

Antiepileptic Drugs: Expanded Options and Improved Tolerance

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ABSTRACT. *Five new antiepileptic drugs (AEDs) have been approved in the last five years and several new formulations and new dose strengths for both the classical and newer agents exist. Patients arriving for neurodiagnostic studies are often on complex regimens with medications being weaned and new agents being added. All technologists need a working knowledge of the known mechanisms and indications for these drugs in addition to an understanding of their potential adverse effects. Fortunately the latter problems are limited in this recent generation of drugs and their broad spectrum of action is leading to improved seizure control and better quality of life for our patients.*

KEY WORDS. *Adverse effects, antiepileptic drugs, EEG, indications, mechanisms, sleep.*

INTRODUCTION

Treatment options for epilepsy have again increased markedly since 1995, when antiepileptic medications were last reviewed in this journal. Topiramate, tiagabine, zonisamide, levetiracetam, and oxcarbazepine have been introduced and are finding their place in modern epilepsy management. (Table 1 summarizes the timeline of antiepileptic medications, including their formulations, currently available in the United States.) New dosing for the initial titration of lamotrigine has increased the

Table 1. Timeline of the antiepileptic medications currently available in the United States. Included are the year of release and available formulations. The bold line separates medications available prior to 1996 when antiepileptic drugs were reviewed in AJET, from those more recently released.

| | Tablet/ Capsule | IV | IM | Sprinkle Capsule | Chewable | Suspension/ Syrup/Elixir | Extended- Release |
|---------------|--------------------|------|------|---------------------|--------------------|-----------------------------|----------------------|
| Phenobarbital | + | 1912 | + | | | + | |
| Phenytoin | 1938 | | | | 1995 | 1995 | 1995 |
| Primidone | 1954 | | | | | | |
| Ethosuximide | 1960 | | | | | <1982 | |
| Carbamazepine | 1974 | | | | <1982 | 1988 | 1997 |
| Valproate | 1978 | 1997 | | 1996 | | 1978 | 2002 |
| Felbamate | 1993 | | | | | 1993 | |
| Gabapentin | 1993 | | | | | 1993 | |
| Lamotrigine | 1994 | | | | 1998 (Dispersible) | | |
| Fosphenytoin | | 1996 | 1996 | | | | |
| Topiramate | 1996 | | | 1999 | | | |
| Tiagabine | 1997 | | | | | | |
| Levetiracetam | 1999 | | | | | 2003 | |
| Oxcarbazepine | 2000 | | | | | 2001 | |
| Zonisamide | 2000 | | | | | | |

safety and tolerability of this medication. Fosphenytoin, the new intravenous (IV) formulation for phenytoin, has proven to be much safer and has replaced IV phenytoin in most pediatric and many adult formularies. There also is a deeper understanding of how many of the older and newer agents affect the resting activities of the patient's EEG during wakefulness and sleep as well as their effects on ictal and interictal discharges. This review summarizes the older anticonvulsants and reviews the newer agents with respect to their mechanism of action, effects on the EEG, effects on sleep architecture, selected clinical trials, and safety issues. In addition to understanding the modes of action and physiology of anticonvulsants, electroneurodiagnostic technologists should familiarize themselves with the formulations available, including the parenteral formulations, multiple tablet strengths, sustained release preparations, and the expanding dispersible and liquid formulations extending the use of many of the medications to younger children.

APPROACH TO THE PATIENT

The initial decision as to whether and how seizures should be treated depends on the proper classification of the event and, ultimately, the epilepsy syndrome. Unfortunately, not all cases are easily classified, especially during infancy or when the seizures are not well observed. Classification systems, even with their imperfections, offer definite advantages. Particularly important in both children and adults is the extension of the seizure classification system to include epilepsy

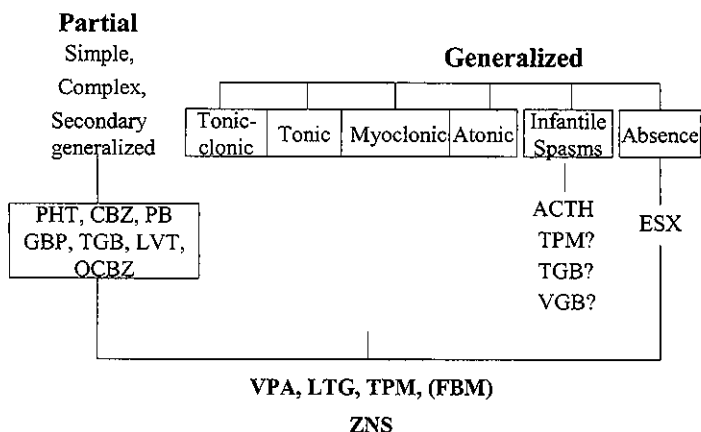


FIG. 1. Treatment options for partial and generalized seizure disorders. PHT, phenytoin; CBZ, carbamazepine; PB, phenobarbital; GBP, gabapentin; TGB, tiagabine; LVT, levetiracetam; OCBZ, oxcarbazepine; ACTH, adrenocorticotropic hormone; TPM, topiramate; VGB, vigabatrin; ESX, ethosuximide; VPA, valproic acid; LTG, lamotrigine; FBM, felbamate; ZNS, zonisamide.

