Optimizing Treatment of Adolescents With Partial-Onset Seizures

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Optimizing Treatment of Adolescents With Partial-Onset Seizures

PROGRAM DESCRIPTION
Epilepsy is the most common neurological disease in adolescence. Adolescence is a period of rapid physical, psychological, and emotional development. The presence of a chronic disease like epilepsy only adds to the burden of transitioning to adulthood. Adolescents with epilepsy are more than twice as likely to repeat a school grade and have poorer social competence as are those without epilepsy. Thus, optimal management is essential for maximizing health-related quality of life and psychosocial and academic functioning during this sensitive period of development. This supplement addresses issues related to the diagnosis and management of partial-onset seizures in adolescents, reviews both evidence-based and expert-opinion-based recommendations for pharmacologic and nonpharmacologic management, and examines data on emerging therapies for inadequately controlled partial-onset seizures in this patient population.

PROGRAM GOAL
To update neurologists on current issues related to the diagnosis and management of partial-onset seizures in adolescents.

LEARNING OBJECTIVES
At the conclusion of this activity, participants will be better able to:
- Describe the diagnosis and classification of partial-onset seizures
- Discuss issues related to the management of epilepsy in adolescents, including the impact of epilepsy and its treatment on driving, academics, and psychosocial function
- Define the risks and benefits of available therapies for treating partial-onset seizures in adolescents
- Discuss data from recent clinical trials of emerging therapies in adolescents and adults with partial-onset seizures.

TARGET AUDIENCE
This activity has been developed for neurologists.

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Introduction

Adolescents with epilepsy comprise patients with childhood-onset syndromes that persist into adulthood and patients with epilepsy syndromes that begin in adolescence. As patients transition from pediatric to adult neurology care, pediatric and adult neurologists may be called on to manage epilepsy in adolescents. The management of epilepsy in adolescence poses several challenges. Issues related to autonomy (eg, self-management of medication, getting enough sleep, and maintaining a healthy diet) can have a significant impact on seizure control. Optimal epilepsy management also is essential for maximizing health-related quality of life (HRQOL), psychosocial development, and academic functioning during adolescence.1–3 This supplement addresses issues related to the diagnosis and management of partial-onset seizures in adolescents, reviews evidence-based and expert-opinion–based recommendations for pharmacologic and nonpharmacologic management, and examines data on investigational therapies for inadequately controlled partial-onset seizures in this patient population.

Epidemiology

Epilepsy affects about 3 million Americans, including 300,000 <18 years of age.4 Of the estimated 200,000 new cases of epilepsy that occur in the United States each year, about 50,000 are in the pediatric population.4 In the National Survey of Children’s Health (NSCH), the lifetime prevalence of epilepsy among US children aged birth to 17 years is 1%. The current prevalence is 0.6%.3 The adjusted incidence rate of new-onset epilepsy among children, aged 1 month through 17 years, residing in Olmsted County, Minnesota, between 1980 and 2004 is estimated at 44.5 cases per 100,000 persons/year.5

Epilepsy is the most common neurologic disease in adolescence. In the NSCH analysis, the lifetime prevalence of epilepsy/seizure disorders among those 12 to 17 years of age was 1.4%.3 The incidence rate of epilepsy per 100,000 persons/year among adolescents is 24.8 (Table 1) and is higher among males (29.5) than females (19.9).3 Among adolescents and adults, the most common electroclinical syndromes at initial diagnosis are juvenile absence epilepsy and juvenile myoclonic epilepsy (JME) (Table 2).5

Table 1. Incidence of Seizure Types in Adolescence and Distribution of New-Onset Cases by Electroclinical Syndrome

<table>
<thead>
<tr>
<th>Electroclinical Syndrome at Initial Diagnosis (Adolescence/Adulthood)</th>
<th>Distribution of New-Onset Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile absence epilepsy</td>
<td>39%</td>
</tr>
<tr>
<td>JME</td>
<td>39%</td>
</tr>
<tr>
<td>Epilepsy with GTC seizures alone</td>
<td>21%</td>
</tr>
</tbody>
</table>

Wirrell EC, et al.7 GTC=generalized tonic-clonic.
Terminology and Classification of Seizures

Generalized seizures are defined as originating within and rapidly including bilaterally distributed networks. In contrast, partial-onset seizures originate within brain networks limited to one hemisphere. Partial-onset seizures typically are highly localized in onset, but there may be more than one onset area in a given patient. While a patient may exhibit involvement of more than one network and more than one seizure type, ictal onset must be consistent for each seizure type. Generalized seizures are classified as tonic-clonic, absence seizures (typical, atypical, or absence with special features), myoclonic (myoclonic, myoclonic atonic, myoclonic tonic), clonic, tonic, and atonic. According to the International League Against Epilepsy’s revised terminology and concepts for organization of seizures and epilepsies, classification terms such as simple partial or complex partial are no longer used because they are considered imprecise. However, partial-onset seizures may be described by characteristics (eg, impairment of consciousness/awareness, localization, progression of ictal events) that may facilitate the evaluation of individual patients or may be useful for a specific purpose, such as differentiating between epileptic seizures and nonepileptic events or evaluating for surgery. Among those with nonidiopathic partial-onset epilepsy, cryptogenic should be distinguished from probable symptomatic epilepsy because cryptogenic epilepsy has a significantly better long-term outcome than symptomatic epilepsy.

Diagnostic Consultation

During a diagnostic consultation for a teenager with suspected or established epilepsy, sensitivity to both the patient’s growing need for autonomy and the parents’ concerns is important. Although the focus of the initial patient interview and subsequent consultations should be the adolescent, because the history depends to a high degree on witness account, it is necessary to interview the parents.

To appeal to the adolescent’s need for autonomy and help foster a sense of control:

- Address the adolescent first, before the parents.
- Ask the adolescent to introduce the parents to you.
- Explain to the adolescent what will happen during the initial consultation.
- Explain to the adolescent why it is necessary to talk to the parents.
- Obtain the history from the adolescent directly, with assistance from the parent when needed.
- Explain the diagnosis, evaluation, and treatment to the adolescent.
- Provide a strategy for remembering medication (eg, cell phone alarm) and making up missed or late medication to the adolescent.
- During the evaluation, allow the adolescent an opportunity to supply information and ask questions without the parents present.
- At the end of each visit, ask whether the adolescent has any questions (if not, suggest possible questions).
- Provide Internet references and adolescent chat room addresses.
- Address correspondence directly to the adolescent patient, but ask for permission to send copies of letters to the parents.

The interview and neurological examination are key components of the initial assessment. For patients with a possible first seizure, it is important to establish whether an actual seizure has occurred and, if so, whether it is the first episode. A careful, detailed history provided by a reliable observer often can help determine whether a seizure has occurred. The history should include associated factors (eg, age, family history, health at seizure onset, precipitating events other than illness), symptoms immediately before and during the seizure (eg, subjective sensations, mood or behavioral changes, motor and vocal symptoms, changes in respiration or other autonomic symptoms, loss of consciousness), and symptoms following the seizure (eg, amnesia for events, lethargy/sleepiness, headache, transient focal weakness, nausea or vomiting). The next goal of the assessment is to identify the cause of the seizure. In some cases, a detailed history and physical/neurological examination may provide sufficient information to determine the probable cause of the seizure or to establish a need for other tests, such as neuroimaging.

Recommended Investigations

For the adolescent with a first seizure, basic blood tests (complete blood cell count; measurement of creatinine, calcium, electrolyte levels; liver function tests) should be performed. Laboratory tests should be individualized based on clinical circumstances (eg, vomiting, diarrhea, dehydration, alterations in alertness). It is important to inquire about drug or alcohol exposure during the interview (preferably without parents present), because many substances or withdrawal from substances may precipitate seizures in an individual without epilepsy. If drug exposure or substance abuse is a concern, toxicology screening should be considered. Lumbar puncture is of little value in a child or adolescent with a first nonfebrile seizure unless there is concern about meningitis or encephalitis.

An electroencephalogram (EEG) is recommended for differentiating seizures from other events, classifying the initial seizure, and predicting risk for seizure recurrence. Results of the EEG may influence the counseling of the patient and the decision to perform neuroimaging studies. In addition, the EEG may provide supportive evidence for the presence of a specific clinical syndrome. A sleep deprivation study or 24-hour ambulatory EEG should be considered if the routine EEG is normal.

Positive findings on magnetic resonance imaging (MRI) are found in 20% to 30% of children with a first seizure. However, structural abnormalities requiring intervention are found in only about 1% of cases. Table 3 summarizes recommendations for structural imaging in children and adolescents. Repeat structural imaging in adolescents is recommended if there is a failure to control seizures, worsening

<table>
<thead>
<tr>
<th>Imaging Indicated</th>
<th>Imaging Usually Not Indicated</th>
</tr>
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<tbody>
<tr>
<td>Localization-related seizures</td>
<td>Childhood absence epilepsy</td>
</tr>
<tr>
<td>Focal history, abnormal exam, focal EEG abnormalities</td>
<td>Juvenile absence epilepsy</td>
</tr>
<tr>
<td>Developmental regression</td>
<td>JME</td>
</tr>
<tr>
<td>&lt;2 years old</td>
<td>BECTS</td>
</tr>
<tr>
<td>Symptomatic generalized epilepsy syndrome</td>
<td></td>
</tr>
<tr>
<td>Increased intracranial pressure</td>
<td></td>
</tr>
<tr>
<td>History of status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Atypical course for BECTS/IGE</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Gaillard WD, et al. Boldface indicates syndromes that may occur during adolescence. *Except BECTS.

