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Pediatric Epilepsy: Diagnostic and Treatment Considerations

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NEEDS STATEMENT

The primary goal in taking care of children with epilepsy is seizure control. To achieve this, the physician must select appropriate treatments, a task that requires a diligent history of the current illness, family history, physical and neurologic examinations, electroencephalogram, and judicious use of neuroimaging studies such as computed tomography and magnetic resonance imaging. If the seizure disorder merits pharmacologic management, the next important step is the appropriate choice of an antiepileptic drug (AED). Failure to accurately identify the seizure type and epilepsy syndrome beforehand may result in the selection of an AED with less than optimal effectiveness or one that exacerbates the seizure disorder.

Although many AEDs may cause dose-related sedation, patients may also suffer idiosyncratic side effects such as allergic reactions, weight change, and behavioral abnormalities. Weight gain or weight loss may be advantageous in selected patients, and thus AEDs associated with these side effects may be preferred. Early identification of potentially life-threatening idiosyncratic adverse events such as anticonvulsant hypersensitivity syndrome (AHS) is important to limit their severity. Cross-reactivity between AEDs must be recognized in order to prevent recurrent episodes of AHS.

ACCREDITATION STATEMENT

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LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

1. Recognize the importance of seizure type and epilepsy syndrome when selecting antiepileptic drug therapy
2. Characterize subgroups of idiopathic generalized epilepsy based on predominant seizure type and age of onset
3. Recognize electroencephalogram characteristics of idiopathic generalized epilepsy
4. Identify AEDs associated with significant weight changes
5. Recognize and manage anticonvulsant hypersensitivity syndrome

TARGET AUDIENCE

This activity is intended for physicians who treat children with epilepsy.

DISCLOSURE OF UNLABELED USE

This activity contains discussions of published and/or investigational uses of lamotrigine, levetiracetam, topiramate, and zonisamide, which are not restricted to the Food and Drug Administration–approved indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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ESTIMATED TIME OF COMPLETION

This activity should take approximately 1.0 hour to complete.

METHOD OF PARTICIPATION

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SUPPORT STATEMENT

This activity is supported by an educational grant from UCB Pharma.

FACULTY

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Introduction

At least 4% of the population will experience a nonfebrile seizure, and approximately 40% of patients with a first generalized tonic–clonic seizure (GTC) will go on to develop epilepsy, a condition of recurrent seizures.[1] Since 1993, 9 new antiepileptic drugs (AEDs) have become available for the treatment of epilepsy—all approved by the Food and Drug Administration (FDA) as adjunctive therapy for partial seizures (Table 1).

The 9 new AEDs represent important additions to the physician's therapeutic armamentarium, but this plethora of choices may prove daunting when one must choose a specific drug for an individual child. Some of these medications have approvals for monotherapy (lamotrigine, oxcarbazepine, topiramate), and several are specifically indicated for pediatric populations—tiagabine for children 12 years and older, levetiracetam and oxcarbazepine for children 4 years and older, gabapentin for children 3 years and older, and lamotrigine and topiramate for children 2 years and older. Formulations practical for children include oral solutions for gabapentin, levetiracetam, and oxcarbazepine, and "sprinkles" for topiramate. Felbamate, the first of the new AEDs, also received FDA approval for monotherapy and pediatric use and has an oral suspension, but its use is relatively limited because of associated risks of aplastic anemia and hepatic failure. It is, therefore, excluded from the rest of this discussion.

The 2 cases described herein illustrate the importance of selecting the specific AED appropriate for a given epilepsy syndrome, as well as the need to identify and manage adverse effects that may result from treatment with various AEDs.

Case 1. Idiopathic Generalized Epilepsy

A 13-year-old girl was seen in the epilepsy clinic for poorly controlled seizures that began occurring when she was 5 years old, were accompanied by generalized convulsions, and occured without warning. At presentation, her mother

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Table 1. The 'New' AEDs

Felbamate
Gabapentin
Lamotrigine
Levetiracetam
Oxcarbazepine
Pregabalin
Tiagabine
Topiramate
Zonisamide

reported that the patient would suddenly fall to the ground, shake for a couple of minutes, and urinate uncontrollably. This would be followed by a period of sleepiness and lethargy. She was placed on carbamazepine, but her seizures continued to recur every few months. At age 9, phenobarbital was added to her drug regimen.

At the time of her visit, she was taking carbamazepine 800 mg per day and phenobarbital 90 mg per day. Despite this, her seizures had become more frequent, occurring approximately weekly.