syndromes (ILEA 1981, 1989). The recognition of various epilepsy syndromes, which are defined as a cluster of signs and symptoms customarily occurring together, allows more accurate diagnosis and more effective tailoring of drug therapies. Separating partial onset from generalized seizures and then determining whether the epilepsy syndrome is localized or generalized allows the clinician to select the most useful first-choice antiepileptic drug (AED) (Dreifuss and Porter 1997). Further subdivisions of the epilepsy syndrome based on its being idiopathic, symptomatic, or cryptogenic allow treatment to be tailored. Classifying specific syndromes by type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and, sometimes, prognosis allows one to individualize drug selection. The likely developments of other seizure types, remission of age-related syndromes, and the results of therapy may, however, necessitate a change in classification. Figure 1 provides a schema of the available antiepileptic medications and the types of seizures they are likely to ameliorate.

CLASSIC ANTIEPILEPTIC DRUGS

The primary AEDs used to treat partial seizures and focal epilepsy are similar in overall efficacy, as shown by four major studies (Mattson et al. 1985, 1992; de Silva et al. 1989). During the mid-1980s, results of two Veterans Administration studies of partial epilepsy were reported. In the first, carbamazepine, phenobarbital, phenytoin, and primidone were compared in patients randomized and treated for up to a mean of

36 months. Patients treated with carbamazepine experienced more complete control of partial seizures than did those given phenobarbital or primidone, and the rate of seizure remission was higher in the carbamazepine and phenytoin groups than in the barbiturate group. The second Veterans Administration multicenter study compared carbamazepine with valproate. Although no differences in efficacy between the drugs were observed for secondarily generalized tonic-clonic seizures, the carbamazepine group had more favorable time to first seizure, seizure score, seizure rate, and seizure count. In two large collaborative trials in the United Kingdom enrolling children and adults, no differences in efficacy could be found among carbamazepine, phenobarbital, phenytoin, and valproate. Phenobarbital was removed from the study in children because of adverse effects, clearly differentiating it from other therapies. In patients with partial onset of generalized tonic-clonic seizures, complete control was achieved in 48% with carbamazepine, 49% with phenytoin, and 52% with valproate (de Silva et al. 1989, Heller et al. 1995). The best response in primary generalized epilepsy was with valproate, with 61% seizure free. Another review of AED efficacy and safety in the treatment of tonic-clonic seizures was reported by Ramsay and DeToledo in 1997. Complete control of generalized tonic-clonic seizures was achieved in 53% of patients, and did not differ significantly with carbamazepine, phenytoin, or valproate.

The most common adverse effect of the classic AEDs is neurotoxicity, seen with almost all AEDs. More serious adverse effects, which may be life threatening, usually are idiosyncratic. Among these, rash is most common and typically develops in the first 6 months of treatment. In more serious cases, desquamation of the mucous membranes, fever, and symptoms of generalized hypersensitivity may be present (Pellock and Willmore 1991). Nearly all of the classic AEDs are associated with rash, with a frequency of 5–10%, although many may not proceed to the more serious, life-threatening types of dermatitis. Valproate rarely causes this hypersensitivity reaction. Other severe, idiosyncratic reactions include hepatitis, arthritis, nephritis, vasculitis, and hematologic complications. Carbamazepine has been linked to rare instances of fatal aplastic anemia and agranulocytosis, with an incidence of approximately 1/650,000 patients treated per year (Pellock and Willmore 1991). This syndrome is more common in the elderly and much less common in children. Valproate may cause idiosyncratic hepatic failure, which is seen more often in children under the age of 2 years who are receiving polypharmacy with other AEDs in association with valproate. The incidence of fatal hepatotoxicity associated with valproate is estimated to be 1/10,000–1/49,000 patients treated (Bryant and Dreifuss 1996).

The adverse effects of AEDs that have been in long-term use are well known. Phenytoin is associated with cosmetic problems, including gingival hypertrophy, hirsutism, acne, and, rarely, coarsening of facial features. Phenobarbital and primidone can produce behavior disturbances, typically manifested as hyperactivity and inattention in as many as 50% of children or as irritability in adults. Poorer

performance on psychometric tests has been documented in individuals taking barbiturates. Connective-tissue disorders, including frozen shoulder and Dupuytren's contracture, also have accompanied barbiturate use, as have decreased libido and impotence. Up to half of patients receiving valproate gain weight, which may be controlled with dietary management. Higher doses of valproate may produce tremor, hair thinning, and thrombocytopenia. Infrequently occurring adverse effects include neuropathy and cerebellar degeneration with phenytoin, hyponatremia with carbamazepine, and pancreatitis and decreased hearing with valproate.

