New Antiepileptic Agents

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Abstract

Recent US Food and Drug Administration approval of new antiepileptic drugs (AEDs) offers a significant improvement in the treatment of childhood epilepsy. After a period of many years, during which no new AEDs became available, 7 new AEDs were introduced in the United States beginning in 1993. Approximately 25% of pediatric patients who remain refractory to therapy with conventional epileptic drugs now have the availability of more successful outcomes with several new drugs. These new drugs include felbamate, gabapentin, lamotrigine, topiramate, tiagabine, vigabatrin, oxcarbazepine. Information regarding the efficacy of these AEDs, as well as their side effects in the pediatric population has been summarized as an update for the pediatric dentist. (*Pediatr Dent.* 2004;26:58-62)

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Epilepsy—characterized by recurrent and unprovoked seizures—is a brain disorder in which clusters of nerve cells, or neurons, in the brain signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing stranger sensations, emotions, and behavior, or convulsions (seizures with motor manifestations), muscle spasm, and loss of consciousness.[1]

Approximately 1 to 2% of the US population has some form of epilepsy; 30% of those patients are children, and approximately 125,000 new cases of epilepsy are reported annually.[2] Therapy with standard antiepileptic drugs (AEDs) has been effective in controlling seizures (the clinical manifestation of abnormal neuronal hyperactivity) in approximately 75% of those children and adults.[3] However, for many years there were no treatment options for those children that remain refractory. In 1993, 7 new drugs were introduced in the United States, 5 of which stand out as optional drugs in the therapy of 25% of the population treated unsuccessfully. Although the use of new AEDs in children is somewhat limited due to a lack of firm data outlining the appropriate use of these agents in the pediatric population, and despite the fact that the majority of these new drugs are approved by the US Food and Drug Administration (FDA) for use only in adults, the availability of these new agents has broadened the therapeutic options for all patients, including children, who suffer from epilepsy.[5] It is very probable that pediatric dentists will treat many of the children receiving these new neurological treatments. Hence, the need for familiarization with these drugs and awareness of their secondary effects is essential. Many of these secondary effects involved behavior disturbances. Modifications in the dental treatment may be required as well as precautions in the prescription of any other drugs such as sedatives or analgesics, since they can interact with these agents. The intent of this manuscript is to update pediatric dentists on the new AEDs available for children in the United States and review the traditional treatment for, classification of, and etiologies related to epilepsy.

A classification of seizures is provided to assist in the understanding of this manuscript (Table 1).

Etiology

Epilepsy is a disorder with many possible causes, including illness, brain damage, and abnormal brain development. It may develop due to an abnormality in brain wiring, an imbalance of nerve-signaling chemicals called neurotransmitters, or some combination of these factors. In some cases, epilepsy may result from changes in non-neuronal brain cells called glia. These cells regulate concentrations

of chemicals in the brain that can affect neuronal signaling. About half of all seizures have no known cause; however, seizures can usually be clearly linked with some of the following problems[1]:

1. genetic factors;
2. medical disorders such as a brain tumor, alcoholism, Alzheimer's disease, stroke, and heart attack;
3. infectious diseases like meningitis, AIDS, and viral encephalitis;
4. other developmental and metabolic disorders such as cerebral palsy, neurofibromatosis, hydrocephalus, and autism;
5. head injury;
6. prenatal injury and developmental problems;
7. poisoning.

New antiepileptic drugs

Current developments in the availability of the new AEDs are unprecedented. These new drugs are the most welcome addition to the therapeutic options in the treatment of epilepsy. As a group, these drugs tend to have fewer adverse effects and less pharmacokinetic interactions.[6] These are all new drugs and not modifications of traditional AEDs. These new AEDs are reviewed according to their chronological order of release.