The patient's medical and developmental histories were unremarkable. She attended regular school and was in the seventh grade, although the quality of her schoolwork had deteriorated since the onset of weekly seizures. Family history revealed that the patient's mother had seizures as a child and adolescent, but reportedly "grew out of them" without AED treatment. The patient's physical and neurologic examination was normal. An ambulatory electroencephalogram (EEG) was obtained.

On the basis of history, a normal neurologic examination, and EEG results, carbamazepine was replaced by topiramate. After titration up to a daily topiramate dose of 150 mg per day, the patient became seizure-free. The phenobarbital was slowly tapered over the next few months and discontinued without recurrence of seizures.

Discussion points. Not all children with epilepsy require pharmacologic treatment. For those who do, however, the choice of an AED depends upon many factors, including age, concomitant medical and psychiatric illnesses, other medications, history of allergic reactions, medication formulation, and cost. The most fundamental guidance comes from identification of seizure type and epilepsy syndrome; physicians should attempt to classify seizures and epilepsy syndromes according to the International League Against Epilepsy (ILAE) Classification to inform treatment decisions (Figure 1).[2]

Children with localization-related (partial, focal) epilepsy are more likely to respond to certain AEDs, whereas those with idiopathic generalized epilepsy (IGE; primary generalized epilepsy), are likely to respond to another group of AEDs (Figure 2).[3] Choosing an inappropriate AED for the type of epilepsy is a major reason for AED failure and may result in status epilepticus.[4]

What is IGE? Idiopathic generalized epilepsy accounts for 20% to 40% of all epilepsies.[5] Although the term *idiopathic* is commonly defined as *unknown*, the word takes on a different meaning in the ILAE Classification.[6] In the case of IGE, *idiopathic* implies a known or suspected genetically determined low seizure threshold as the etiology of the seizure disorder. Oligogenic or polygenic complex inheritance is likely. Active inquiry into the genetics of the various IGE syndromes is ongoing. Juvenile myoclonic epilepsy (JME) is one type of IGE, and its genetics have been systematically probed. For at least some cases of JME, there is consistent evidence of genetic linkage on chromosome 6.[7]

Most cases of IGE present at a relatively young age (Figure 3)[5] and include a normal neurologic examination. The EEG may demonstrate generalized epileptic abnormalities but is otherwise normal. Neuroimaging is normal, as there is no structural cause for the seizures, and the prognosis is generally good.

There are 4 main types of IGE syndromes: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), JME, and epilepsy with GTC on awakening.[6] CAE presents between ages 4 and 8 years, and has typical absence seizures as the primary seizure type. The presence of GTCs in CAE may be a negative prognostic factor. JAE presents between ages 10 and 17 years. It involves GTCs in about 80% of cases and myoclonic seizures in 15%. JME begins in adolescence, between ages 12 and 18 years, and is marked by myoclonic and GTC seizures upon awakening. Clusters of myoclonic seizures may progress into GTC, as triggered by fatigue and alcohol. Epilepsy with GTC upon awakening is characterized by GTCs that occur shortly after awakening >90% of the time. This syndrome is also exacerbated by sleep deprivation.

I. Localization-related (focal, local, partial) epilepsies and syndromes

A. Idiopathic (with age-related onset)
1. Benign childhood epilepsy with centrotemporal spike (rolandic)
2. Childhood epilepsy with occipital paroxysms
3. Primary reading epilepsy

B. Symptomatic
1. Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)
2. Syndromes characterized by seizures with specific modes of precipitation (eg, reflex epilepsy, startle epilepsy)
3. Temporal lobe epilepsies
4. Frontal lobe epilepsies
5. Parietal lobe epilepsies
6. Occipital lobe epilepsies

C. Cryptogenic

II. Generalized epilepsies and syndromes

A. Idiopathic (with age-related onset—listed in order of age)
I. Benign neonatal familial convulsions
2. Benign neonatal convulsions
3. Childhood absence epilepsy (pyknoepilepsy)
4. Juvenile myoclonic epilepsy ("impulsive petit mal," or Janz's syndrome)
5. Epilepsy with grand mal seizures on awakening
6. Epilepsies with seizures precipitated by specific modes of activation

B. Cryptogenic or symptomatic (in order of age)
I. West's syndrome (infantile spasms, Biltz-Nick-Salaam Krampfe)
2. Lennox-Gastaut syndrome
3. Epilepsy with myoclonic-astatic seizures
4. Epilepsy with myoclonic absences

C. Symptomatic
1. Nonspecific etiology
   a. Early myoclonic encephalopathy
   b. Early infantile epileptic encephalopathy with suppression burst
2. Specific syndromes*

III. Epilepsies and syndromes undetermined whether focal or generalized

A. With both generalized and focal seizures
1. Neonatal seizures
2. Severe myoclonic epilepsy of infancy
3. Epilepsy with continuous spike waves during slow-wave sleep
4. Acquired epileptic aphasia (Landau-Kleffner syndrome)

B. Without unequivocal generalized or focal features†

IV. Special syndromes

A. Situation-related seizures
1. Febrile convulsions
2. Isolated seizures or isolated status epilepticus
3. Seizures occurring only when there is an acute metabolic or toxic event associated with factors such as alcohol, drugs, eclampsia, nonketotic hyperglycemia

* Epileptic seizures may complicate many disease states. Diseases in which seizures are a presenting or predominant feature are included in this category.