EFFECTS OF ANTIEPILEPTIC DRUGS ON THE EEG

The effects of the classical AEDs on the EEG have been reviewed most recently in **Antiepileptic Drugs**, 5th ed. (Bazil and Pedley 2002). On an individual basis, changes in the interictal activities are variable and inconsistent; however, decades of observation have revealed general observations that are summarized in Table 2. These include the different frequencies of rhythmic fast activities promoted by the benzodiazepines and barbiturates, as well as the minor changes in the alpha rhythm seen with carbamazepine. Also presented are the well-described effects of the classical AEDs on ictal activities and provoked EEG responses such as those following intermittent photic stimulation. Data regarding the newer medications is more limited and is distilled from only a small handful of studies, some of which included normal volunteers and others patients treated with the drug of interest and at times on polypharmacy. The most reliable information is summarized for those agents also in Table 2. An important general observation is that none of the newer medications appear to meaningfully change the resting activities at blood levels in the appropriate therapeutic windows. Unfortunately, little has been published regarding EEG changes with these drugs at supratherapeutic concentrations. Clinical observations discussed later in this review regarding the broad spectrum anti-convulsant nature of many of the newer agents are supported by more prominent reduction of interictal or activated discharges by these drugs. Care must certainly be taken as both tiagabine and vigabatrin have also been demonstrated to induce either new seizure types or new interictal discharges in some patients, as previously noted with phenytoin, carbamazepine, and valproate (Wong and Lhatoo 2000).

EFFECTS OF ANTIEPILEPTIC DRUGS ON SLEEP

During the late 1800s, studies by Gowers and Fere demonstrated the marked diurnal variation in seizures and the predilection for many seizure types to cluster either during sleep or at times of sleep onset or arousal. More recent studies have enhanced our understanding of both the effects of seizures on sleep activities as well as the effects of the AEDs on sleep architecture itself. A brief review is found in the

Table 2. *Effects of antiepileptic drugs on the EEG.*

| Medication | Resting Activities at Therapeutic Levels | Resting Activities at Supratherapeutic Levels | Interictal or Activated Discharges |
|-----------------|---|--|---|
| Benzodiazepines | ↑ rhythmic fast (25–35 Hz) ↓ alpha voltage | ↑ rhythmic beta voltage, then sustained ↑ slow frequency activities progress to coma with fast spindle and ↑ in slow theta/delta mix | ↓ generalized to focal d/c ↓ or aborts photoparoxysmal responses |
| Carbamazepine | mild alpha slowing, ↑ random theta | exaggeration of therapeutic changes | no change or ↑ interictal d/c |
| Ethosuximide | NC | ? | ~50% ↓ in spike/wave d/c |
| Felbamate | NC | ? | ↓ sharp/slow d/c in LGS |
| Gabapentin | NC | ? | NC |
| Lamotrigine | NC | ? | ↓ interictal spike d/c ↓ 3 Hz s/w d/c ↓ photoparoxysmal responses rare activation of generalized d/c |
| Levetiracetam | NC | ? | ↓ generalized and focal d/c |
| Oxcarbazepine | NC | ? | NC |
| Phenobarbital | ↑ rhythmic fast (18–25 Hz), frontally predominant | spindle rhythms, (4–12 Hz) with ↑ slow frequencies; +/- bi, triphasics progress to coma with B-S or ECS | ↓ generalized and focal d/c |
| Phenytoin | NC | first ↓ alpha frequencies, then ↑ theta and rhythmic delta, finally high voltage delta | NC |
| Tiagabine | NC | ? | may ↓ interictal spike d/c may induce new d/c type or seizures |
| Topiramate | ↓ alpha and ↑ theta and delta activities | ↑ theta and delta activities, posterior slowing | |
| Valproic acid | NC | slower alpha, ↑ random theta | ↓ generalized d/c little effect on focal d/c ↓ photoparoxysmal responses |
| Vigabatrin | NC | ? | ↓ generalized and focal d/c may induce polyspike/wave d/c |

NC, no change; ?, unknown or controversial effect; ↑, increase; ↓, decrease; B-S, burst suppression; d/c, discharge; ECS, electrocerebral silence; LGS, Lennox-Gastaut syndrome; s/w, spike and wave

Table 3. *Effects of chronic use of antiepileptic medications on sleep. (Reprinted by permission of Lippencott Williams & Wilkins from Bazil and Pedley 2002.)*

| Medication | Sleep Latency | Total Sleep Time | Sleep Efficiency | Arousals and Awakenings | % Stage 1 | % Stage 2 | % Stage 3 and 4 | % REM Sleep |
|-----------------|---------------|------------------|------------------|-------------------------|-----------|-----------|-----------------|-----------------------------|
| Benzodiazepines | ↓ | ↑ | ↓ | ↓ | ↓ | ↑ | ↓ | ↓ |
| Carbamazepine | ↓ | ↑ | ↑ | ↓ | ↑ | NC | ↑ | Mild ↓ or NC in % ↓ density |
| Ethosuximide | ? | ? | ↓ | ↑ | ↑ | NC | ↓ | ↑ |
| Gabapentin | ? | ↑ | ↑ | ↑ | ↓ | NC | ↑ | ↑ |
| Lamotrigine | NC | NC | NC | NC | NC | NC | ↓ | ↓ |
| Phenobarbital | ↓ | NC | ↓ | ↓ | ↑ | ↑ | NC | ↑ |
| Phenytoin | ↓ | NC | ↓ | ↑ | ↑ | ↑ | NC or mild ↓ | NC in %, density |
| Valproic acid | NC | NC | NC | ↑ | | NC | ↑ | NC |
| Vigabatrin | NC | NC | ? | NC | ? | ? | ? | ? |