Felbamate

Felbamate (Felbatol) was introduced in the United States in 1993 as adjunctive or monotherapy to treat partial seizures with or without secondary generalization in adults.[7] It is also used in children to treat Lennox-Gastaut syndrome—a severe form of childhood epilepsy characterized by several types of seizures, developmental delay, and behavior disturbances. Based on anecdotal reports, felmabate may also be effective in the treatment of absence seizures, juvenile myoclonic (brief body jerk) epilepsy, Landau-Kleffner syndrome (a rare form of childhood epilepsy, which results in severe language disorder), and juvenile spasm. The most common adverse effects of felbamate are anorexia, weight loss, and insomnia.[8] Aplastic anemia occurs with an estimated risk of 1 in every 4,000 to 5,000 patients treated and can be seen approximately 5 months after the initiation of treatment. The risk of hepatic failure is estimated to be 1 in every 26,000 to 34,000 patients treated.[7,9] Felbamate, when combined with carbazepine (eg, Tegretol), phenytoin (eg, Dilantin), or valproic acid (eg, Depakene), may raise or lower the blood level of these drugs, which may increase the chances for unwanted effects.[10]

Gabapentin

Since gabapentin (Neurontin) was released in 1994, it has become popular as a new AED because of its ability to be titrated quickly, mild adverse effect profile, lack of enzyme-altering properties, and general lack of significant drug-drug interactions. It has demonstrated efficacy against partial seizures in both adults and children.[3] There is no evidence that gabapentin is effective against primarily generalized seizures (also called idiopathic epilepsy, which is not associated with neurological abnormalities), including absence seizures (characterized by interruption of activities, blank stare, and brief upward rotal eyes). Gabapentin is also effective in the treatment of neuropathic pain at epileptic doses, but the FDA has not approved the drug for this indication.[6] Consequently, this agent may be beneficial in epileptic patients with chronic pain syndromes such as diabetic neuropathy and trigeminal neuralgia.[11] Clinical trials have demonstrated that

Table 1. Classification of Seizures

1. Partial seizures (focal seizures)
a. Simple partial seizures:
• with motor signs;
• with somatosensory/special symptoms;
• with autonomic symptoms;
• with psychic symptoms
b. Complex partial seizures:
• simple partial onset followed by impairment of consciousness;
• with impairment of consciousness at onset;
c. Partial seizures evolving to generalized seizures:
• simple partial evolved to generalized seizures;
• complex partial evolved to generalized seizures;
• simple partial to complex partial to generalized seizures
2. Generalized seizures (convulsive or nonconvulsive)
a. Absence seizures (formerly termed petit mal seizures):
• typical absence seizures;
• atypical absence seizures
b. Myoclonic seizures
c. Clonic seizures
d. Tonic seizures
e. Tonic-clonic seizures (formerly termed grand mal seizures)
f. Atonic seizures
3. Unclassified epileptic seizures (all those that cannot be classified because of inadequate or incomplete data)
a. Neonatal seizures
b. Severe myoclonic epilepsy in infancy
c. Special syndromes
d. Febrile convulsions
4. Status epilepticus (seizure activity lasting longer than 30 minutes and resulting in a fixed epileptic condition)

Neuroland. Status Epilepticus. http://neuroland.com/sz/seizure_class.htm

gabapentin is well tolerated and devoid of significant adverse effects. However, behavioral changes have been reported in children that are generally manifested as combined aggression, hyperexcitability, and tantrums; withdrawal and somnolence have also been noted.[4,9]

Lamotrigine

Released in 1995, lamotrigine (Lamictal) is approved for the add-on treatment of partial seizures. It has proved effective in treating patients with primary generalized seizures, including tonic-clonic (sudden sharp contraction of muscle), absence, myoclonic, and atonic (loss of tone and unconsciousness), and in patients with Lennox-Gastaut syndrome or seizures secondary to brain injury.[12] The toxicity profile of lamotrigine includes common adverse effects seen with other AEDs, including dizziness, diplopia, headache, ataxia, blurred vision, nausea, somnolence, and vomiting.[13] The greatest concern is the potentially life-threatening rash associated with the agent (about 10% overall incidence), which can evolve into potentially lethal Steven-Johnson syndrome (a hypersensitivity reaction with manifestations in the skin and mucous membranes).[7]

Lamotrigine also may have some positive psychotropic benefits and may benefit patients diagnosed with bipolar disorder.[13] Lamotrigine taken with acetaminophen over a long period of time may result in a reduction of its effectiveness and, thus, increase the risk of seizures.[14]