† All cases with generalized tonic–clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization-related, such as in many cases of sleep grand mal.

Figure 1. Epilepsies and epileptic syndromes.

Table 2. Anticonvulsant Hypersensitivity Syndrome, Clinical Manifestations[16]

Skin and mucus membranes: Exanthematous eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis, macular erythematous pruritic rash, papules, pustules, periorbital or facial edema, desquamation of skin

Liver: Vomiting, tender hepatomegaly, jaundice and clinical evidence of hepatic dysfunction, granulomatous hepatitis or fulminant hepatic necrosis

Kidney: Hematuria, oliguria, interstitial nephritis, acute renal failure

Central nervous system: Aseptic meningitis, status epilepticus following drug withdrawal

Heart: Pericarditis, carditis, congestive cardiac failure

Lungs: Cough, pneumonitis, adult respiratory distress syndrome, respiratory failure

Musculoskeletal system: Myalgia, myositis, myopathy, arthralgia, rhabdomyolysis

Other: Fever, flu-like symptoms, pharyngitis, exudative tonsillitis, malaise, fatigue, headache, difficulty in swallowing, lymphadenopathy, splenomegaly, decreased appetite, pancreatitis, thyroiditis, delayed onset hypothyroidism, colitis, syndrome of inappropriate secretion of antidiuretic hormone, serositis, uveitis

Table 3. Management of Anticonvulsant Hypersensitivity Syndrome[16]

Therapeutic Modality	Justification and Remarks
Hospitalization	Possibility of multi-organ involvement, severe clinical course and likelihood of uncontrolled seizures after anticonvulsant is withdrawn.
Withdraw the incriminating drug	Accumulation of drug metabolites that are responsible for the reaction.
Use of alternate anticonvulsant	To prevent rebound seizures and management of status epilepticus. It might not be possible to use valproate in the acute phase due to the presence of concomitant hepatic dysfunction. Diazepam can be used. Valproate or gabapentin may represent safe alternatives for the long-term management. Cross-sensitivity with lamotrigine and felbamate should be ruled out.
Nutrition and intravenous fluids	Enteral nutrition is preferred. Parenteral nutrition if significant oral intake is not possible for several days in view of mucosal lesions, organ damage and poor general health. Intense fluid management: supplementary intravenous fluids if skin lesions are extensive due to the possibility of fluid loss through the ulcerating skin lesions.
Prevention and treatment of infection	Admission to isolation room or intensive care unit depending upon the severity and extent of cutaneous sloughing. Prophylactic antimicrobial agents not required. Prompt treatment of infections.
Skin care	Denuded skin should be cleansed carefully, as it is a primary portal for infection.
Management of ocular disease	Daily ophthalmologic consultation. Separation of eyelids and mucosal surfaces of the palpebral and bulbar conjunctivae in order to prevent symblepharon.
Symptomatic treatment and other general measures	H_1-antagonists used for the treatment of pruritus: diphenhydramine and/or hydroxyzine. H_2-antagonists used in patients with mucosal sloughing and suspected Stevens-Johnson syndrome. Suitable antipyretic and analgesic agents. Careful pulmonary toilet: nebulized medications, incentive spirometry.
Corticosteroids	Use of prednisone and methylprednisolone as immunomodulators, as these are used in the treatment of severe cutaneous adverse reactions. Risks involved: immunosuppression, sepsis, prolonged recovery, relapse after withdrawal. Other forms of immunomodulation: plasmapheresis, cyclophosphamide, cyclosporine, intravenous immunoglobulin.
Intravenous immunoglobulin	Case reports justifying its use have been published.
Patient counseling	Provide a list of anticonvulsant drugs that are contraindicated in the patient. Patients should wear medication identification bracelet. Screening of first-degree relatives for the determination of risk for anticonvulsant hypersensitivity syndrome.