BECTS=benign epilepsy of childhood with centrotemporal spikes; IGE=idiopathic generalized epilepsy.
seizures, or alterations in seizure manifestations.\textsuperscript{12} Imaging may not be necessary in adolescents with idiopathic partial or generalized epilepsy when the clinical presentation is typical, the neurological examination is normal, and characteristic features are evident on EEG.\textsuperscript{9,12} Computed tomography with and without contrast can be considered when MRI is not available (eg, emergent evaluation), recognizing that some symptomatic causes (eg, small tumors, mesial temporal sclerosis) will not be detected.\textsuperscript{12}

### Differential Diagnosis of Partial-Onset Seizures

The differential diagnosis of partial-onset seizures involves distinguishing between epileptic and nonepileptic seizures as well as among different syndromes. Table 4 highlights the differential diagnosis between epileptic seizures and nonepileptic events in adolescents.\textsuperscript{13} The presence of psychogenic nonepileptic attacks (PNEAs) is the most common (>90\%) condition misdiagnosed as epilepsy at epilepsy referral centers. Although most patients with PNEAs are young

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Key Distinguishing Features</th>
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</thead>
<tbody>
<tr>
<td><strong>PNEAs</strong></td>
<td>• Historical features favoring PNEA: Resistance to AEDs, very high seizure frequency unaffected by AEDs, specific triggers that are unusual for epilepsy (eg, getting upset, pain), attacks occur in the presence of an audience (particularly in the physician’s office), presence of certain comorbid diagnoses (eg, fibromyalgia, chronic pain), positive psychosocial history/psychiatric diagnoses</td>
</tr>
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<td></td>
<td>• Characteristics of motor features favoring PNEAs: Very gradual onset/termination; discontinuous, irregular, or asynchronous activity; pseudosleep; side-to-side head movements; pelvic thrusting; opisthotonic posturing; stuttering; weeping; preserved awareness during bilateral motor activity; persistent eye closure; pleomorphic events</td>
</tr>
<tr>
<td></td>
<td>• Detailed description of the spells, often including characteristics inconsistent with epileptic seizures</td>
</tr>
<tr>
<td></td>
<td>• Presence of histrionic behaviors favors PNEAs</td>
</tr>
<tr>
<td></td>
<td>• Symptoms favoring epileptic seizures: Significant postictal confusion, incontinence, occurs out of sleep, significant injury (especially tongue-biting for tonic-clonic seizures), stereotyped events</td>
</tr>
<tr>
<td></td>
<td>• Presence of repeated normal EEGs favors PNEAs</td>
</tr>
<tr>
<td><strong>Panic attacks/panic disorder</strong></td>
<td>• Identification of fear as an aura of mesiotemporal epilepsy is clear if it evolves into a clear seizure</td>
</tr>
<tr>
<td></td>
<td>• Panic attacks typically include intense autonomic symptoms (especially cardiovascular and respiratory) that typically peak within 10 minutes</td>
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<tr>
<td></td>
<td>• Comorbid anxiety or mood disorders favor panic attacks</td>
</tr>
<tr>
<td><strong>Migraine</strong></td>
<td>• Migraine symptoms usually evolve in minutes versus seconds for seizure symptoms</td>
</tr>
<tr>
<td></td>
<td>• Presence of associated migraine symptoms (eg, headache) or more obvious seizure symptoms</td>
</tr>
<tr>
<td><strong>Acute dystonic reactions</strong></td>
<td>• Acute dystonic reactions occur in response to dopamine receptor blockers (eg, antipsychotics, antiemetics); typically occur within 1 to 4 days of starting medication; characterized by twisting movements</td>
</tr>
<tr>
<td><strong>Hemifacial spasm</strong></td>
<td>• Unilateral facial twitching of hemifacial spasm, typically affecting the periocular muscles then spreading to other ipsilateral facial muscles over months/years</td>
</tr>
<tr>
<td><strong>Hypnic jerks</strong></td>
<td>• Hypnic jerks occur only upon falling asleep</td>
</tr>
<tr>
<td></td>
<td>• On video EEG monitoring, hypnic jerks occur in wake to stage 1 transition and have no EEG correlate</td>
</tr>
<tr>
<td><strong>Parasomnia/narcolepsy</strong></td>
<td>• Historical features consistent with somnambulism or other parasomnia</td>
</tr>
<tr>
<td></td>
<td>• Cataplexy occurs during wakefulness, often induced by emotion, and can occasionally be confused with seizures</td>
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<tr>
<td></td>
<td>• EEG and imaging typically normal</td>
</tr>
<tr>
<td></td>
<td>• Occur exclusively in sleep</td>
</tr>
<tr>
<td></td>
<td>• Video EEG monitoring may be required to distinguish from nocturnal seizures</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>• Hypoglycemia rarely is associated with a complete LOC; when it does, it resembles syncope</td>
</tr>
<tr>
<td></td>
<td>• Hypoglycemia usually is preceded by prodromes of hunger, weakness, tremulousness, malaise, abnormal behaviors</td>
</tr>
<tr>
<td></td>
<td>• Circumstances favoring hypoglycemia include diabetes, use of insulin or oral antihyperglycemics, fasting</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>• Syncope, but not epileptic seizures, can cause a flaccid, motionless episode of LOC lasting from seconds to minutes</td>
</tr>
<tr>
<td></td>
<td>• Clonic-like or myoclonic-like motor symptoms associated with syncope tend to last only a few seconds and stop once the patient is horizontal</td>
</tr>
<tr>
<td></td>
<td>• Syncope usually is triggered by clear precipitants</td>
</tr>
<tr>
<td></td>
<td>• Features favoring syncope: Presyncope syndromes, older age, history of cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>• Features favoring epileptic seizures: Tongue biting, head turning, posturing, urinary incontinence, cyanosis, prodromal déjà-vu, postictal confusion</td>
</tr>
<tr>
<td><strong>Tics/tic disorders</strong></td>
<td>• Although they can fluctuate, tics are not episodic and typically occur throughout the day</td>
</tr>
<tr>
<td></td>
<td>• Tics are sporadic and stereotyped and tend to disappear during sleep</td>
</tr>
<tr>
<td></td>
<td>• Tics are preceded by a temporarily suppressible urge to move or vocalize, and expression of the tic is followed by relief</td>
</tr>
<tr>
<td></td>
<td>• Onset of tics/tic disorders is usually between ages 5 and 10 years</td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>• TIA symptoms are typically negative, whereas seizure symptoms are typically positive</td>
</tr>
<tr>
<td></td>
<td>• Focal symptoms in TIA are maximal at onset, whereas partial-onset seizure symptoms tend to evolve over seconds</td>
</tr>
<tr>
<td></td>
<td>• TIAs rarely, if ever, cause loss of consciousness</td>
</tr>
</tbody>
</table>

Adapted from Benbadis S.\textsuperscript{13} AEDs=antiepileptic drugs; LOC=loss of consciousness; TIA=transient ischemic attack.
Table 5. Epilepsy Syndromes That May Be Present During Adolescence

<table>
<thead>
<tr>
<th>Childhood-Onset Epilepsy Syndromes That May Persist Into Adolescence</th>
<th>Epilepsy Syndromes That May Begin in Adolescencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Late-onset childhood occipital epilepsy (Gastaut type, late onset)</td>
<td>• Reading epilepsy</td>
</tr>
<tr>
<td>• Benign myoclonic epilepsy in infancy</td>
<td>• Photosensitive epilepsies</td>
</tr>
<tr>
<td>• Lennox-Gastaut syndrome</td>
<td>• Juvenile absence epilepsy</td>
</tr>
<tr>
<td>• Generalized epilepsy with febrile seizures plus</td>
<td>• JME</td>
</tr>
<tr>
<td>• Childhood absence epilepsy</td>
<td>• Epilepsy with generalized tonic-clonic seizures</td>
</tr>
<tr>
<td>• Epilepsy with myoclonic absences (Tassinari syndrome)</td>
<td>• Epilepsy with generalized tonic-clonic seizures on awakening</td>
</tr>
<tr>
<td>• Eyelid myoclonia with absences (Jeavons syndrome)</td>
<td>• Progressive myoclonic epilepsies</td>
</tr>
<tr>
<td>• Myoclonic atonic epilepsy of early childhood (Doose syndrome)</td>
<td>• Mesial temporal lobe epilepsy</td>
</tr>
<tr>
<td>• Autosomal dominant nocturnal frontal lobe epilepsy</td>
<td>• Benign partial seizures of adolescence</td>
</tr>
<tr>
<td>• Panayiotopoulos syndrome</td>
<td>• Familial focal epilepsy with variable focb</td>
</tr>
<tr>
<td></td>
<td>• Other familial temporal lobe epilepsies</td>
</tr>
</tbody>
</table>

aOnset also may occur in adulthood for some of these syndromes; bOnset from childhood to adulthood.

Table 6. Syndromes Characterized by Partial-Onset Seizures That May Occur During Adolescence

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Features</th>
<th>EEG</th>
<th>Structural Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNFLE</td>
<td>• Clusters of typically brief, nocturnal motor seizures with hyperkinetic/dystonic features and/or tonic manifestations</td>
<td>Video EEG during sleep: Ictal frontal discharges or ictal, anterior, rhythmic, slow–wave activity</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>• Sleep is interrupted but resumes immediately after seizure</td>
<td></td>
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<tr>
<td></td>
<td>• Seizures may be associated with an aura</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Awareness usually is preserved during seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Secondarily GTC seizures occur infrequently in two thirds of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTLE</td>
<td>• Often a history of febrile seizures, trauma, hypoxia, and intracranial infections before age 5 years</td>
<td>Interictal EEG: Sharp- or spike-slow–wave focus or normal or mild and nonspecific abnormalities</td>
<td>Hippocampal sclerosis in MTLE-HS</td>
</tr>
<tr>
<td></td>
<td>• Initial nonfebrile seizure types that draw clinical attention include complex partial-onset seizures or secondarily generalized convulsions; these have been preceded by a history of simple partial-onset seizures</td>
<td>Ictal EEG: Often normal at seizure onset; typical pattern consists of rhythmic, crescendo-like theta activity with decreasing frequency and increasing amplitude</td>
<td>In MTLE without HS, anatomical evidence of localization</td>
</tr>
<tr>
<td></td>
<td>• Most common ictal symptoms include epigastric aura, fear, and oroalimentary automatisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign partial seizures of adolescence</td>
<td>• Single seizure or cluster of 2–5 partial-onset seizures, with period of seizures lasting ≤36 h</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>• Partial motor and somatosensory seizures that may progress to impaired cognition and/or secondarily GTC seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial focal epilepsy with variable foci</td>
<td>• Family history of partial-onset seizures arising from different cortical locations (temporal, frontal, centroparietal, and occipital)</td>
<td>Interictal focal epileptiform abnormalities with a single focus over time and location concordant with clinical symptoms</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>• Individual patient has same electroclinical pattern of single location partial-onset epilepsy</td>
<td>EEG abnormalities frequently brought on or facilitated by sleep</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Seizures often nocturnal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other familial temporal lobe epilepsies</td>
<td>• Mild partial-onset seizures with mainly auditory hallucinations for FLTE and déjà vu or other experimental phenomena or hallucinations alone or with autonomic disturbances for FMTLE</td>
<td>FLTE: Normal or mild and nonspecific abnormalities with rare interictal epileptiform abnormalities</td>
<td>Normal or mild and nonspecific abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Visual, olfactory, vertiginous, or cephalic features also common for FLTE</td>
<td>FMTLE: Usually normal and with mild, focal slow waves or sparse, usually unilateral, sharp–slow-wave complexes in the temporal region</td>
<td>Hippocampal atrophy can be found in severe cases of FMTLE</td>
</tr>
<tr>
<td></td>
<td>• Fear/panic and visual, auditory, or somatosensory hallucinations also common for FMTLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mainly brief aphasic seizures may occur in FLTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infrequent GTC seizures</td>
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<tr>
<td></td>
<td>• Excellent response to treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Panayiotopoulos CP.c,d
FLTE=familial lateral temporal lobe epilepsy; FMTLE=familial mesial temporal lobe epilepsy; HS=hippocampal sclerosis.