NC, no change; ?, unknown or controversial effect; ↑, increase; ↓, decrease

previously referenced chapter by Bazil and Pedley (2002), while Mendez and Ratke more comprehensively reviewed this topic in 2001. Reprinted from this article is a summary (Table 3) of the effects of chronic use of AEDs on sleep. Well known are the reductions in REM sleep produced by the benzodiazepines, barbiturates, and carbamazepine, as well as the decrease in total sleep time and increase in sleep latencies seen with phenytoin and carbamazepine. Interestingly, gabapentin used alone has been shown to increase REM sleep percentages and decrease overall awakenings. In an add-on study of patients with epilepsy, the combination of lamotrigine and gabapentin also increased REM and sleep stability.

UPDATE ON THE EARLY 1990s ANTIEPILEPTIC MEDICATIONS

After almost a decade of experience with felbamate, gabapentin, and lamotrigine, their place in modern epilepsy treatment is still evolving. Felbamate is used once again in a limited fashion. Gabapentin has continued to show extremely limited toxicities, received its FDA approval for use in the pediatric population, and an additional approval for treatment of post-herpetic neuralgia. As such, the medication has taken on a prominent role in chronic pain management, both cancer-related and general neuropathic pain. Regarding lamotrigine, there has been a revision in initial dosage and dose escalation for children, based on a pharmacokinetic model that was validated against serum concentration data obtained from pediatric clinical trials. This appears to have reduced the frequency of serious rash associated with lamotrigine (defined as rashes requiring hospitalization and discontinuation of treatment), including Stevens-Johnson syndrome, to approximately 8/1000 (<1%) in children aged less than 16

years and 3/1000 (0.3%) in adults (Glaxo Wellcome Inc 2001), values lower than those cited in the package insert. Certainly, however, this agent should be discontinued at the first sign of rash, unless the rash is clearly not drug related.

Felbamate (Felbatol®)

Felbamate was approved for use in the United States in August 1993. It is a dicarbamate; its mechanism of action is to block both the N-methyl-D-aspartate receptor, altering calcium permeability, and voltage-dependent sodium channels (Rho et al. 1994). It is indicated for the treatment of partial seizures in adults, with or without secondary generalization, and for the adjunctive treatment of partial and generalized seizures in children with Lennox-Gastaut syndrome (LGS) (Pellock 1997). The initial evaluation of this AED showed no significant systemic adverse events, but there were subsequent reports of potentially fatal cases of aplastic anemia and hepatotoxicity (Bourgeois 1997, O'Neil et al. 1996, Pellock and Brodie 1997). These reports caused a marked decrease in the drug's use; however, no felbamate-associated aplastic anemia cases were reported in children younger than 13 years, and the frequency of hepatotoxicity is similar to that reported for valproate (Bryant and Dreifuss 1996, Bourgeois et al. 1993). Thus, felbamate remains a treatment option for children with truly refractory epilepsy, especially those with encephalopathic epilepsy characterized by myoclonic and atonic seizures. For adults with partial seizures, three studies demonstrated proof of efficacy when felbamate was used as adjunctive therapy or monotherapy (Faught et al. 1993, Sachdeo et al. 1992, Taylor et al. 1998).

Guidelines for the use of felbamate now stress that this agent should be used for adults and for children with severe epilepsy refractory to other therapies, especially for patients with encephalopathic epilepsies, such as LGS. Before treatment is begun, a careful history concerning past indications of hematologic toxicity and hepatotoxicity and of autoimmune disease should be sought. Women with autoimmune disease account for the largest portion of those who developed aplastic anemia. Dose escalation should be made slowly, and dosages of concomitant drugs must be corrected for known interactions where possible. Monotherapy with felbamate leads to fewer systemic side effects, but it is unknown whether the rare but potentially life-threatening side effects decrease with felbamate monotherapy. Clinical monitoring rather than specific blood testing should be done frequently, and patients should be educated regarding symptoms that may signify either hematologic toxicity or hepatotoxicity.

