate, or zonisamide) hastens the metabolism of the latter, reducing drug concentrations and efficacy. Conversely, when lamotrigine is given with valproate, an inhibitor of lamotrigine glucuronidation and clearance, there is a greater chance of serious rash than with EIAEDs.52 For further references on these important considerations involved with initiating and maintaining polytherapy, the reader is referred to two recently published extensive reviews of AED drug interactions.55

Pharmacodynamic adverse effects, such as dose-related neurotoxic and cognitive side effects, are common when using polytherapy.56 Cognitive impairment occurs commonly and is often subtle and difficult to identify without specifically questioning the patient. Some adverse effects such as sedation, cognitive impairments, gait disturbance, and hair changes are consistently underreported. Routine use of adverse event screening instruments helps in the identification of adverse effects that limit quality of life.57 Some AEDs (e.g., Topiramate) have a greater tendency to cause adverse effects when used in polytherapy than when used as monotherapy.55,58 Thus, before initiating polytherapy, the clinician should design a patient-specific AED regimen that minimizes adverse events and drug interactions, while maximizing efficacy, and continuously monitor that patient for signs of toxicity.

How to Initiate Polytherapy
A commonly employed method of introducing an adjunctive drug is to hold the current AED at a constant dose, and gradually titrate the new AED to the target dose.51 As rapid dose escalation may lead to side effects and AED therapy discontinuation, adjunctive drug should be started at a low dose, and increased slowly to maximize patient tolerability and avoid dose-related side effect. If adverse effects emerge, there are two possible approaches as follows: (1) reduce the baseline AED to “make room” for adjunctive therapy, dose-related adverse effects may be due to both AEDs, not solely due to the new one (i.e., flexible dose approach)34; or (2) reduce the new AED, thereby accepting a lower target dose of this therapy (i.e., fixed-dose approach). Recently, a randomized trial suggested that flexible dose approach is better than the fixed-dose one. An adjunctive AED can be further increased as needed to achieve optimal therapeutic doses and if possible, it is sensible to attempt to monotherapy with the newly added AED.59 Some advocate initial lowering of the baseline AED prior to initiating a new adjunctive AED.52 However with this approach, the risk of breakthrough seizures is increased. Thus it is preferable to hold an initial baseline drug at a constant dose during titration of a new adjunctive AED until the target dose of that drug is reached. Similar decisions need to be made when adding a third, fourth, or fifth AED to a patient’s regimen. Use of more than two AEDs is generally discouraged due to an increased likelihood of pharmacokinetic and pharmacodynamic AED interactions. Triple AED polytherapy benefits approximately 20 to 50% of patients by achieving a 50% or greater reduction of seizures.31 Another recent study suggested that two or three AEDs may effectively control seizures, but four or more AEDs were not beneficial.60 While introducing third AED, it is reasonable to maintain the baseline AED regimen while titrating the third AED to a target dose, and then tapering off the least effective AED. If an adverse effect develops during titration of newest AED, immediately taper off the least effective AED to improve tolerability. Alternatively, if one of the AEDs can be singled out as ineffective or poorly tolerated, consider titrating the new AED while simultaneously tapering the ineffective or intolerable AED.

Reducing Unnecessary Polytherapy
Polytherapy continues to be common practice, especially in institutionalized epilepsy patients. Clinicians should regularly reexamine the necessity of polytherapy in all patients, but especially the elderly, institutionalized, children, and women.51 Polytherapy has been associated with decreased patient compliance, reduced quality of life, and increased costs, as well increased side effects. Therefore, reserving polytherapy for patients who have no other alternative is reasonable. When reduction of polytherapy has been unsuccessful due to increased breakthrough seizures, another means of enabling polytherapy reduction is to reconsider nonpharmacologic approaches to augment management of the patient’s epilepsy. Additional diagnostic testing to explore candidacy for epilepsy surgery or VNS therapy should be strongly considered since these treatments may afford patients a greater chance of reducing or eliminating polytherapy.

Latest Developments in Drug Therapy
In a double-blind, randomized trial, efficacy of adjunctive treatment has been small, prompting search for new compounds. Although a ≥50% reduction in seizure frequency is accepted as demonstrating efficacy, the clinical relevance of such an improvement is limited and goal should be complete freedom from seizures. In the past 2 years, several new drugs were introduced. Rufinamide has shown effectiveness in Lennox-Gastaut syndrome in infants and children (class-I evidence). Vigabatrin is being used as an adjunctive treatment...
for complex partial seizures in adults and as monotherapy for infantile spasms in children from 1 month to 2 years of age (class-I evidence). Stiripentol has been approved under the orphan-drug procedure in Europe for treatment of Dravet’s syndrome (class-I evidence). Reticabine (ezagabine in the United States and Canada) is approved for adjunctive treatment of refractory partial seizures with or without secondary generalization in adults (class-I evidence). Unlike other AEDs, this drug acts by opening potassium channels. Recently, the therapeutic use of steroids has been shown to reduce seizure burden in many epileptic pathologies, which may result from improved drug distribution into the brain. Dexamethasone is known as a potent anti-inflammatory drug, but also exerts powerful “blood brain barrier (BBB) repair” potency. Recent laboratory findings suggest that a detriment to brain delivery of AEDs is a hostile neuronal environment (e.g., brain edema) resulting from a disrupted BBB. Other drugs that are undergoing phase-3 trials include brivaracetam (binds to the synaptic vesicle protein 2A molecule) and perampanel (modulates glutamate neurotransmission).}