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women, PNEAs can occur in children and adolescents. The gender difference favoring women appears to begin in adolescence. Other than PNEAs, non-epileptic phenomena that occur in adolescence and may resemble partial-onset seizures include migraine, hemifacial spasm, parasomnias, tics/tic disorders, and transient ischemic attacks.

Epilepsy syndromes that may be present during adolescence include childhood-onset epilepsy syndromes that may persist into adolescence and epilepsy syndromes with an onset in adolescence (Table 5).6,14,15 Syndromes characterized by partial-onset seizures include autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), mesial temporal lobe epilepsy (MTLE), benign partial seizures of adolescence, familial focal epilepsy with variable foci, and other familial temporal lobe epilepsies (Table 6).16 JME sometimes is misdiagnosed as partial epilepsy (with or without secondarily generalized seizures), leading to delays in diagnosis and appropriate therapy. Confusion arises in part because lateralized or persistently focal EEG abnormalities may occur in JME.14,17,18 Absence seizures in JME typically are short with only mild impairment of consciousness and common automatisms; mistaking them for partial seizures is relatively common.19 Myoclonic seizures in JME may be misinterpreted as focal clonic seizures because they may be focally distributed or reported as such.19 Myoclonic jerks are considered the sine qua non of diagnosis of JME and occur in 100% of cases.20 When taking the patient history, it is critical to ask patients about the occurrence of myoclonic jerks and presence of precipitating factors. Myoclonic jerks may occur unilaterally, and some may be experienced only as a sensation of electric shock within the body. Myoclonus may not be reported spontaneously by the patient, and terms that patients often use to describe jerks include shakes, clumsiness, twitches, and nervousness. Sometimes, myoclonic jerks are noticed only by the patient’s family and not by the patient, so interviewing family members may be helpful. Table 7 describes additional features of JME that may aid in differentiating it from partial epilepsy.21–23

Several partial-onset epilepsy syndromes have a known genetic component (Table 8).24 Genetic testing may be useful in clinical practice to support diagnosis of a specific epilepsy syndrome and may influence the treatment choice.
Adolescents with epilepsy may require treatment for an initial diagnosis or may have an epilepsy syndrome continuing from childhood. As patients continue into adolescence, it may be necessary to reassess their regimen and switch medications. Older drugs commonly used to treat partial-onset seizures in adolescents include carbamazepine, phenobarbital, phenytoin, and valproate. Carbamazepine, phenobarbital, and phenytoin are indicated for the treatment of partial-onset seizures (complex partial seizures for carbamazepine and phenytoin), but the labeling does not differentiate between monotherapy and adjunctive treatment. Valproate is indicated as monotherapy or adjunctive therapy in patients with complex partial seizures that occur alone or with other seizure types. During the past decade, several new treatments have emerged, and studies have evaluated pre-existing antiepileptic drugs (AEDs) in adolescents with partial-onset seizures (Table 9).30–33

### Current Recommendations for First-Line Treatment of Partial-Onset Seizures

The American Academy of Neurology (AAN) guidelines for the treatment of patients with new-onset epilepsy were published in 2004 and are being revised.34 Recommended first-line pharmacotherapy for partial-onset seizures in adolescents includes carbamazepine, sodium valproate, phenytoin, gabapentin, lamotrigine, topiramate, and oxcarbazepine.34,35 However, gabapentin is only approved by the US Food and Drug Administration (FDA) as adjunctive therapy, and lamotrigine is FDA approved as adjunctive therapy in addition to monotherapy in patients ≥16 years of age who previously received monotherapy with carbamazepine, phenobarbital, phenytoin, primidone, or valproate (ie, not indicated as first-line treatment).36,37

According to consensus of European expert opinion for the treatment of pediatric epilepsy published in 2007, carbamazepine and oxcarbazepine are the treatments of choice for first-line monotherapy of complex partial seizures. Treatment with valproate also is appropriate.38 If carbamazepine or oxcarbazepine is used first and is not efficacious or tolerated, then a trial of valproate monotherapy is recommended; if phenytoin is used first and is not efficacious or tolerated, carbamazepine or oxcarbazepine is recommended, with valproate as another option.

A 2005 survey of 43 US pediatric and adult epileptologists established an expert consensus regarding the initial treatment and second-line monotherapy of adolescents or adults with symptomatic partial-onset seizures.39 Carbamazepine, oxcarbazepine, lamotrigine, and levetiracetam were considered appropriate. When first-line monotherapy failed, the agents most often selected for monotherapy were carbamazepine, oxcarbazepine, lamotrigine, levetiracetam, and topiramate.

Actual usage patterns of AEDs may differ from society recommendations and FDA approvals. In our clinical experience, drugs appropriate for partial seizures as add-on therapy may be used as monotherapy in select patients. As no one drug is definitely more effective in seizure control than another appropriate agent, the choice often is made based on overall tolerability of the drug, drug interactions, and potential to improve or worsen any coexisting conditions, such as migraine or mood disorders. AEDs commonly used to treat partial-onset seizures include levetiracetam, oxcarbazepine, lamotrigine, and lacosamide.

### Treatment of Refractory Epilepsy With Partial Seizures

Treatment-resistant epilepsy is defined as a “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (as monotherapy or in combination) to achieve sustained seizure freedom.”40 This definition implies that the AEDs used must be appropriate for the patient’s seizure type and administered at a therapeutic dose for a sufficient time to observe a clinical response. It has

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**Table 9. Newer AEDs Approved by the US FDA for Partial-Onset Seizures in Adolescents (ie, 13–17 Years of Age) and Actual Usage Patterns**

<table>
<thead>
<tr>
<th>AED</th>
<th>Monotherapy Partial-Onset Seizures</th>
<th>Adjunctive Therapy Partial-Onset Seizures</th>
<th>Actual Usage in Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezogabine (Potiga)²¹ⁱ²</td>
<td>X</td>
<td>X</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)³⁶</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Lacosamide (Vimpat)⁴⁸</td>
<td>X (≥17 y)</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)²⁷</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)⁴⁸</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)³¹</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Perampanel (Fycompa)⁵⁰</td>
<td>X</td>
<td>X</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)²⁸</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)²²</td>
<td>X</td>
<td>X</td>
<td>Adjunctive</td>
</tr>
<tr>
<td>Topiramate (Topamax)²⁰</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)²⁷</td>
<td>X</td>
<td>X</td>
<td>Monotherapy/adjunctive</td>
</tr>
</tbody>
</table>

²⁷In clinical development for adjunctive therapy in adolescents with treatment-resistant partial-onset seizures but not yet FDA approved for this indication.
been estimated that between 10% and 40% of children with epilepsy have treatment-resistant epilepsy.41

Before concluding that a patient has treatment-resistant epilepsy, it is important to rule out or correct pseudoresistance.42 Pseudoresistance refers to the persistence of seizures due to inappropriate or inadequate treatment of the underlying disorder. Some of the most common reasons for pseudoresistance are an incorrect diagnosis (of epileptic seizures or type of seizures or syndrome present), the wrong drug or drugs (eg, inappropriate for seizure type, pharmacokinetic or pharmacodynamic interactions, inadequate dosing), and lifestyle issues (eg, poor adherence, alcohol or drug abuse).32,43 When a patient’s seizures are not responding to therapy, the diagnosis should be revisited by reviewing the accuracy of the seizure and/or syndrome classification and brain imaging results.44 Additional interviews with the patient and the parents may help to better characterize the patient’s clinical symptoms and precipitating factors. Lifestyle factors, including adherence, substance abuse, and other factors that may impact seizures (eg, sleep, diet) should be assessed and addressed before treatment-resistant epilepsy is diagnosed. Video EEG monitoring is indicated for all patients who continue to have seizures despite medications, with the aim of recording a seizure episode to determine whether a change in EEG occurs during the clinical event and whether the clinical attack is consistent or inconsistent with seizure types that may be unaccompanied by EEG changes (ie, to establish whether the diagnosis (of epileptic seizures or type of seizures or syndrome present), the wrong drug or drugs (eg, inappropriate for seizure type, pharmacokinetic or pharmacodynamic interactions, inadequate dosing), and lifestyle issues (eg, poor adherence, alcohol or drug abuse).32,43 When a patient’s seizures are not responding to therapy, the diagnosis should be revisited by reviewing the accuracy of the seizure and/or syndrome classification and brain imaging results.44 Additional interviews with the patient and the parents may help to better characterize the patient’s clinical symptoms and precipitating factors. Lifestyle factors, including adherence, substance abuse, and other factors that may impact seizures (eg, sleep, diet) should be assessed and addressed before treatment-resistant epilepsy is diagnosed. Video EEG monitoring is indicated for all patients who continue to have seizures despite medications, with the aim of recording a seizure episode to determine whether a change in EEG occurs during the clinical event and whether the clinical attack is consistent or inconsistent with seizure types that may be unaccompanied by EEG changes (ie, to establish whether the patient is having epileptic vs psychogenic nonepileptic attacks).45 A brain MRI also should be performed or repeated.12,45 In most cases, the combination of video EEG monitoring and high-quality MRI will allow the neurologist to confirm the diagnosis of epilepsy; determine whether the seizures are localization-related or generalized; distinguish among genetic, structural-metabolic, and unknown causes of epilepsy; and differentiate among localization-related epilepsies.6,45 Laboratory evaluations should be considered when indicated (eg, to investigate genetic, metabolic, or infectious/inflammatory causes of intractable seizures).41 For adults with refractory partial-onset seizures, the AAN recommends monotherapy with oxcarbazepine, topiramate, or lamotrigine, and add-on therapy with gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, or zonisamide.46 However, lamotrigine is indicated as monotherapy in patients ≥16 years of age, and zonisamide is approved only in adults.37,47 The AAN recommends gabapentin, lamotrigine, topiramate, or oxcarbazepine for pediatric patients with refractory partial-onset seizures.46 At the time of the AAN guidelines, levetiracetam was approved only for this indication in adults, but it currently is approved as adjunctive therapy for partial-onset seizures in children aged ≥1 month and adults.46,48 Following publication of the AAN guidelines, lacosamide was approved for add-on therapy of partial-onset seizures in patients ≥17 years of age.49