Gabapentin (Neurontin®)

Gabapentin, a gamma-aminobutyric acid (GABA) analog, is indicated for the adjunctive treatment of partial and secondarily generalized seizures. The mechanism

of action of gabapentin may be multimodal, but it has no demonstrated effect on interictal epileptiform discharges. Different mechanisms may contribute to its overall action as an anticonvulsant, anti-nociceptive, anxiolytic, and neuroprotective agent (U.S. Gabapentin Study Group 1994). Since its release in 1994, it has become popular because of its ability to be titrated quickly, its mild adverse-effect profile, its lack of enzyme-altering properties, and its general lack of significant drug-drug interactions. It has demonstrated efficacy against partial seizures in both adults and children.

Controlled studies in adults proved the efficacy of gabapentin as add-on therapy and as monotherapy in refractory partial and/or secondarily generalized seizures (Beydoun et al. 1997, Khurana et al. 1996, Lee et al. 1996, Tallian et al. 1996, Trudeau et al. 1996, Wilson et al. 1998, Wolf et al. 1995). In adults with refractory partial epilepsy, our experience suggests titration to 3600–4800 mg/day. Trials in children show similar results to those in adults with partial seizures. In early trials studying childhood absence, gabapentin showed no greater efficacy than placebo (Pellock et al. 1996). In an open-label, add-on study of gabapentin in 32 children with refractory partial epilepsy, a response rate for reduction of partial or generalized seizures of at least 50% was seen in 11 patients (34.4%), and two children (6.25%) became seizure free (Khurana et al. 1996).

Clinical trials have shown gabapentin to be well tolerated and without significant adverse effects. As discussed above, behavioral changes were reported in children; they are manifested as combined aggression, hyperexcitability, and tantrums, but withdrawal and somnolence also were noted (Khurana et al. 1996, Lee et al. 1996, Pellock et al. 1996, Tallian et al. 1996, Taylor et al. 1998, Wolf et al. 1995). In practice, this reaction is seen in fewer than 10% of children treated and, more common although not always seen, in children with prior behavioral difficulties. Symptoms are reversible with discontinuation of gabapentin or dosage reduction, and sometimes they ameliorate over time with no action taken. Other adverse effects seen during clinical trials include somnolence, dizziness, fatigue, ataxia, nystagmus, and weight gain (Khurana et al. 1996, Lee et al. 1996, Pellock et al. 1996, Tallian et al. 1996, Trudeau et al. 1996, Wilson et al. 1998, Wolf et al. 1995).

Lamotrigine (Lamictal®)

Lamotrigine is a triazine AED with a putative mechanism of action that blocks voltage-dependent sodium channels (Leach et al. 1995). This mechanism does not explain its broad range of clinical utility. Initially indicated for adjunctive treatment of partial seizures, it has proven to be a broad-spectrum agent, including a specific role in treating LGS (Motte et al. 1997, Besag et al. 1995). Because the dosing is influenced by concomitant therapy, effective maintenance dosages for children are 1–15 mg/kg/day and for adults are 200 to more than 600 mg/day (Besag et al. 1995, Pellock 1997). Valproate inhibits the conversion of lamotrigine, and its half-life

is shortened by enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital. Lamotrigine is effective in controlling a variety of seizure types in both children and adults. Its efficacy in the treatment of refractory partial seizures in adults led to its initial indication (Jawad et al. 1989, Matsuo et al. 1993, Messenheimer et al. 1994). Subsequently, it was shown to be effective in treating adult patients with primary generalized seizures including tonic-clonic, absence, myoclonic, and atonic types (Besag et al. 1995, Jawad et al. 1989, Motte et al. 1997, Pellock 1997). Lamotrigine is effective in reducing seizure frequency in a broad range of partial and generalized seizure types and in childhood epileptic syndromes. The experience includes juvenile myoclonic epilepsy (Brodie et al. 1995), infantile spasms (Steiner et al. 1994), Rett syndrome (Timings and Richens 1993), and absence seizures (Veggiotti et al. 1994). Myoclonic seizures, however, may not respond to lamotrigine therapy (Uldall et al. 1993). Open-label trials involving 285 children, aged 1–13 years, with treatment-resistant epilepsy, revealed that 34% of all evaluable patients experienced at least a 50% decrease in seizure frequency at 12 weeks and 41% experienced the same improvement at 48 weeks (Besag et al. 1995). Children with absence seizures, typical and atypical, appeared to have the best response. In addition, global evaluations reported improvement in 69% of children at 12 weeks and 74% at 48 weeks. Similar results were noted in a long-term continuation study, with 73% maintaining improvement during follow-up of up to 4 years (Besag et al. 1997). Improved global functioning, which included increased attention and alertness in children, was reported in both pediatric and adult trials and is especially pronounced in children with concomitant developmental and/or attentional problems (Besag et al. 1995, 1997; Pellock 1997).

The toxicity profile of lamotrigine includes events seen with other AEDs, including dizziness, diplopia, headache, ataxia, blurred vision, nausea, somnolence, and vomiting (Besag et al. 1995, Matsuo et al. 1993, Messenheimer et al. 1994). Of most concern is the potentially life-threatening rash associated with the agent. Lamotrigine-associated rash initially was described as being macular-papular or erythematous in its typical appearance, displaying characteristics of a delayed hypersensitivity reaction. This rash typically appeared within the first four weeks of therapy and rarely was seen after eight weeks. Subsequently, several patients developed a much more serious rash, an erythema multiforme-type eruption that progressed to desquamation with involvement of mucous membranes to resemble Stevens-Johnson syndrome or Lyell's syndrome.