Differentiation of these syndromes relies heavily on age at onset and predominant seizure type (absence, myoclonic, or GTC). Given their similarities, these syndromes may be viewed as part of a spectrum of conditions (Figure 4).[8] Although it may not always be possible to differentiate among types of IGE, it is important to distinguish IGE from localization-related or symptomatic/cryptogenic epilepsy.

It should be remembered that IGE might present in adulthood. A study of 121 patients with IGE included 34 (28%) with adult onset.[5] These patients often receive the misdiagnosis of nonlesional partial epilepsy. An EEG showing generalized epileptic activity can help in correct diagnosis. However, a normal EEG is nondiagnostic, and further studies, such as prolonged video/EEG monitoring, may be required.

IGE should also be distinguished from the other 2 types of generalized epilepsies—symptomatic and cryptogenic. When the cause of the epilepsy can be identified, it is termed *symptomatic*. Examples include brain malformations such as Aicardi syndrome, lissencephaly-pachygyria, and metabolic diseases such as ceroid-lipofuscinosis, and Gaucher's disease. When an anatomic or metabolic cause is suspected but undefined, the epilepsy is termed *cryptogenic*. IGE has a much better prognosis than do symptomatic or cryptogenic generalized epilepsies, with >80% of IGE cases responding to treatment.[6] This favorable prognosis is an important piece of information that will guide treatment and can be reassuring to patient and family.

Role of EEG. Physicians are presented with something of a diagnostic dilemma when a patient presents with a history of a GTC. Did the seizure have a focal onset and spread to become a GTC (localization-related seizure with secondary generalization)? Or was this a generalized seizure from the onset, with no underlying focal lesion (idiopathic generalized epilepsy)?

An EEG can be very useful in making this distinction. Patients with IGE have an EEG with a normal background, with no focal slowing due to underlying lesions, or generalized slowing suggestive of an encephalopathy. The only abnormality may be an indication of epileptic activity, which may take the form of sharp waves, spikes, spike–wave complexes, and polyspikes. These appear as generalized epileptic discharges (Figure 1). The epileptiform activity is of high amplitude, and is followed by a slow wave. Typically, the generalized epileptic discharges are maximally frontal, best appreciated at the Fp1/Fp2 or F3/F4 electrodes. Absence seizures are associated with spike–wave complexes, whereas myoclonic seizures are accompanied by polyspikes. A response to photic stimulation with a strobe light during the EEG often occurs in patients with IGE.

Treatment of IGE. The treatment of epilepsy has become more complex with the addition of the new AEDs to the armamentarium of older drugs—such as carbamazepine, phenobarbital, phenytoin, and valproate.[9] Although multiple methods of action have been identified for the new AEDs, (eg, sodium channel blockade, γ-aminobutyric acid [GABA]-ergic, facilitation of chloride influx, potentiation of $GABA_A$ responses, blockade of calcium channels, and others), the state of the art has not yet progressed to matching of a particular mechanism of action with the needs of a particular patient.[10] However, specific treatment options have evolved for partial seizures versus primary generalized seizures, and this differentiation serves as an important starting point for AED selection.[3]

None of the AEDs, whether new or old, have specific FDA indications for the treatment of IGE. In general practice, the drug of choice is valproate, but several of the newer AEDs—lamotrigine, levetiracetam, topiramate, and zonisamide—also have efficacy.[4,6] Indeed, topiramate has an indication for primary generalized tonic–clonic seizures, a specific seizure type within the classification of IGE.

The expanded treatment options offered by the new AEDs may be valuable in specific instances. For example, if a patient has significant weight gain on valproate, then topiramate and zonisamide may be better choices, as both are associated with weight loss. Valproate may also have drug–drug interactions with lamotrigine, warfarin, and zidovudine, which may result in toxicity, or at the very least require additional monitoring and dosage adjustments. An alternative to valproate in this circumstance would be levetiracetam, which has no reported drug–drug interactions. For patients with comorbid migraine, both topiramate and valproate may be appropriate, as both have formal indications for migraine prophylaxis.

Carbamazepine, phenytoin, phenobarbital, and all of the new AEDs are commonly used to treat localization-related epilepsies. However, some of these AEDs (carbamazepine, gabapentin, oxcarbazepine, phenytoin, and tiagabine) are not recommended for IGE, as they may fail to be effective or even exacerbate seizures.[4] When the diagnosis is difficult, a provisional diagnosis such as "epilepsy with GTC seizures, type (IGE vs focal)?" should be applied. Until the diagnosis is clarified, broad-spectrum