Perampanel was FDA approved in October 2012 and is indicated as adjunctive therapy for treatment of partial-onset seizures with or without secondary generalization in epilepsy patients ≥12 years of age.50 Perampanel is a noncompetitive antagonist of AMPA-type glutamate receptors and reduces excessive excitatory neurotransmission.51 Three multicenter, randomized, double-blind, placebo-controlled phase III studies have assessed the safety and efficacy of perampanel as add-on therapy in adolescents and adults ≥12 years of age with refractory partial-onset seizures.52–54 Each study consisted of a 6-week baseline phase, a 6-week titration phase during which perampanel was titrated by 2 mg/d, and a 13-week maintenance phase. For all three studies, patients eligible for randomization experienced at least five partial seizures during the baseline period, had failed at least two AED trials in the previous 2 years, and were taking stable doses of up to three approved AEDs. Studies 30452 (N=388) and 30553 (N=386) evaluated perampanel dosages of 8 or 12 mg/d, whereas study 30654 (N=706) evaluated dosages of 2, 4, or 8 mg/d. Overall, perampanel, at dosages of 4, 8, and 12 mg/d, produced statistically significant median reductions in seizure frequency compared with placebo (Table 10).52–54 Responder rates in the perampanel 4, 8, and 12 mg/d groups ranged from 29% to 38%. Compared with placebo, the 50% responder rates were significantly greater for perampanel 4 mg/d and 8 mg/d in Study 30654 and 8 and 12 mg/d in Study 305,53 but did not achieve significance at the 8 or 12 mg/d dosages in Study 30452 (Table 10). FDA-approved AEDs not currently approved for use as adjunctive therapy in adolescents with treatment-refractory partial-onset seizures but that are in phase III development for this indication include ezogabine, pregabalin, and zonisamide.

Table 10. Adjunctive Treatment With Perampanel in Adolescents and Adults With Refractory Partial-Onset Seizures

<table>
<thead>
<tr>
<th>Median Reduction in Seizure Frequency</th>
<th>≥50% Responder Rate</th>
<th>Seizure-Free Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Krauss GL, et al</strong>54; Study 306 (13-week maintenance phase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perampanel 2 mg/d (n=180)</td>
<td>13.6%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Perampanel 4 mg/d (n=172)</td>
<td>23.3%*</td>
<td>28.5%*</td>
</tr>
<tr>
<td>Perampanel 8 mg/d (n=169)</td>
<td>30.8%*</td>
<td>34.9%*</td>
</tr>
<tr>
<td>Placebo (n=185)</td>
<td>10.7%</td>
<td>17.9%</td>
</tr>
<tr>
<td><strong>French JA, et al</strong>52; Study 304 (13-week maintenance phase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perampanel 8 mg/d (n=133)</td>
<td>26.3%*</td>
<td>37.6%</td>
</tr>
<tr>
<td>Perampanel 12 mg/d (n=134)</td>
<td>34.5%*</td>
<td>36.1%</td>
</tr>
<tr>
<td>Placebo (n=121)</td>
<td>21.0%</td>
<td>26.4%</td>
</tr>
<tr>
<td><strong>French JA, et al</strong>53; Study 305 (13-week maintenance phase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perampanel 8 mg/d (n=129)</td>
<td>30.5%*</td>
<td>33.3%*</td>
</tr>
<tr>
<td>Perampanel 12 mg/d (n=121)</td>
<td>17.6%*</td>
<td>33.9%*</td>
</tr>
<tr>
<td>Placebo (n=136)</td>
<td>9.7%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

*P<0.05 vs placebo; **P<0.01 vs placebo; ***P<0.001 vs placebo; †Among completers of the maintenance period.
Role of Nonpharmacologic Strategies for Treatment-Resistant Partial-Onset Seizures

Nonpharmacologic strategies include dietary therapies, alternative therapies, surgery, and vagus nerve stimulation (VNS). For adults, responsive cortical stimulation, deep brain stimulation, laser-based ablation surgery, transcranial magnetic stimulation, and trigeminal nerve stimulation are possible alternatives that are pending FDA approval.

Dietary Therapies
The ketogenic diet is a high-fat, low-protein, and very low-carbohydrate diet most commonly used for children 5 to 10 years of age with refractory epilepsy. Approximately one third to one half of children achieve a cessation of or marked reduction in seizure activity with a ketogenic diet. Results of a small study suggest that adolescent retention on the ketogenic diet is similar to that of younger children, but retention may be lower among patients with partial-onset seizures. The ketogenic diet is similarly effective in children and adults in patients with different seizure types, including partial-onset seizures. Potential candidates for the ketogenic diet include patients with medically intractable seizures (including those being considered for epilepsy surgery), those with poor tolerability with AEDs, and patients with specific neurologic/neurometabolic syndromes. In addition, the ketogenic diet may be beneficial for partial epilepsy patients with recent deterioration of seizure control and neurological status.

The Atkins diet severely restricts carbohydrates during an initia-
tion phase but does not restrict calorie or protein consumption. A case series evaluated the Atkins diet in 6 children, adolescents, and adults with refractory epilepsy. Half of the patients (including patients 7, 10, and 18 years of age) experienced a reduction in seizures and were able to reduce AED medications, providing preliminary evidence for a benefit of the Atkins diet in this patient population. Other dietary therapies being studied include a modified Atkins diet and a low glycemic index diet.

Complementary and Alternative Therapies
Complementary and alternative medicine (CAM) therapies include biologically-based practices (eg, herbs, vitamins), mind-body medicine (eg, meditation, prayer, art or music therapies), manipulative and body-based practices (eg, acupuncture, chiropractic manipulation), and energy medicine (eg, infeld and electromagnetic therapies). Whole medical systems (eg, Ayurveda, homeopathy, traditional Chinese medicine) are recognized separately. Although there is little well controlled evidence to support the use of CAM therapies in patients with epilepsy, a few randomized trials of meditation and yoga suggest possible beneficial effects. The CAM therapies, in particular herbal remedies (eg, St John’s Wort, ginseng, Gingko biloba), are commonly used by patients with epilepsy without their physician’s knowledge. It is important to ask patients with epilepsy whether they are using any CAM therapies, especially herbal products, to allow evaluation of possible risks associated with seizure exacerbation or drug interactions with AEDs.

Vagus Nerve Stimulation
VNS is approved for use as adjunctive therapy in adolescents and adults with treatment-resistant partial-onset seizures and should be considered after two AEDs fail to control seizures or are not tolerated and when epilepsy surgery is not an option. This treatment involves implantation of a device to systematically stimulate the vagus nerve, which has widespread central and peripheral projections.

In various studies, overall responder rates with VNS were 28% to 68%. Response to VNS is sustained over long-term treatment and appears to improve over time. Patients who have failed epilepsy surgery also benefit from VNS. This treatment modality is well tolerated; the most common side effects include voice alteration, hoarseness, cough, and shortness of breath.

Surgery
Surgery commonly is considered after the failure of at least two appropriate AED trials in patients with partial-onset seizures. In appropriately selected patients, seizure freedom is about 70% with temporal resection and 25% with frontal resection. Evidence suggests that surgery performed earlier following a diagnosis of treatment-resistant epilepsy may offer greater benefit than surgery performed after several years of intractable seizures. Therefore, surgery should be strongly considered for potential candidates.

Two randomized controlled trials have compared surgery with continued medical management (CMM) in patients with treatment-resistant temporal lobe epilepsy. In one study, patients ≥16 years of age with temporal lobe epilepsy whose seizures were inadequately controlled despite the use of two or more AEDs (one of which was phenytoin, carbamazepine, or valproic acid) were randomly assigned to surgery (n=40) or CMM (n=40); four patients in the surgery group did not undergo surgery. Patients were followed for 1 year, during which time the AEDs were switched or doses increased in all patients in the CMM group versus nine (22%) in the surgical group. At 1 year, the cumulative proportion of patients who were free of seizures impairing awareness (ie, complex partial or secondarily generalized seizures) was 58% in the surgical group versus 8% in the CMM group (P<0.001). Overall, 38% of surgical patients and 3% of CMM patients were free of all seizures, including auras, at 1 year (P<0.001). Quality of life improved in both groups but statistically was significantly better at 1 year among patients who received surgery versus CMM (P<0.001).

The Early Randomized Surgical Epilepsy Trial was a multicenter, randomized, parallel-group study that examined whether surgery soon after the failure of two AEDs is superior to CMM. Patients ≥12 years of age with MTLE were randomized to surgery (n=15) or CMM (n=23); the only two adolescents in the study were in the CMM group. Fourteen of the patients assigned to surgery underwent surgery, and seven patients in the CMM group underwent surgery prior to the 2-year visit. The mean number of AEDs was comparable in both treatment groups and remained stable throughout the study. During the 2-year follow-up, 73% of patients in the surgical group versus none in the CMM group remained seizure-free (P<0.001). Quality of life was superior in the surgical group compared with the CMM group at months 6, 12, and 18 (P<0.009), but not at month 24 (P=0.08). However, when patients in the CMM group who had undergone surgery were excluded from the analysis, the difference was statistically significant at 2 years (P=0.01). The findings of these two studies strongly support early consideration of surgery to optimize seizure control and HRQOL in patients with temporal lobe epilepsy. However, the advantages of surgery must be weighed against potential risks, such as a long recovery time (with lost work/school time), neurological complications that may affect postoperative functioning, medical (eg, deep vein thrombosis, wound infection) and psychiatric (eg, depression) complications, and the formation of a new brain lesion that may cause seizures.
Patients with epilepsy should be monitored regularly for treatment effectiveness (ie, occurrence, frequency, and severity of seizures), and side effects should be assessed at every visit. The frequency of patient visits should be individualized. In our experience, a patient who is stabilized on a simple regimen and is doing well can be seen every 6 to 12 months. Patients with a more complex AED regimen or issues (eg, comorbidities, side effects) may need to be seen every 3 to 4 months. Other patients may require more frequent visits, especially if their seizures are not well controlled.