NEW ANTIEPILEPTIC DRUGS

Because treatment of epilepsy with the classic AEDs, the above agents notwithstanding, is ineffective in 25–30% of patients or is associated with intolerable adverse effects, more AEDs were needed. Multiple new drugs have become available

that have broadened therapeutic options, especially for those with refractory seizures or intolerable adverse effects from the classic AEDs. For most patients, these new agents have also come with extremely rare idiosyncratic effects and more tolerable dose-related side effects.

Topiramate (Topamax®)

Topiramate is a sulfamate-substituted monosaccharide with apparently multiple mechanisms of action. Four distinct mechanisms are blockage of voltage-dependent sodium and calcium channels, potentiation of GABA-mediated effects, and antagonism of glutamate receptors (excitatory). Topiramate, like other broad-spectrum AEDs, was first approved for adjunctive treatment of partial seizures in adults. Its role in children continues to be defined, but available data support a role in multiple childhood epilepsy syndromes including encephalopathic epilepsy.

Topiramate was studied extensively to define its role in treating partial seizures as both monotherapy and adjunctive therapy (Faught 1997, Rosenfeld et al. 1997, Sachdeo et al. 1997). Data from studies in children suggest its usefulness for patients with LGS, infantile spasms, and refractory partial seizures (Clark et al. 1997; French et al. 1995; Glauser 1997; Ritter et al. 1998, 2000; Sachdeo et al. 1999). Topiramate was evaluated as add-on therapy in a multicenter, open-label study of 18 patients, aged 4–30 years, with LGS (French et al. 1995). Topiramate produced at least a 50% reduction in seizure frequency in six of eight patients who continued therapy. Positive effect on attention and interaction was noted in all patients. Central nervous system (CNS) adverse effects, however, caused discontinuation in some patients. A double-blind, placebo-controlled, multicenter trial of topiramate as adjunctive therapy in the treatment of LGS enrolled 98 patients aged 2–42 years (Sachdeo et al. 1999). The median percent reduction in drop attacks was significantly better for the topiramate group than for the placebo group ($p = 0.04$). Global evaluation scores also showed considerable improvement. Central nervous system adverse effects again were common, but no patients discontinued therapy because of them.

The toxicity profile of topiramate is primarily one of CNS adverse effects. The primary adverse effects seen in clinical trials with adults were somnolence, dizziness, fatigue, abnormal thinking, headache, diplopia, ataxia, speech difficulty, psychomotor slowing, nystagmus, paresthesia, impaired concentration, and confusion (Faught 1997, Sachdeo et al. 1997). Similar problems were noted in children. Weight loss, nephrolithiasis, and increased intraocular pressure, which is caused by topiramate inhibiting carbonic anhydrase, have occurred in adult and pediatric patients. Specific warnings exist regarding metabolic acidosis as well as hyperhydrosis. Behavioral adverse effects were the most problematic in children (Glauser 1997), along with anorexia and sleep disorders. A new titration schedule is now part of the prescribing information (Ortho-McNeil 2001). More rapid titration

does not produce life-threatening side effects, but it significantly increases the potential for neurotoxic side effects in some patients (Pellock et al. 2000).

Tiagabine (Gabitril®)

Tiagabine is a nipecotic acid derivative that selectively inhibits the reuptake of GABA into the neurons and glia (Brodie 1995). It has no clear effects on EEG background, and when studied in patients, a few demonstrated resolution of epileptiform discharges. There were rare instances, however, where new seizure types were induced. It is indicated for adjunctive treatment of partial seizures; early trials showed its efficacy as monotherapy. Encouraging results in the treatment of partial and secondarily generalized seizures have come from trials examining the efficacy of adjunctive therapy and monotherapy with tiagabine (Leppik 1995, Schachter 1995, Uthman et al. 1998). A decrease in the frequency of these seizures was noted.

Tiagabine is well tolerated. The efficacy and safety data were found to remain true in long-term follow-up studies (Dodrill et al. 1998). As monotherapy, tiagabine is associated with achieving positive changes on psychological tests. When tiagabine was not used as monotherapy, there were no changes on test results except in patients receiving high doses, where it appeared to cause some alterations in mood, especially if titration was rapid (Boellner et al. 1996). Data available on tiagabine for the treatment of pediatric epilepsy suggest equal efficacy to that seen in adults (Pellock 2001). Results from several add-on trials demonstrated between 33% and 50% seizure reduction with a trend towards being more effective in localization-related epilepsy syndromes.