**Nondrug Therapy**

Patients with drug-resistant epilepsy should be evaluated early for surgical treatment, particularly if they have a surgically remedial syndrome, such as unilateral hippocampal sclerosis or other resectable lesions. The decision to offer surgery require individualized risk–benefit assessment that includes pros and cons of additional trials of AEDs. A range of surgical procedures can be performed, depending on the indication. The prototype is anterior temporal lobectomy, which is superior to continued medication in providing long-term relief from seizures in drug-resistant temporal-lobe epilepsy (class-I evidence). Other potentially curative procedures include resection of structural lesions (lesionectomy) such as glial tumors and vascular malformations. Even when magnetic resonance imaging reveals no lesions, resection may be performed on basis of functional imaging (ictal single–photon emission computed tomography or interictal positron emission tomography) with or without invasive electroencephalography (EEG) monitoring. However, outcomes of surgical treatment in such cases are less favorable than in lesional cases. When resection of epileptogenic lesion is not possible, palliative procedures to disrupt the pathways important for propagation of epileptiform discharges may be considered. Corpus callosotomy is useful in children with clinically significant learning disabilities and severe generalized epilepsy, especially when atomic seizures are present. Multiple subpial transaction is reserved for situations where epileptogenic focus cannot be removed because of close proximity to eloquent cortex. In hemispherectomy or functional hemispherotomy, an extensively diseased and epileptogenic cerebral hemisphere is removed or functionally disconnected. The vagus nerve stimulator is a multi-programmable pulse generator. It is implanted in patient’s upper chest and delivers electrical current to the vagus nerve, usually left nerve, in the neck. It is approved as an adjunctive therapy for adults and adolescents older than 12 years of age whose refractory partial-onset seizures. The ketogenic diet (a high-fat, low-protein, and low-carbohydrate diet) is used in children with drug-resistant epilepsy. It decreases number of seizures by more than 50% in approximately half of children after 1 year. The diet seems to be effective for all seizure types. The major problem is adherence to the restrictive (and unpleasant) dietary regimen. Therefore, a modified Atkins’ diet is under evaluation.

**New and Emerging Therapies**

Several new treatments of drug-resistant epilepsy are under investigation. These devices use intracranial and extracranial treatment systems, which typically provide either electrotherapy or pharmacotherapy and are in some cases automatically administered when a seizure is detected by sensors. A multicenter, double-blind, randomized trial studied one such intracranial device, delivering scheduled electrical stimulation bilaterally to the anterior nucleus of the thalamus, in drug-resistant focal epilepsy. After 2 years, median reduction in seizure frequency was 56%; 54% of patients had a seizure reduction of at least 50% and 14 patients were seizure-free for at least 6 months. The Food and Drug Administration (FDA) panel recently recommended approval of the device. Another device undergoing a phase-3 clinical trial is a “closed-loop system” which on detecting epileptiform activity delivers electrical stimulation to the site of this activity. The limited data regarding the device appear to be favorable. Other therapeutic strategies in progress include stereotactic radiosurgery, stem-cell therapy, and gene therapy.

**Personalized Medicine**

The heterogeneous etiology of epilepsy, the large number of different syndromes and seizure types, together with an individually variable response to AEDs, make the treatment of this condition still challenging. Genetic factors are the explanation of the interindividual variability in the response to different AEDs; different genes can be mutated thus affecting drug pharmacokinetics, drug pharmacodynamics, or causing epilepsy itself. In addition, studies have shown that epigenetic mechanisms are involved in brain modifications due to epilepsy. The term “precision medicine” aims to personalization the treatment for every individual to target toward the precise molecular pathogenesis of disease. Some of the rare genetic epilepsies enable treatment stratification through testing for the causal mutation, for example, SCN1A mutations in patients with Dravet’s syndrome. Early genotype-guided diagnosis allows avoidance of sodium channel-blocking AEDs and represents an example of stratification to improve AED efficacy. This approach should not only be based on genomic strategies but also requires integration of clinical measures, including EEG and imaging, with genomics and other omics modalities. It is likely that there is more than one mechanism, and using disease stratification procedures, including examining the role of inflammation, will lead to disease subphenotypes, which
may stimulate novel therapeutic approaches including the development of new drug-diagnostic combination products. Precision medicine is the future for antiepileptic treatment and can bring a better outcome also for some kind of epilepsy syndrome that in the past had been considered quite intractable.76

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Conflict of Interest
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References
17 Reutens DC, Berkovic SF. Idiopathic generalized epilepsy of adolescence: are the syndromes clinically distinct? J Neurology 1995;45(8):1469–1476
40 Waldhaeusl S, Patel M. Mitochondria, oxidative stress, and temporal lobe epilepsy. Epilepsia 2010;51(8):23–45
45 Smith D, Chadwick D. The management of epilepsy. J Neurol Neurosurg Psychiatry 2001;70(suppl 2):I115–I121
60 Stephen LJ, Brodie MJ. Seizure freedom with more than one antiepileptic drug. Seizure 2002;11(6):349–351
71 Kosseff EH, Dorward JL. The modified Atkins diet. Epilepsia 2008;49(suppl 8):37–41