Adolescents with seizures will likely continue to have seizures as adults. It is important to select a medication that can be well tolerated without a long-term health impact and to monitor patients for side effects that may affect their HRQOL or their health. Certain AEDs (eg, phenytoin, valproate) may have adverse effects on bone health. Enzyme-inducing AEDs, such as carbamazepine and phenytoin, increase levels of serum lipids and C-reactive protein (CRP) and thus may increase cardiovascular risk. One study in adults with partial epilepsy found that switching from carbamazepine or phenytoin to the noninducing AEDs lamotrigine or levetiracetam resulted in significant decreases in atherogenic cholesterol and CRP. Weight gain may occur during AED therapy, especially with valproate, pregabalin, and to a lesser degree with carbamazepine and high-dose gabapentin. Lamotrigine, levetiracetam, lacosamide, perampanel, and phenytoin are considered weight-neutral, whereas felbamate, topiramate, and zonisamide may induce weight loss. There may be adverse hormonal effects with AEDs. In particular, valproate treatment has been associated with an increased risk of polycystic ovary syndrome in adolescents and young women.

Children and adolescents with epilepsy should be monitored for cognitive and behavioral/psychiatric well-being, HRQOL, and psychosocial adjustment. The American Epilepsy Society (AES) Web site provides a “Cognitive and Behavioral Effects of Epilepsy Practice Tool,” which can be accessed at: http://www.aesnet.org/practice/practice-tools. The AES recommends assessing sleep behaviors and the sleep environment and providing adolescents and their parents with suggested lifestyle changes to improve sleep for maximizing seizure control and cognitive and behavioral functioning. In addition to asking about the patient’s sleep habits, the Epworth Sleepiness Scale can be used to assess the patient’s level of daytime sleepiness.

While patients taking any AED should be monitored for adverse events, black box warnings warrant special consideration. The carbamazepine labeling has black box warnings concerning the risk of serious skin reactions as well as the risk of aplastic anemia and agranulocytosis. Black box warnings for valproate include hepatotoxicity, teratogenicity, and pancreatitis. A black box warning for lamotrigine warns of the risk of life-threatening serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death. The labeling for perampanel carries a black box warning regarding serious psychiatric and behavioral reactions. Reactions such as aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking perampanel, and patients should be monitored closely during the titration period and at higher doses. Patients and caregivers should be advised to contact a health care provider immediately should any changes in mood, behavior, or personality occur during or after treatment with perampanel that are atypical for the patient.

Therapeutic drug monitoring can guide dose adjustments, help to establish an individual therapeutic drug concentration, aid in the identification of drug toxicity, and help determine the extent of adherence. In particular, it is useful to obtain a baseline when the patient is stable to provide a basis of comparison should efficacy or tolerability problems arise.

### Investigational Therapies for Inadequately Controlled Partial-Onset Seizures

Investigational therapies for refractory partial-onset seizures in late-stage clinical development include brivaracetam, eslicarbazepine acetate, and rufinamide.

**Brivaracetam**

Brivaracetam is an analog of levetiracetam and acts by binding to synaptic vesicle protein 2A (SV2A) and inhibiting voltage-gated sodium channels. In one phase IIb study, brivaracetam (50 mg/d, but not 5 or 20 mg/d) significantly reduced the weekly frequency of partial-onset seizures compared with placebo in 208 patients, 16 to 65 years of age, with refractory partial-onset seizures. However, a subsequent phase IIb study (N=157) did not demonstrate a statistically significant difference between brivaracetam (50 or 150 mg/d) and placebo with regard to change from baseline in weekly partial-onset seizure frequency. Two multicenter, randomized, double-blind, placebo-controlled trials evaluated adjunctive brivaracetam in patients (16–70 years of age) with partial-onset epilepsy inadequately controlled with one or two AEDs. Both studies consisted of an 8-week baseline period and a 12-week treatment period. Patients who had at least eight partial-onset seizures during the baseline period were randomized. In one study, patients were randomized to brivaracetam (5 mg/d, n=97; 20 mg/d, n=100; 50 mg/d, n=101) or placebo (n=98). The percentage reduction from baseline in partial-onset seizure frequency/week was significantly greater with brivaracetam 50 mg/d compared with placebo (12.8% difference, P=0.025). In the second study, which randomized patients to brivaracetam (20 mg/d, n=99; 50 mg/d, n=99; 100 mg/d, n=100) or placebo (n=100), statistical significance was not achieved on the primary efficacy end point of percent reduction over placebo in partial-onset seizures in the 50 mg/d arm. However, statistical significance was achieved for the brivaracetam 100 mg/d arm (11.7% difference, P=0.037). Notably, a short-term randomized, controlled study of brivaracetam in healthy volunteers supports a favorable cognitive profile for brivaracetam, but findings will need to be confirmed in long-term studies of children and adolescents with epilepsy.

**Eslicarbazepine Acetate**

Eslicarbazepine acetate is a prodrug of the S-enantiomer of the active mono-hydroxy derivative of oxcarbazepine. This agent is an antagonist of voltage-gated sodium channels and is believed to act by stabilizing voltage-gated sodium channels in an inactive state and preventing rapid firing. All completed phase III studies of eslicarbazepine acetate in patients with uncontrolled partial-onset seizures were performed in adults ≥18 years of age. Randomized
patients had at least four partial-onset seizures in each of the two 4-week periods of the 8-week baseline despite being on a stable dose of one to two AEDs or one to three AEDs. Eslicarbazepine 800 and 1,200 mg/d significantly reduced mean seizure frequency compared with placebo (Table 11). The median reduction in seizure frequency was greater for eslicarbazepine 800 and 1,200 mg/d compared with placebo, although statistical significance was reported in only one study (Table 11). Responder rates generally were higher for the eslicarbazepine 800 and 1,200 mg/d groups than the placebo groups, as were the proportion of seizure-free patients, although statistical significance findings differed among the three studies (Table 11). An integrated analysis of safety data from 797 patients found that when used in conjunction with one to three AEDs, eslicarbazepine acetate was associated with a low incidence of cognitive treatment-emergent adverse events. Ongoing phase III studies include two studies of eslicarbazepine monotherapy in patients 16 to 70 years of age, with inadequately controlled partial-onset seizures; a study of adjunctive eslicarbazepine acetate in children and adolescents (2–16 years of age) with refractory partial seizures; and a trial of adjunctive eslicarbazepine in patients ≥16 years of age with refractory partial seizures.

### Rufinamide

Although its exact mechanism of action is unclear, rufinamide blocks voltage-dependent sodium channels. Rufinamide is FDA approved for Lennox-Gastaut syndrome in children ≥4 years of age and in adults. Two phase III, double-blind, randomized, placebo-controlled studies evaluated rufinamide (up to 3,200 mg/d) as add-on treatment in adolescents and adults (aged ≥21 years for the Brodie study and 12–80 years for the Biton study) with inadequately controlled partial-onset seizures. One study consisted of an 8-week baseline phase followed by a 2-week titration period and an 11-week maintenance phase, and the other study comprised an 8-week baseline phase followed by a 12-day titration period and a 12-week maintenance phase. Randomized patients experienced at least six partial seizures during the 8-week baseline period despite being on a stable dose of one to two AEDs or one to three AEDs. In both studies, rufinamide reduced the median seizure frequency by at least 20% compared with placebo (Table 11). About 30% of rufinamide-treated patients in both studies demonstrated at least a 50% decrease in partial seizure frequency. Almost twice as many rufinamide-treated patients as placebo-treated patients achieved seizure freedom in the study by Brodie and colleagues (3.8% vs 1.9%), although the difference was not statistically significant. The efficacy and safety of adjunctive rufinamide (26.9–48 mg/kg/d) in children and adolescents with drug-resistant partial-onset seizures is further supported by a prospective, open-label Italian study that included 70 patients, 3 to 21 years of age. At 1 year, 39% of patients had a ≥50% reduction in seizure frequency, and 4% of patients were seizure-free. In addition, a randomized, double-blind, placebo-controlled monotherapy trial of rufinamide (3,200 mg/d) in 104 inpatients, aged ≥12 years, with uncontrolled partial-onset seizures demonstrated a reduction in seizures and a longer time to first, second, and third seizures with rufinamide versus placebo.

Rufinamide (200, 400, 800, and 1,600 mg/d) as add-on therapy appears to have a favorable cognitive profile, as demonstrated in an international, randomized, double-blind, placebo-controlled, dose-ranging study in 189 patients, 15 to 64 years of age, with treatment-resistant partial seizures. At all doses tested, rufinamide did not produce impairment on any cognitive test during 12 weeks of treatment, although a higher dosage of rufinamide was used in subsequent trials.