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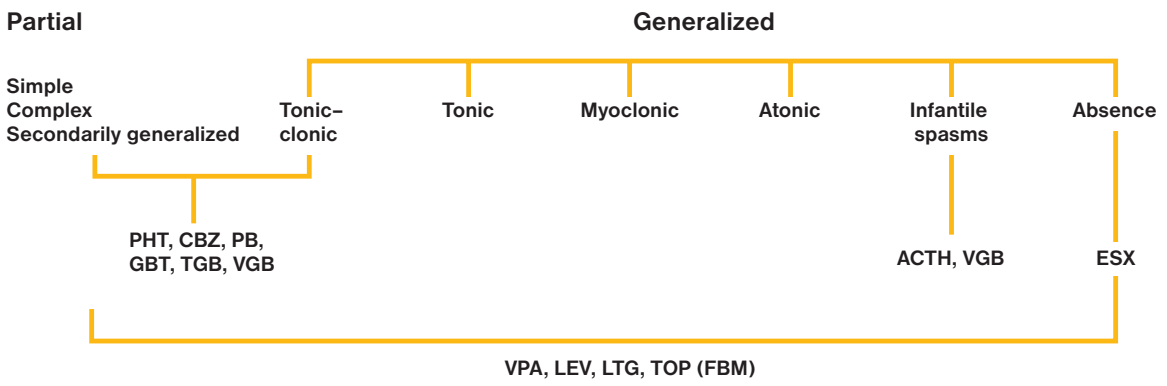
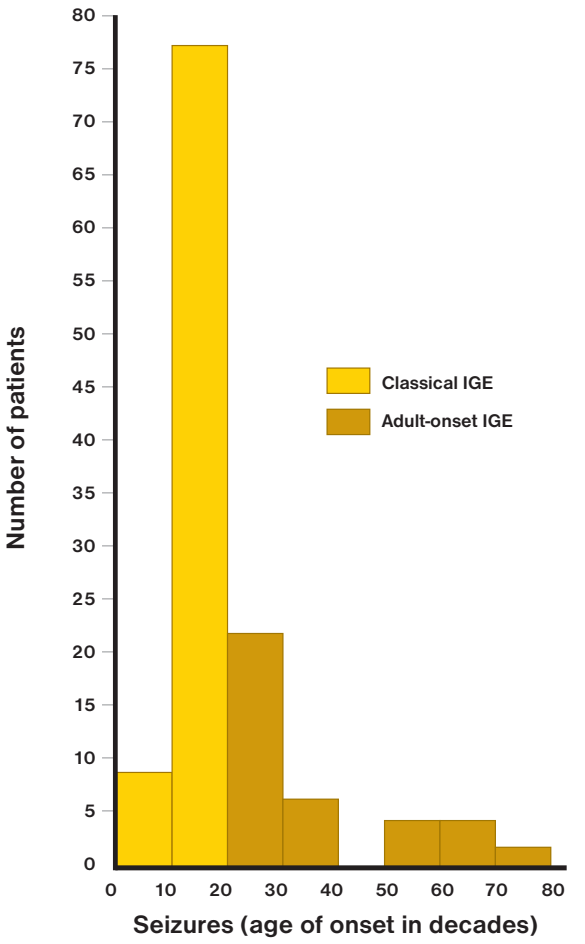


ACTH, adrenocorticotropic hormone; **CBZ,** carbamazepine; **FBM,** felbamate; **GBT,** gabapentin; **ESX,** ethosuximide; **LEV,** levetiracetam; **LTG,** lamotrigine; **PB,** phenobarbital; **PHT,** phenytoin; **TGB,** tiagabine; **TOP,** topiramate; **VGB,** vigabatrin; **VPA,** valproate

Figure 2. Treatment options for partial and generalized seizures.[3]



IGE, idiopathic generalized epilepsy

Figure 3. Age distribution of IGE in a first seizure clinic.[5]

AEDs such as lamotrigine, levetiracetam, topiramate, valproate, and zonisamide should be used.

Case 2. Treatment-Related Adverse Events

A 6-year-old boy, whose first seizure occurred the day before his third birthday, was referred to a neurologist after being seen by his pediatrician. His mother described this event as a brief, blank staring spell associated with speech arrest, and eye deviation to the left.

The patient's gestation and birth were normal, and there was no family history of epilepsy. He was not taking any medications and had no known allergies. His neurologic examination was normal, although there was a paucity of spontaneous speech for his age. An EEG revealed theta waves and well-formed occasional spikes in the left frontal and temporal regions. A computerized axial tomography scan revealed a 2-cm mass lesion in the left frontal lobe, which contained calcification. A biopsy confirmed the diagnosis of a low-grade oligodendroglioma. Because of its location near Broca's motor speech area, only a partial surgical resection was performed and followed by radiotherapy. Yearly follow-up with magnetic resonance imaging has revealed no further tumor progression.