Because of its mechanism of action and the production of increased GABAergic tone, tiagabine was expected to be successful in treating infantile spasms. In a long-term, prospective trial, seizures were decreased over time with tiagabine treatment (Shinnar et al. 2001). The most common adverse effects are somnolence, dizziness, and headache (Brodie 1995, Leppik 1995). Somnolence most frequently was reported in children, with 3 of 47 discontinuing therapy in one study because of ataxia, somnolence, or depression (Pellock 2001). Nonconvulsive status epilepticus or twilight state was reported in adults taking higher dosages of tiagabine (48–60 mg/day); this resolved with dosage reduction. A review shows that these conditions occurred at almost the same rate as with placebo (Shinnar et al. 2001).

Levetiracetam (Keppra®)

Levetiracetam is a pyrrolidine derivative with antiepileptic properties. Its antiepileptic effect does not derive from any known mechanism involved in inhibitory and excitatory neurotransmission. A brain-specific binding site, however, has been demonstrated in synaptic plasma membranes (Gower and Matagne 1994). Levetiracetam

is rapidly and almost completely absorbed after oral administration and is not affected by food. Levetiracetam is not protein bound and its metabolism is not cytochrome P450 dependent, with 66% of the dose renally excreted unchanged. Pharmacokinetics are linear with peak plasma levels at one hour after administration and a plasma half-life of 6–8 hours, yet dosing can be successful twice daily (Bialer et al. 1999).

There have been three multicentered, double-blind, multinational, studies in adult patients with partial onset seizures. A responder was defined as a >50% decrease in seizures. Combined, for all three trials in 904 patients, efficacy rates were 41.3%, 31.6%, 27.7%, and 12.6% for 3000 mg, 2000 mg, and 1000 mg levetiracetam and placebo, respectively (Shorvon et al. 1999). Currently pediatric exposure is quite limited, although it is expected that efficacy in partial seizures should be maintained. In one open label trial, 12/24 achieved a >50% responder rate (Glaser et al. 1999). Comprehensive applicability to other seizure types is currently unknown. Individual studies have demonstrated a better than 50% responder rate in some patients with generalized tonic-clonic seizures, absence seizures, and atonic seizures. Dosing in children is approximately one-third higher on a mg/kg basis than in adults. (Glaser et al. 1999)

Levetiracetam is well tolerated and has a good safety profile. In one trial of 219 patients the most common adverse events were asthenia (32.4%), somnolence (19.2%), and dizziness (18.7%). All were considered minor, with 79.6% improving with lessening of their side effects over time. No potentially life-threatening complications were seen. In children similar adverse effects have been reported along with nervousness (Glaser et al. 1999). There are data to support that 7% of adults develop limiting behavioral effects prompting cessation of the medication (White et al. 2003), and anecdotal reports suggest these rates may be higher in children. In addition, rare cases of psychosis have occurred 7 to 14 days following drug initiation (Kossoff et al. 2001).

Oxcarbazepine (Trileptal®)

Approved for adjunctive use in January 2000 and as monotherapy in December 2001, oxcarbazepine is a keto analog of carbamazepine, whose biotransformation in humans differs significantly from that of the parent compound. It is rapidly and almost completely reduced to the pharmacologically active 10-monohydroxy derivative, which reaches plasma concentrations several times higher than those of the unchanged drug. Oxcarbazepine and its monohydroxy derivative exert antiseizure activity by blockade of voltage-dependent sodium channels in the brain. Oxcarbazepine was evaluated for anticonvulsant efficacy in more than 10 clinical trials using a dose range of between 600 mg in monotherapy and 936 mg in polypharmacy. An approximate dosage of 30 mg/kg/day was recommended for children. The most common adverse experiences reported are similar to those seen

with carbamazepine and include fatigue, dizziness, drowsiness, and headache as well as nausea and vomiting and visual disturbances (Beydoun 2000). This drug possesses an advantage in that its decreased toxicity, especially rash, make it a welcome addition to the AED armamentarium.

Zonisamide

Zonisamide is chemically similar to indole. Zonisamide has been demonstrated to affect voltage-dependent sodium channels (Rock et al. 1989) as well as blocking T-type calcium channels (Suzuki et al. 1992). Zonisamide is rapidly and almost completely absorbed. Zonisamide has a half-life of 50–68 hours (Matsumoto et al. 1983) and is extensively metabolized. The drug undergoes reductive biotransformation to the open ring metabolite, 2-sulfamoylacetylphenol (Ito et al. 1982). Typical starting doses are 100 mg/day in adults and 2–4 mg/kg/day in children in twice a day or three times a day dosing. Maintenance is typically 200–600 mg/day in adults and 4–8 mg/kg/day in children.

Efficacy was evaluated initially in adults with partial complex seizures (Schmidt et al. 1993, Wilder et al. 1986). These studies yielded very similar results with 29–30% achieving >50% seizure reduction. Studies comparing efficacy compared to carbamazepine in partial seizures (Seino et al. 1988) and valproate in generalized seizures (Oguni et al. 1988) produced similar efficacy. Of particular interest to practitioners treating children with epilepsy are the early reports of efficacy in myoclonus. Though numbers are small, responses have been seen in patients with various syndromes of myoclonic epilepsy (Henry et al. 1988, Kyllerman and Ben-Menachem 1998, Yagi and Seino 1992, Yamatogi and Ohtahara 1990–83). Also, there is growing evidence that zonisamide may be effective in infantile spasms (Glauser and Pellock 2002).