### Table 11. Adjunctive Treatment With Eslicarbazepine Acetate in Adults (≥18 Years) With Refractory Partial-Onset Seizures

<table>
<thead>
<tr>
<th></th>
<th>LS Mean Seizure Frequency/4 Weeks</th>
<th>Median Reduction in Seizure Frequency</th>
<th>≥50% Responder Rate</th>
<th>Seizure-Free Rate</th>
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</thead>
<tbody>
<tr>
<td>Elger C, et al83 (12-week maintenance phase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESL 400 mg/d (n=100)</td>
<td>6.73 (P=NS)</td>
<td>26%</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>ESL 800 mg/d (n=98)</td>
<td>5.7b</td>
<td>36%</td>
<td>34%a</td>
<td>4%</td>
</tr>
<tr>
<td>ESL 1,200 mg/d (n=102)</td>
<td>5.4c</td>
<td>45%</td>
<td>43%c</td>
<td>8%a</td>
</tr>
<tr>
<td>Placebo (n=102)</td>
<td>7.6</td>
<td>16%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Gil-Nagel A, et al84 (12-week maintenance phase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESL 800 mg/d (n=85)</td>
<td>5.7a</td>
<td>37.9%</td>
<td>34.5%</td>
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</tr>
<tr>
<td>ESL 1,200 mg/d (n=80)</td>
<td>5.5a</td>
<td>41.9%</td>
<td>37.7%a</td>
<td>3.9%</td>
</tr>
<tr>
<td>Placebo (n=87)</td>
<td>7.3</td>
<td>17.0%</td>
<td>22.6%</td>
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</tr>
<tr>
<td>Ben-Menachem E, et al85 (14-week maintenance phase8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ESL 400 mg/d (n=96)</td>
<td>9.3</td>
<td>18.7%</td>
<td>17.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>ESL 800 mg/d (n=101)</td>
<td>7.1c</td>
<td>32.6%c</td>
<td>40.0%c</td>
<td>8.0%a</td>
</tr>
<tr>
<td>ESL 1,200 mg/d (n=98)</td>
<td>7.4c</td>
<td>32.8%c</td>
<td>37.1%c</td>
<td>4.1%</td>
</tr>
<tr>
<td>Placebo (n=100)</td>
<td>10.9</td>
<td>0.8%</td>
<td>13.0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

### Table 12. Adjunctive Treatment With Rufinamide in Patients ≥16 Years of Age With Refractory Partial-Onset Seizures

<table>
<thead>
<tr>
<th></th>
<th>Median Reduction in Seizure Frequency</th>
<th>≥50% Responder Rate</th>
<th>Seizure-Free Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodie MJ, et al86 (11-week maintenance phase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFN 3,200 mg/d (n=156)</td>
<td>20.4%A</td>
<td>28.2%A</td>
<td>3.8%</td>
</tr>
<tr>
<td>Placebo (n=157)</td>
<td>−1.6% (ie, increase)</td>
<td>18.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Biton V, et al87 (12-week maintenance phase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RFN 3,200 mg/d (n=176)</td>
<td>23.3%B</td>
<td>32.5%C</td>
<td>Not reported</td>
</tr>
<tr>
<td>Placebo (n=181)</td>
<td>9.8%</td>
<td>14.3%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

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8A = <0.05 vs placebo; 8B = <0.01 vs placebo; 8C = <0.001 vs placebo; 8D = All patients started the maintenance phase at the full maintenance dose, except the ESL 1,200 mg/d group, which started at 800 mg/d for the first 2 weeks of the maintenance phase before reaching 1,200 mg/d. ESL=eslicarbazepine acetate; LS=least squares.

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Rufinamide is FDA approved for Lennox-Gastaut syndrome in children ≥4 years of age and in adults. Two phase III, double-blind, randomized, placebo-controlled studies evaluated rufinamide (up to 3,200 mg/d) as add-on treatment in adolescents and adults (aged ≥21 years for the Brodie study and 12–80 years for the Biton study) with inadequately controlled partial-onset seizures. One study consisted of an 8-week baseline phase followed by a 2-week titration period and an 11-week maintenance phase, and the other study comprised an 8-week baseline phase followed by a 12-day titration period and a 12-week maintenance phase. Randomized patients experienced at least six partial seizures during the 8-week baseline period despite being on a stable dose of one to two AEDs or one to three AEDs. In both studies, rufinamide reduced the median seizure frequency by at least 20% compared with placebo (Table 11). About 30% of rufinamide-treated patients in both studies demonstrated at least a 50% decrease in partial seizure frequency. Almost twice as many rufinamide-treated patients as placebo-treated patients achieved seizure freedom in the study by Brodie and colleagues (3.8% vs 1.9%), although the difference was not statistically significant. The efficacy and safety of adjunctive rufinamide (26.9–48 mg/kg/d) in children and adolescents with drug-resistant partial-onset seizures is further supported by a prospective, open-label Italian study that included 70 patients, 3 to 21 years of age. At 1 year, 39% of patients had a ≥50% reduction in seizure frequency, and 4% of patients were seizure-free. In addition, a randomized, double-blind, placebo-controlled monotherapy trial of rufinamide (3,200 mg/d) in 104 inpatients, aged ≥12 years, with uncontrolled partial-onset seizures demonstrated a reduction in seizures and a longer time to first, second, and third seizures with rufinamide versus placebo. Rufinamide (200, 400, 800, and 1,600 mg/d) as add-on therapy appears to have a favorable cognitive profile, as demonstrated in an international, randomized, double-blind, placebo-controlled, dose-ranging study in 189 patients, 15 to 64 years of age, with treatment-resistant partial seizures. At all doses tested, rufinamide did not produce impairment on any cognitive test during 12 weeks of treatment, although a higher dosage of rufinamide was used in subsequent trials.
Adolescence is a period of great change, both physically and socially. As the adolescent transitions into adulthood, issues emerge, such as those related to driving, drinking, social/sexual relationships, preparation for college or employment, and the general increase in responsibility. Adolescence is a time during which individuals are forming their identities, maturing intellectually, preparing for independent living, and striving for autonomy. Transitioning from childhood into adulthood is complicated by the presence of a chronic illness, such as epilepsy. Whether an adolescent patient has an epileptic syndrome continuing from childhood or new-onset epilepsy, management of epilepsy during this developmental period requires special attention to the issues intrinsic to adolescence.

Stigma and Self-Esteem

Epilepsy may have a profound impact on an adolescent’s self-esteem. Compared with younger children, adolescents tend to be more embarrassed when seizures occur in public. A fear of social embarrassment may lead to self-restriction of activities and unwillingness to participate in social events, which may contribute to social isolation. In an international survey of 212 adolescents and young adults with epilepsy, more than one third of respondents indicated they had kept their epilepsy a secret from others. The main reasons for secrecy were a fear of being treated differently (particularly by other children) and the belief that others should not know about their condition. Areas of concern are shown in Figure 1.

Figure 1. Areas of Regular Concern for Children and Adolescents With Epilepsy

Epilepsy can be particularly stigmatizing among adolescents. An in-depth interview of 22 adolescents with epilepsy identified peer acceptance as a major issue. Nineteen participants reported being bullied and feeling socially isolated. Several adolescents related experiences of being rejected by friends because of their epilepsy, and half of the respondents expressed fears about rejection from peers, especially boyfriends or girlfriends, if they found out about their illness.

Unless the situation is managed well, the stigmatizing effect of a disorder that involves a loss of control and requires regular medication is likely to have a negative impact on the adolescent. Teenagers may respond by attempting to hide their condition or by taking risks, such as refusing to accept medication or ignoring other precautions.

Because adolescents may view taking an AED as a distinguishing and stigmatizing feature of their illness, some may avoid taking daytime doses. Once-daily or twice-daily medications may be helpful in such cases. Cosmetic adverse effects (eg, weight gain, hirsutism, coarsening of facial features, gingival hyperplasia) may affect the self-esteem of teenagers who tend to be self-conscious about their appearance. Avoiding medications such as phenytoin that cause cosmetic adverse effects in teenagers and taking steps to avoid weight gain with AED treatment (eg, by AED selection, modification of lifestyle factors) may help prevent negative consequences on self-esteem and adherence. To help patients with self-esteem issues, clinicians can enlist the support of family members and can help adolescents develop strategies to deal with other people’s beliefs by allowing patients to discuss their own fears and concerns about epilepsy and encouraging them to take responsibility for informing others about their epilepsy. Participating in online communities or in-person support groups may help adolescents with epilepsy feel less socially isolated and may provide a resource for learning how to deal with issues of stigma and self-esteem. The Epilepsy Foundation and its state chapters offer support groups for adolescents with epilepsy and day camps for children with epilepsy.

Achieving and Maintaining Autonomy

Parents may react to their child’s epilepsy diagnosis by smothering the child, whereas adolescents may rebel against the diagnosis by ignoring treatment recommendations and activity restrictions. However, it is most helpful to encourage the patient and parents to maximize the patient’s autonomy and self-management of epilepsy. For the adolescent with epilepsy, issues of autonomy involve basic elements of self-care (eg, eating right, getting enough sleep) as well as managing the medication regimen. It also is important to educate teenagers about the possible consequences of alcohol and recreational drug use. Older adolescents will be particularly concerned about the impact epilepsy and state laws will have on their ability to drive. Any recommended activity restrictions need to be communicated to patients and their parents and tailored to the individual patient, based on their seizure type and control. For females, issues surrounding...
Case Study 1

Allison is an overweight 16-year-old female with a 7-year history of ADNFLE. She recently presented to a new neurology clinic after her family moved to a different state. Allison is taking valproic acid, and her seizures occur about twice a month. They previously occurred several times a week. Since she has switched to a different school, she has not told new friends about her epilepsy, and her parents have not shared this information with the teachers and administration. Allison has been invited to a few sleepover parties but has avoided these because she is afraid that she may have a seizure. In addition, Allison recently began dating another student at her new school. Her mother wants her to start using birth control. The neurologist discussed with Allison switching to a different AED to try to achieve better seizure control and help address her weight problem. He also was concerned about the increased risk of polycystic ovary syndrome with valproic acid. In addition, he counseled Allison about the potential interactions between AEDs and oral contraceptives. A decision was made to switch to zonisamide 200 mg two times a day (which may help with weight loss). She was instructed to make up any missed doses of zonisamide, at any time, right up to the next dose. The neurologist also advised Allison to begin taking supplemental folic acid. Following the switch, Allison’s nocturnal seizures decreased to about once a month.

contraception and possibly pregnancy may become prominent as they enter into more mature social relationships.

Adolescents should be informed that insufficient sleep will lower their seizure threshold. Teenagers typically need about 9 hours of sleep. As children enter adolescence, their body clocks change and they tend to remain awake later. However, because many teenagers need to get up early for school, they do not get enough sleep during the week and try to catch up on sleep during the weekend. This pattern can lead to chronic sleep deprivation. Sleep disrupted by seizures or other causes also can cause sleep deprivation. Adolescents should be counseled about good sleep hygiene (eg, avoid playing on the computer or watching television shortly before going to bed, avoid caffeine after mid-afternoon, limit naps during the day). If patients are taking seizure medications that may keep them up or make them drowsy, it may be helpful to instruct the patients to take such medications early in the day and shortly before bedtime, respectively. When poor sleep habits are suspected of contributing to seizure activity, adolescents should be asked to track their seizures in relation to their sleep habits for a few months and then encouraged to consider how they can improve their sleep habits.

Many adolescents experiment with alcohol and recreational drugs. Heavy drinking or certain drugs may increase seizure risk, or patients may miss their prescribed AEDs as part of rebellious behavior or for fear of mixing their medication with other substances. Although alcohol intoxication probably does not cause seizures, alcohol withdrawal is associated with an increased risk of seizures. Patients should be made aware that the combination of alcohol ingestion and sleep deprivation (ie, staying up late with friends while drinking) may provoke seizures.