The patient was started on phenytoin, but during radiotherapy he developed a maculopapular rash, which spread from his face to his chest, back, and extremities. He also had a fever of 101°F. A viral syndrome was suspected, and the phenytoin was continued. The rash continued to progress for several days, until the patient developed tender cervical lymphadenopathy. Phenytoin was then discontinued, and carbamazepine was added, but the rash continued to get worse. After 3 more days, carbamazepine was discontinued, and valproate was started. Blood work revealed that his liver function tests were 3 times the upper limit of normal. A topical steroid cream was prescribed for the rash. Two days after the carbamazepine was stopped, the fever returned to normal. The rash slowly disappeared over the next 3 weeks, and his liver function tests returned to normal.

During the next year, the patient's seizure frequency decreased to about 1 every 4 months, but he gained 15 lb, which meant his body weight then exceeded 120% of ideal. The valproate was replaced with topiramate, and the patient began to lose weight. After 6 months of topiramate therapy, he had returned to his ideal body weight, and there were no more seizures. However, his speech seemed to be worse, and he had trouble expressing complicated ideas. The topiramate dose was reduced, which improved the language problems, but he had a breakthrough seizure. Topiramate was discontinued and levetiracetam added. His teachers observed a slight increase in impulsive behavior, which has required closer supervision and stricter limit setting. The patient has had no seizures for the last 6 months.

Discussion points. Adverse events may be classified into three broad categories; dose-dependent (eg, somnolence, ataxia), chronic (eg, weight change, gingival hyperplasia), and idiosyncratic (eg, rash, blood dyscrasias, liver toxicity).[10] These categories may overlap; for example, weight change is both a chronic and idiosyncratic reaction.

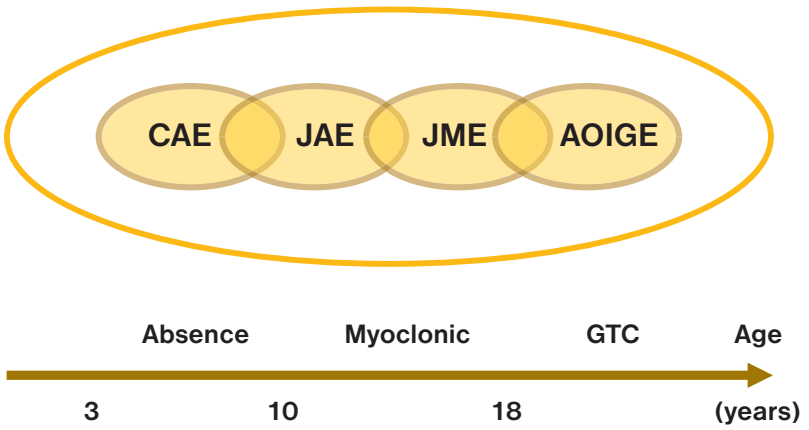
"Low and slow" introduction of an AED may prove useful in allowing a patient to habituate to the medication and eliminating dose-related side effects. In addition, slow dose titration may diminish the incidence of idiosyncratic side effects such as rash with AEDs such as carbamazepine, lamotrigine, and phenytoin.[10]

Rash. One of the most frequent adverse effects of AEDs is the development of an allergic rash.[11] The incidence of rash associated with phenytoin use is 2% to 13%[12]; with carbamazepine use, 3% to 16%; with valproate use, 6%[13]; and with phenobarbital use, 2.4%.[12] With respect to the new generation of AEDs, gabapentin, levetiracetam, tiagabine, and topiramate have an associated incidence of rash similar to that of placebo.[13] In clinical trials, the risk of rash was 3% with zonisamide, relative to 2% with placebo. Oxcarbazepine has a risk of rash of 1.4% to 5.3%. Lamotrigine had a risk of rash of 10% in clinical trials for epilepsy and 14% in trials for bipolar disorder. The risk of serious rash with lamotrigine is 0.8% in children <16 years old. Concomitant treatment with lamotrigine and valproate doubles the risk of serious rash from 0.6% to 1.2%.[13] There may be an increased risk of severe rash when anticonvulsants are used together with radiotherapy.[14]

Although a rash associated with use of an AED will generally resolve after discontinuation of the drug, patients may want to continue using the AED if it has controlled their seizures effectively. However, continuing the AED is problematic because the rash may herald the development of Stevens-Johnson syndrome, toxic epidermal necrolysis, or anticonvulsant hypersensitivity syndrome (AHS). Because one cannot reliably distinguish a benign rash from a potentially serious one in its early stages, in most cases the AED causing the rash should be discontinued. Continuing the AED in a "wait and see" approach may result in a worse prognosis if a serious allergic reaction develops.