Adverse events in both the U.S. and European studies were somnolence, ataxia, anorexia, confusion, and abnormal thinking. Discontinuation rates because of adverse events in the U.S. studies were 14% in the zonisamide group and 1% in the placebo group. In the European studies, the discontinuation rate because of adverse events was 3% in the zonisamide group; there were no discontinued cases in the placebo group (Dainippon 1994, Seino et al. 1995). In further studies, 13 (11 in the United States and 2 in Europe) of 505 patients developed nephrolithiasis. Ten of the 13 patients above had positive histories of renal calculi, urinary tract surgery, etc. (Yanai et al. 1999). In addition, the following adverse events were reported: Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, and acute renal failure in Japan (Dainippon 1994). A small number of patients with hyperthermia associated with decreased sweating (oligohydrosis) have been reported. These individuals are almost all children or mentally retarded adults. Adequate hydration leads to recovery without drug discontinuation.

Vigabatrin

Vigabatrin is available in most countries but is not approved in the United States because of its toxicity. Its proven efficacy in partial seizures in adults is also seen in children, but a greater spectrum of pediatric use is expected, particularly in infantile spasms. Vigabatrin is a specific, nonreversible GABA-aminotransaminase inhibitor. Thus, the enzyme responsible for metabolism of GABA in the CNS is blocked, with resultant increased intracellular and extracellular GABA that inhibits abnormal postsynaptic firing (Grant and Heel 1991). These qualities translate into increased alpha and beta activities on the resting EEG. There appears to be a significant reduction in the interictal epileptiform discharges on the EEGs of epileptic patients that does not appear to be directly related to its efficacy in controlling seizures (75-LM2002). Early human studies were stopped in the United States when animal models showed intramyelinic edema. Extensive pathologic studies have failed to show this problem in humans. Subsequently, however, psychosis and peripheral visual field constriction were reported as possible neurotoxic adverse effects (Krauss et al. 1998, Shields and Sankar 1997). Controlled trials in adults showed that vigabatrin is well tolerated and effective as add-on therapy and monotherapy in treating partial seizures (French et al. 1996, Grant and Heel 1991, Krauss et al. 1998, Shields and Sankar 1997). In children it was proven safe and efficacious in a variety of seizure disorders including partial seizures, generalized seizures, infantile spasms, and LGS; however, it may exacerbate myoclonic seizures (Appleton 1995).

Particular enthusiasm was generated by vigabatrin's salutary effects in children with infantile spasms (West's syndrome). Initial results suggested a particularly beneficial effect on infantile spasms associated with tuberous sclerosis (Dulac et al. 1991). In a retrospective European study of 192 patients with infantile spasms treated with vigabatrin as initial monotherapy, 68% showed complete cessation of spasms within two weeks of treatment and 50% were spasm free at six-month follow-up (Aicardi et al. 1996, Appleton et al. 1999). Of the 131 who initially responded, 21% later relapsed.

Adverse effects related to vigabatrin usually affect the CNS. These include hyperactivity (the most common reason for medication discontinuation in one study), weight gain, facial edema, drowsiness, insomnia, ataxia, somnolence, and stupor (Appleton 1995, Dulac et al. 1991, French et al. 1996, Grant and Heel 1991).

THE TECHNOLOGISTS ROLE IN ANTIEPILEPTIC DRUG THERAPY AND MONITORING

The availability of the new AEDs presents the clinician with what might seem like over-whelming choices. Many clinicians depend on long experience with older AEDs and only turn to the newer agents when classic drugs fail. One must question

whether this approach is optimal. Might gabapentin and oxcarbazepine have advantages, through decreased adverse effects, over other AEDs for the treatment of partial seizures? Will topiramate and lamotrigine replace valproate as first-line agents for LGS and encephalopathic epilepsies or primary generalized epilepsies? The final decision will be multifactorial and will depend on the balance between efficacy and perceived adverse effects. These adverse effects may be of the more chronic but more typically occurring type, or they may be of the idiosyncratic, life-threatening type. An example of the latter was seen with felbamate, and its use is typically as a fourth-line agent.

At each neurodiagnostic study, the technologist must confirm the medications being used, the formulations, dosing, and recent changes in the patient's management and seizure control. The information documented on the study request regarding clinical events of concern and current therapies may not be accurate or may no longer be relevant. In addition, this history taking provides the technologist with a time to assess the patient's understanding of their medications and dosing and whether new or evolving adverse effects are present. An astute technologist can appreciate lack of understanding on the patient's part and suspect drug non-compliance. This information, as well as any perceived medication-related side effects, should be documented on the technologist section of the study.

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