Adherence with AEDs is critical for maintaining seizure control. Rebelliousness and a desire to fit in with peers may drive nonadherence in adolescents with epilepsy. Other factors, such as forgetfulness, also may contribute. Two cross-sectional online surveys that included 153 US adolescents with epilepsy and their matched caregivers (n=153) examined self-reported adherence rates and other aspects of self-care. Overall, 35% of adolescents and 31% of their caregivers reported the patient had been nonadherent, defined as having missed a dose or stopped an AED within the past month; 55% of adolescents and 58% of caregivers reported the patient having missed a dose or stopped taking an AED in the time period between the past month and more than 3 months ago. In addition, 39% of adolescents who had missed a dose of medication or had stopped taking medication had suffered a seizure, presumably as a consequence of nonadherence. Other negative consequences of missed doses/stopping medication according to adolescent/caregiver report included missing school (10%/13%), visiting the emergency department (8%/10%), requiring a doctor visit (8%/7%), missing a social event (5%/6%), and being hospitalized (2%/3%). Almost 20% of adolescents indicated they were fearful of the physician’s anticipated reaction to their admission that they didn’t take their medication as prescribed. The most commonly reported reason for nonadherence was forgetfulness or not having medication on hand (70% adolescent/66% caregiver report). Other reasons are shown in Figure 2.
The findings of this study suggest that while social reasons do contribute to non-adherence among adolescents, they are not the most commonly cited reasons. The caregiver was considered responsible for medication adherence in most families (~88%). Caregiver/parent reminders were described as the most common method for reminding patients to take their medication, and fitting medication into the daily schedule and using a pillbox were methods used by about half of the patients. Overall, these results suggest that simplification of the AED regimen and increased use of reminder strategies that don’t depend on the parents may be useful to improve adherence among adolescents. It is important to educate patients and their parents about the need to take epilepsy medication as directed (including all doses), even when the patient has been asymptomatic; any attempts to reduce or discontinue medication should be done under physician supervision. Clinicians can help patients feel more comfortable about communicating about adherence by being open, honest, and direct about health-related behaviors and engaging with patients more directly about their condition and other related issues (e.g., comorbidities, social issues).

Notably, results of this survey indicate that adolescents with epilepsy rely heavily on their caregivers for medication management and adherence. Although this high degree of dependence may be viewed as an adaptive response to prevent seizures and their negative consequences, this situation may “impair the transition for adolescents to independence in managing their medical condition.” Educating adolescent patients about the need for adherence, providing them with the tools and resources to manage their medication, and encouraging them to assume responsibility for their self-care are important steps for helping adolescents with epilepsy transition to adulthood. Part of self-management of medication involves establishing a strategy for dealing with a missed dose or doses. The specifics of such a strategy will depend on the patient’s regimen, but should be made clear and ideally should involve a written plan.

Another important component of self-management is having a seizure plan (i.e., a physician-recommended plan for what to do when the patient has a seizure). In the survey described previously, about half of adolescents reported having a seizure plan. The seizure emergency plans included a variety of items, such as taking rescue medication, avoiding injury, monitoring the seizure duration, relaxing or sleeping after the seizure, calling parents, and visiting the emergency department.

As part of self-care, patients with epilepsy will need to modify or restrict their activity under certain circumstances. For example, when bathing, patients should consider taking a shower rather than a bath, having an adult be aware of when they are in the shower, and not locking the bathroom door. To avoid scalding, it is recommended that patients with epilepsy use safety devices that limit water temperature and avoid shower levers that can be knocked out of position easily, increasing water temperature. Females with epilepsy should avoid curling and straightening irons to prevent burns should a seizure occur. Regular safety guidelines should be followed when participating in athletic activities (e.g., helmets for biking, swimming in a supervised area and with a swim buddy).

Learning to drive is a major step in gaining independence in adolescence. Therefore, driving restrictions are an important concern. Being unable to drive because of epilepsy can interfere with employment and socialization and make patients feel different from their peers. However, seizures that occur while driving can lead to an accident, potentially resulting in property damage, injury, and even death. In the United States, patients with controlled epilepsy usually are allowed to drive with legal restrictions that vary from state to state. Most states have requirements that necessitate that the patient be seizure-free for a specified length of time and require a physician’s statement confirming that seizures are well controlled and that the patient will not present an unreasonable risk to public safety if allowed to drive. In addition, six states (California, Delaware, Nevada, New Jersey, Oregon, Pennsylvania) require physicians to report to the state patients who have seizures, whether or not the seizures are well controlled. It is important to communicate with patients openly about seizure risk and driving and educate them about legal restrictions in their state.

The Epilepsy Foundation provides legal information about epilepsy and driving and includes links to driving laws by state. State-specific driving laws can be accessed at the Epilepsy Foundation Web site. Issues around contraception and even pregnancy may arise for female adolescents with epilepsy. Several enzyme-inducing medications would be changed and an extended-release formulation of carbamazepine. Despite adherence to the new regimen, Connor continued to experience seizures. Blood tests were negative and did not reveal any signs of substance abuse. A routine EEG showed right temporal epileptiform spikes, and an MRI revealed mesial temporal sclerosis. At this point, the neurologist added levetiracetam to Connor’s treatment regimen. Connor was referred for video EEG monitoring, at which time medications would be changed and an evaluation made as to whether he is a good candidate for epilepsy surgery.

Case Study 2

Connor is a 16-year-old male who presented following a partial-onset seizure that lasted for about 1 minute, occurred at home shortly before dinner time, and was witnessed by his parents. The seizure was preceded by a sense of déjà vu. A careful history revealed that the patient had experienced similar seizures on two other occasions while by him. The results of Connor’s physical and neurological exams were normal. An EEG revealed right temporal sharp waves. The neurologist diagnosed Connor with partial-onset seizures and started him on carbamazepine 200 mg twice daily, with the dose titrated to 200 mg three times a day. Connor has had long-standing learning difficulties in school. He is on the baseball team, and his parents are worried about him playing the rest of the season. In addition, Connor recently began taking driving lessons and is looking forward to obtaining his permit. The neurologist advised Connor and his parents that he could continue playing baseball, but he should make sure to wear his helmet. He also reviewed the state driving regulations for people with epilepsy with Connor and his parents. The neurologist also discussed with Connor the need to take precautions, such as letting his parents know when he is showering. He carefully reviewed the medication regimen with Connor and discussed the importance of taking his medications as directed to prevent future seizures. At a follow-up visit 4 weeks later, Connor was continuing to have seizures, and his mother indicated he frequently had been skipping his mid-day dose to avoid having to go to the nurse’s office to take his medication. The neurologist switched Connor to the extended-release formulation of carbamazepine. Despite adherence to the new regimen, Connor continued to experience seizures. Blood tests were negative and did not reveal any signs of substance abuse. A routine EEG showed right temporal epileptiform spikes, and an MRI revealed mesial temporal sclerosis. At this point, the neurologist added levetiracetam to Connor’s treatment regimen. Connor was referred for video EEG monitoring, at which time medications would be changed and an evaluation made as to whether he is a good candidate for epilepsy surgery.
AEDs have the potential to lower contraceptive hormone levels because of pharmacokinetic interactions (Table 13).33,112

If such AEDs are used in adolescent females who are taking contraceptives, then the contraceptive dose may need to be altered to avoid unwanted pregnancy.113,114 It may be prudent to avoid low-dose oral contraceptives in patients taking an enzyme-inducing AED, such as carbamazepine.115 Pharmacokinetic interactions between AEDs and contraceptives may result in reduced AED concentrations. Specifically, concurrent use of oral contraceptives may increase lamotrigine clearance, resulting in diminished lamotrigine levels.37,116,117 For females taking a stable dose of lamotrigine and not taking other drugs that induce lamotrigine glucuronidation, it may be necessary to increase the maintenance dose of lamotrigine by as much as twofold when starting oral contraceptives to maintain a consistent lamotrigine plasma level.37 The plasma concentration of lamotrigine may increase substantially during the nonsteroid week of contraception, resulting in toxic side effects and possibly requiring dose adjustments to the overall maintenance dose of lamotrigine.37,118 According to the Centers for Disease Control’s US Medical Eligibility Criteria for Contraceptive Use, theoretical or proven risks outweigh the advantages of using carbamazepine, oxcarbazepine, phenytoin, primidone, or topiramate concomitantly with combined oral contraceptives (COCs), the contraceptive patch or ring, or the progesterone-only pill (POP).119,120 In addition, theoretical or proven risks are believed to outweigh the advantages of using lamotrigine in conjunction with COCs or the contraceptive patch or ring because of the impact of these contraceptive preparations on lamotrigine concentrations.119,120

The AAN recommends that females with epilepsy take a folic acid supplement (at least 0.4 mg/d) before they become pregnant to reduce the risk of major congenital malformations.121 Folic acid supplementation of sexually active female adolescents with epilepsy also should be considered because planned or unplanned pregnancies can occur.

### Education and Behavioral Issues

Cognitive impairment is common in patients with epilepsy and may occur as a consequence of the disease itself.122 In addition to IQ, cognitive areas that may be affected include attention, language, perceptual skills, executive functions (eg, problem solving), verbal and visual memory, motor speed, dexterity, and coordination. Because most common partial-onset seizures begin in the temporal lobe and immediate structures, patients with temporal lobe epilepsy often have memory problems.122 Cognitive deficits in adolescents with epilepsy may contribute to academic difficulties, such as problems concentrating, keeping up with schoolwork, understanding instructions, and retaining information.96

It is important to recognize and treat comorbid disorders, such as attention-deficit hyperactivity disorder (ADHD), which may impact academic function122 and impair HRQOL.123 Comorbidities, especially psychiatric disorders, are strongly associated with impaired HRQOL in adolescents with epilepsy.123 In a recent nationally representative survey of US children and adolescents, individuals with current epilepsy had higher rates of the following disorders compared with those with no current or previous epilepsy diagnosis: depression (8.4% vs 1.9%), anxiety (17.4% vs 2.7%), ADHD (23.1% vs 6.2%), conduct disorder (15.6% vs 3.2%), and learning disability (56.0% vs 7.3%).123 Behavioral reactions to the diagnosis of epilepsy, such as acting out and not taking medication, also may be problematic in adolescence.