Anticonvulsant hypersensitivity syndrome. AHS is characterized by the triad of fever, rash, and internal organ involvement.[15] AHS has been observed with the traditional AEDs (carbamazepine, phenobarbital, phenytoin, primidone), which have an aromatic ring structure, but it may also occur with lamotrigine (nonaromatic), oxcarbazepine, and valproate (nonaromatic).[16] Originally described as "Dilantin hypersensitivity syndrome" (Dilantin is a brand name of phenytoin), its other synonyms include "drug rash with eosinophilia and systemic symptoms" (DRESS), "Kawasaki disease," "mononucleosis-like syndrome," and "phenobarbital hypersensitivity syndrome." The potential for the newer AEDs to cause AHS has not been well studied.

AHS tends to occur early after AED treatment, between weeks 1 and 12, at a frequency of 1/1,000 to 1/10,000 exposures.[16] Fever is usually the presenting symptom, followed within the next 2 days by skin rash and lymphadenopathy. The rash may progress from macular erythema to Stevens-Johnson syndrome and toxic epidermal necrolysis. The involvement of all organ systems is possible; the liver is most commonly affected (Table 2).[16] Typically, anicteric hepatitis occurs with hepatocellular degeneration and necrosis. Hematologic abnormalities may include eosinophilia, leukopenia, lymphocytosis, and other abnormalities. Additional reported abnormalities include aseptic meningitis, interstitial pulmonary infiltrates, Löffler's syndrome, myopathy, myositis, and nephritis. Early identification of the syndrome is important, as



AOIGE, adult onset idiopathic generalized epilepsy; **CAE,** childhood absence epilepsy; **GTC,** generalized tonic-clonic seizure; **JAE,** juvenile absence epilepsy; **JME,** juvenile myoclonic epilepsy

Figure 4. Spectrum of IGE syndromes.[8]

prompt drug withdrawal usually leads to symptom resolution. In advanced cases, the syndrome may be life-threatening. The mortality rate is in the 5%-to-50% range.

Unfortunately, the syndrome may mimic other disorders, and its diagnosis requires a high index of suspicion. Patch testing[17] and the in vitro lymphocyte toxicity assay (LTA) may assist in diagnosis, but there is no practical diagnostic test. Although most cutaneous drug reactions are benign, prudent care dictates that children who present with fever, rash, and hepatotoxicity while taking an AED should have that AED discontinued.[15]

AHS is an allergic reaction, and its incidence is not well correlated with dosage or serum concentrations. The pathophysiology of AHS is unclear; a favored hypothesis is that it is associated with an underlying genetic deficiency in epoxide hydrolases necessary for arene oxide detoxification, resulting in accumulation of toxic metabolites and antibody production.[16] Other theories implicate graft-versus-host disease or viral infections. Treatment requires discontinuation of the offending AED and supportive care, which may include corticosteroids and intravenous immunoglobulin (Table 3).[16] Family members may also be at risk. The susceptibility of first-degree relatives to AED-related AHS may be predicted with the in vitro LTA.

When an AED is needed for seizure control in patients who have developed AHS, the selection of a nonaromatic AED is preferred. A retrospective study of 20 AHS cases (age range, 1-84 years, including 9 children <14 years old) in a 450-bed teaching hospital yielded data from which investigators calculated a cross-reactivity between phenytoin and carbamazepine of 45%.[11] This result is similar to that from another retrospective study, a chart review of 633 patients who had 1,875 AED exposures,[12] in which the risk of AED-induced skin rashes was evaluated. In that study, 10 of 17 (58%) patients who had a rash due to phenytoin also had a rash from carbamazepine. Similarly, 10 of 25 (40%) patients who had a rash from carbamazepine also developed one from phenytoin. Of the 5 patients who had a rash from phenobarbital, 4 (80%) also had one from carbamazepine or phenytoin.

Although prompt withdrawal of the offending AED is essential to treatment, care must be taken not to precipitate status epilepticus in patients at high risk of seizures. The above findings of cross-reactivity between aromatic AEDs like phenytoin and carbamazepine point to a nonaromatic AED as a better replacement. Because AHS typically affects the liver, an AED that does not undergo hepatic metabolism may be preferred. Consequently, gabapentin and levetiracetam possess at least 2 qualifications (low risk of rash and lack of hepatic metabolism) to support their use in patients with AHS. Patients may wish to wear a medication alert bracelet indicating their susceptibility to AHS.