In addition to disease-related problems, AEDs may adversely affect cognition and behavior. Barbiturates and benzodiazepines have clear adverse cognitive effects124,125 and may cause inattention and hyperactivity.126 Phenytoin and carbamazepine appear to have more modest adverse effects on memory and other cognitive functions.124 Tiagabine, topiramate, and zonisamide have been associated with cognitive slowing and difficulty concentrating.124,126 Gabapentin treatment has been associated with hyperactivity and aggression in patients with learning problems.126 Both aggressive behavior and behavioral improvement have been observed with lamotrigine.124 Depressive symptoms have been associated with several AEDs, including phenobarbital, levetiracetam, topiramate, tiagabine, and zonisamide.126 Psychotic reactions may occur with phenytoin, ethosuximide, vigabatrin, zonisamide, topiramate, lamotrigine, and felbamate.124,126 Serious psychiatric and behavioral reactions may occur with perampanel.50

Adolescents who are considering college or other postsecondary education should be advised that schools cannot deny qualified candidates admission or limit participation in academic and nonacademic programs based solely on their disability (ie, epilepsy).127 In addition, students with a disability have the right to reasonable accommodation. For patients with epilepsy, this may include accommodations such as extended test periods or note-taking services. Patients and their families can find additional information and resources at the Epilepsy Foundation Web site.127

### Transitioning to Adult Care

Adolescents with epilepsy frequently are caught between pediatric and adult care, with neither service able to fully address their special needs.101,128 For older adolescents, there is a need for a more seamless transition of care from the pediatric setting to an adult care setting as well as a need for adolescents with epilepsy to function as independently as possible in promoting their own health.129 In 2011, the American Academy of Pediatrics, American Academy of Family Physicians, and American College of Physicians jointly published a clinical report and consensus statement on strategies to support the health care transition from adolescence to adulthood.129 This process should ensure that high-quality, developmentally appropriate services are available continuously as the patient transitions from adolescence to adulthood. While the transition to adult care ideally should occur between 18 and 21 years of age, the first step in the process (ie, discussing office transitions policy with the patient and the parents) should begin at approximately 12 to 13 years of age or

<table>
<thead>
<tr>
<th>AEDs</th>
<th>Lower Hormone Levels</th>
<th>No Significant Effect on Hormone Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
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<td>Pregabalin</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Lamotrigine</td>
<td>Topiramate (≥200 mg/d)</td>
</tr>
<tr>
<td>Topiramate (&lt;200 mg/d)</td>
<td>Lamotrigine</td>
<td>Topiramate (&lt;200 mg/d)</td>
</tr>
</tbody>
</table>

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**Table 13. Effects of AEDs on Contraceptive Concentrations**

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Adolescents with epilepsy who fail to successfully transition to adult care may lack specialty care; may not receive satisfactory adult services; and may lack adequate follow-up, access to newer therapies, and appropriate management of comorbid conditions. For children and adolescents with epilepsy, the close and comfortable relationship with the pediatric neurology service and concerns about quality of care and accessibility of adult health services may discourage a transition to adult care. The model of a transition clinic, attended jointly by pediatric and adult neurologists in the adult health care setting, has been proposed to facilitate a smooth transfer to adult services for adolescents with epilepsy. Such a model could increase family comfort and encourage dialogue between pediatric and adult neurology providers over several visits while permitting the pediatric neurologist to offer input on the patient’s care in the adult treatment setting.

Figure 3. Health Care Transition Planning Algorithm for All Youth and Young Adults Within a Medical Home Interaction

Conclusions

Epilepsy is the most common neurological disorder among adolescents. The presence of a serious condition such as epilepsy adds to the challenge of transitioning from childhood to adulthood and can adversely impact the adolescent’s psychosocial development and HRQOL. Management of epilepsy during this developmental period is complicated by issues such as nonadherence. The management of patients with partial-onset seizures has evolved during the last decade, and current treatment guidelines for epilepsy are in the process of being revised. Despite the introduction of newer AEDs, treatment-resistant epilepsy remains a significant problem among children and adolescents, affecting between 10% and 40% of this patient population. A national survey of adolescents with epilepsy and their caregivers revealed that seizures were inadequately controlled in 32% to 37% of patients and were poorly or not at all controlled in 10%. Surgery should be strongly considered for adolescents with partial-onset seizures who have failed treatment with at least two AEDs. In addition, emerging pharmacotherapies, including brivaracetam, eslicarbazepine acetate, and rufinamide, are being evaluated in pediatric and adult populations with inadequately controlled seizures. Results from phase III trials of these agents in adolescents and adults with uncontrolled partial-onset seizures are promising, especially considering the treatment-resistant nature of these patient populations.
Optimizing Treatment of Adolescents With Partial-Onset Seizures • www.globalacademycme.com/priarycare


Optimizing Treatment of Adolescents With Partial-Onset Seizures CME Post-Test Answer Sheet

THE SELF-ASSESSMENT QUESTIONS ARE PROVIDED HERE FOR PREVIEW PURPOSES ONLY.

HOW TO RECEIVE CREDIT: Participants wishing to earn CME credit must: 1. Read the supplement. 2. Relate the content material to the learning objectives. 3. Complete the self-assessment questions and the evaluation form online at: www.cealliance.org/credit/CEE80512.

CME QUESTIONS: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

1. The number of Americans <18 years of age who are affected by epilepsy is:
   A. 50,000
   B. 100,000
   C. 300,000
   D. 1 million

2. Among adolescents and adults, the most common electroclinical syndrome(s) at initial diagnosis is (are):
   A. Epilepsy with generalized tonic-clonic (GTC) seizures alone
   B. Epilepsy with GTC seizures alone and juvenile absence epilepsy
   C. Juvenile absence epilepsy and juvenile myoclonic epilepsy (JME)
   D. Juvenile absence epilepsy only

3. Partial-onset seizures do not:
   A. Exhibit involvement of more than one network
   B. Always originate within cortical structures
   C. Exhibit local or wide distribution within a hemisphere
   D. Originate within brain networks confined to one hemisphere

4. Structural imaging is not usually indicated for patients with:
   A. Developmental regression
   B. Increased intracranial pressure
   C. JME
   D. Localization-related seizures other than benign childhood epilepsy with centrotemporal spikes

5. The most common condition misdiagnosed as epilepsy at epilepsy referral centers is:
   A. Migraine
   B. Psychogenic nonepileptic attacks
   C. Syncope
   D. Transient ischemic attacks

6. A common epilepsy syndrome that typically begins in adolescence or adulthood and is characterized primarily by partial-onset seizures is:
   A. Autosomal dominant nocturnal frontal lobe epilepsy
   B. Mesial temporal lobe epilepsy
   C. Panayiotopoulos syndrome
   D. Reading epilepsy

7. Which of the following statements about JME is false?
   A. All patients have myoclonic jerks
   B. Onset is usually during adolescence
   C. Patients may also exhibit persistently focal electroencephalogram (EEG) abnormalities (in addition to typical generalized EEG abnormalities
   D. Structural lesions on magnetic resonance imaging in JME are associated with poor therapeutic response

8. An antiepileptic drug (AED) recommended by the American Academy of Neurology guidelines as a first-line treatment for partial-onset seizures in adolescents is:
   A. Pregabalin
   B. Tiagabine
   C. Topiramate
   D. Zonisamide

9. A newer AED indicated by the US Food and Drug Administration (FDA) as monotherapy for adolescents with partial-onset seizures is:
   A. Lacosamide
   B. Levetiracetam
   C. Oxcarbazepine
   D. Zonisamide

10. Treatment resistance is defined as failure of:
    A. An adequate trial of one tolerated and recommended first-line AED to reduce seizure frequency
    B. An adequate trial of one tolerated and appropriately chosen and used AED to achieve sustained seizure freedom
    C. Adequate trials of two tolerated and appropriately chosen and used AEDs (as monotherapies or in combination) to achieve sustained seizure freedom
    D. Adequate trials of two tolerated and appropriately chosen and used AEDs (as monotherapies or in combination) to reduce seizure frequency

11. Video EEG monitoring is indicated for:
    A. All adolescent patients with epilepsy
    B. All epilepsy patients with a normal EEG pattern
    C. All patients who continue to have seizures despite medical therapy
    D. All patients with suspected temporal lobe sclerosis

12. A high-fat, low-protein, and very low-carbohydrate diet most commonly used for children 5 to 10 years of age with refractory epilepsy is the:
    A. Atkins diet
    B. Ketogenic diet
    C. Low glycemic index diet
    D. Modified Atkins diet

13. Both randomized controlled studies comparing surgery with continued medical management (CMM) in patients with treatment-resistant temporal lobe epilepsy observed:
    A. Improved quality of life in the CMM group versus the surgery group
    B. Statistically significantly greater rates of seizure freedom in the CMM group
    C. Statistically significantly greater rates of seizure freedom in the surgery group
    D. The mean number of AEDs decreased over time in the surgery group

14. An AED that is considered weight-neutral is:
    A. Levetiracetam
    B. Pregabalin
    C. Topiramate
    D. Valproate

15. A novel FDA-approved AED for a symptomatic childhood epilepsy syndrome that has been evaluated in phase III trials for treatment of inadequately controlled partial-onset seizures in adolescents and adults is:
    A. Brivaracetam
    B. Eslicarbazepine acetate
    C. Perampanel
    D. Rufinamide

16. The proportion of adolescents who do not take their AED medication as directed over 1 month is approximately:
    A. 15%
    B. 35%
    C. 65%
    D. 85%

17. The most common reason for medication nonadherence among adolescents with epilepsy is:
    A. Forgetfulness/not having medication on hand
    B. Side effects
    C. Teenage rebellion
    D. Worry about stigmatization/wanting to fit in

18. An AED that lowers oral contraceptive hormone levels is:
    A. Eozagabine
    B. Gabapentin
    C. Lamotrigine
    D. Oxcarbazepine

19. More than half of children and adolescents with epilepsy are also affected by:
    A. Anxiety
    B. Attention-deficit hyperactivity disorder
    C. Depression
    D. Learning disability

20. The first step in the process of transitioning to adult care (ie, discussing office transitions policy with the patient and the parents) for patients with chronic disease should ideally begin at age:
    A. 12 to 13 years
    B. 14 to 15 years
    C. 16 to 17 years
    D. 18 to 19 years

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