Weight change. AEDs associated with weight gain include carbamazepine, gabapentin, and valproate.[18] Valproate-associated weight gain tends to be the most severe and is quite common, occurring in 57% of adults and 40% of children on that medication.[19] Significant weight gain may occur within 3 months of starting valproate; patients may choose to discontinue the drug due to this side effect.

The pathophysiology of weight gain due to valproate remains unclear. Valproate decreases carnitine levels, which impairs β-oxidation of fatty acids, resulting in an increase of available fat for deposition in adipose tissue. A study comparing carnitine supplementation versus placebo in 20 children (average age, 3 years; age range, 6 months-15 years) with primary generalized epilepsy did not reveal a correlation between weight gain and carnitine level.[19] An increase in appetite induced by valproate may be responsible for weight gain associated with its use. Valproate inhibits gluconeogenesis, which decreases glucose levels and may stimulate appetite. Increased insulin secretion may also contribute.

AEDs associated with weight loss include topiramate and zonisamide. These drugs may be preferred in the obese patient who requires AED treatment. Change in weight should be monitored in all patients treated with AEDs.

Conclusion

All AEDs have advantages and disadvantages regarding efficacy, adverse events, and drug–drug interactions. Appropriate selection of an AED for the seizure type and syndrome enhances the likelihood of effective seizure control. Disciplined classification of pediatric epilepsy into seizure type and syndrome, as well as continued research and experience with the new AEDs, will lead to more effective seizure control for many children.

Knowledge of potential adverse events associated with each AED also guides the choice of treatment for an individual patient. Prompt identification of potentially serious idiosyncratic adverse effects such as AHS is necessary for patient safety. Physicians should regularly monitor children for weight changes associated with use of AEDs.

References

1. King MA, Newton MR, Jackson GD, et al. Epileptology of the first seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 30 consecutive patients. *Lancet*. 1998;352:1007-1011.
2. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389-399.
3. Pellock JM, Appleton R. Use of new antiepileptic drugs in the treatment of childhood epilepsy. *Epilepsia*. 1999;40(suppl 6):S29-S38.
4. Benbadis SR, Tatum WO, Gieron M. Idiopathic generalized epilepsy and choice of antiepileptic drugs. *Neurology*. 2003;61:1793-1795.
5. Marini C, King MA, Archer JS, Newton MR, Berkovic SF. Idiopathic generalized epilepsy of adult onset: clinical syndromes and genetics. *J Neurol Neurosurg Psychiatry*. 2003;74:192-196.
6. Benbadis SR. Practical management issues for idiopathic generalized epilepsies. *Epilepsia*. 2005;46(suppl 9):1-8.
7. Pinto D, de Haan GJ, Janssen GAMAJ, et al. Evidence for linkage between juvenile myoclonic epilepsy-related idiopathic generalized epilepsy and 6p11-12 in Dutch families. *Epilepsia*. 2004;45:211-217.
8. Benbadis SR. The management of idiopathic generalized epilepsies. *Acta Neurol Scand*. 2005;112 (suppl 181):63-67.
9. Faught E, Pellock JM. The challenge of treatment selection for epilepsy. *Epilepsia*. 2001;42(suppl 8):4-5.
10. Perucca E. An introduction to antiepileptic drugs. *Epilepsia*. 2005;46(suppl 4):31-37.
11. Sierra NM, Garcia B, Marco J, Plaza S, Hidalgo F, Bermejo T. Cross hypersensitivity syndrome between phenytoin and carbamazepine. *Pharm World Sci.* 2005;27:170-174.
12. Hyson C, Sadler M. Cross sensitivity of skin rashes with antiepileptic drugs. *Can J Neurol Sci*. 1997;24:245-249.
13. Physicians' Desk Reference 59th ed. Montvale, NJ: Thomson PDR; 2005.
14. Eralp Y, Aydiner A, Tas F, Saip P, Topuz E. Stevens-Johnson syndrome in a patient receiving anticonvulsant therapy during cranial irradiation. *Am J Clin Oncol*. 2001:24:347-350.
15. Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother*. 2001;35:533-538.
16. Gogtay NJ, Bavdekar SB, Kshirsagar NA. Anticonvulsant hypersensitivity syndrome: a review. *Expert Opin Drug Saf*. 2005; 4:571-581.
17. Galindo PA, Borja J, Gomez E, et al. Anticonvulsant drug hypersensitivity. *J Investig Allergol Clin Immunol*. 2002;12:299-304.
18. Ness-Abramof R, Apovian CM. Drug-induced weight gain. *Drugs Today*. 2005;41:547-555.
19. Demir E, Aysun S. Weight gain associated with valproate in childhood. *Pediatr Neurol*. 2000;22:361-354.