Topiramate

Topimate (Topamax) was approved in 1997 for use as an adjunctive treatment of partial seizures that affect only one cerebral hemisphere (in part or totally) in adults. Topimate is considered a broad-spectrum AED because it is also effective in the treatment of juvenile myoclonic epilepsy, other primary generalized epilepsies, and Lennox-Gastaut syndrome. Topimate can also be used as monotherapy for partial seizures.[11]Although its role in children continues to be defined, available data support a potential role in the treatment of multiple childhood epilepsy syndromes, including encephalopathic epilepsy. Common side effects include sedation, difficulties concentrating and finding words (speech difficulties), reduced appetite, and weight loss. Other central nervous system side effects include dizziness, somnolence, and confusion. Behavioral adverse effects were the most problematic in children, along with anorexia and sleep disorders.[3] Nephrolithiasis occurs in approximately 2%, and patients should be encouraged to increase their fluid intake to decrease the risk of kidney stone formation.[7]

Tiagabine

Tiagabine (Gabitril) was approved in October 1997 and is indicated as an adjunctive therapy in partial and secondary generalized seizures (associated with neurological abnormal and delayed psychomotor development and indicative of diffuse cerebral pathology). Trials have proved its efficacy as monotherapy.[3] Limited data on the use of tiagabine in the treatment of pediatric epilepsy suggests efficacy equal to that seen in adults. Boeller et al[16] reported the results of the add-on therapy and monotherapy in children with partial seizures, with 90% of patients achieving a decrease in seizure frequency of >50 when treated for at least 6 months.

The most common adverse events experienced by adults and children were somnolence, dizziness, and headache.[15,16] Somnolence was most frequently reported after a single dose in children. Caution when used with other sedatives is recommended, since these drugs may enhance its sedative effects.[17]

Vigabatrin

Vigabatrin (Sabril) is available in most countries but is still not approved in the United States. Studies of vigabatrin in adults have clearly demonstrated its efficacy against partial seizures, with little or no efficacy against other seizure types. In children, the efficacy of this AED does not seem to be limited to partial seizures. In fact, vigabatrin has emerged as a potential first-choice AED against infantile spasms (sudden flexion of the trunk, neck, and limbs, followed by more gradual relaxation)[7,18]

The most common adverse effects of vigabatrin include drowsiness, dizziness, ataxia, tremor, amnesia, depression, weight gain, and hyperactivity in children.[7]

Oxcarbazepine

Oxcarbazepine (Trileptal) has been approved by the FDA as a monotherapy for the treatment of partial seizures in adults and children as young as 4 years old. Oxcarbazepine is similar to carbamazepine in terms of efficacy and indications, and it is generally viewed as an alternative to carbamazepine, especially in patients who cannot tolerate it. In addition, oxcarbazepine is not effective against absence seizures.[19] Side effects associated with oxcarbazepine include nausea, headache, dizziness, diarrhea, vomiting, upper respiratory tract infection, constipation, dyspepsia, ataxia, and nervousness. Clinical trials have demonstrated no significant difference between oxcarbazepine and placebo in the incidence of side effects such as coarsening of facial features, hirsutism, memory problems, weight gain, rash, and hair loss. Allergic skin reactions are fewer than with carbazepine (>10% of patients).[20]

Levetiracetam (Keppra) and zonisamide (Zonegran) are 2 other antiepileptic drugs recently approved by the FDA for the adjunctive treatment of partial seizures in adults. Their use in children has not been documented.

Table 2 summarizes the information described above. Attention has been focused on the side effects, especially in behavior changes. Table 3 summarizes traditional AEDs to facilitate the comparison with these new drugs.[21]

Discussion

The introduction of these new AEDs raises hopes that epilepsy can be controlled with fewer side effects and improved

Table 2. New Antiepileptic Drugs Used in Pediatric Population

New AED	Indications	Side effects	Recommended doses in children	Interaction with other drugs
Felbamate	Lennox-Gastaut syndrome. Juvenile myoclonic epilepsy. Landau-Kleffner syndrome. Juvenile spasm.	Anorexia. Weight loss. Insomnia. Aplastic anemia. Hepatic failure.	15-45 mg/kg/day	Carbamazepine (Tegretol) Phenytoin (Dilantin) Valproic Acid (Depakene) May increase Felbamate's level when combined.
Gabapentin	Partial seizures. Chronic pain syndromes (eg, diabetic neuropathy and trigeminal neuralgia).	Aggression. Hyperexcitability. Tantrums. Withdrawal. Somnolence.	30-90 mg/kg/day	Lack of drugs interaction.
Lamotrigine	Partial seizures. Primary generalized seizures. Lennox-Gastaut syndrome. Seizures secondary to brain damage.	Dizziness. Diplopia. Headaches. Ataxia. Blurred vision. Nausea. Somnolence. Rash that is potentially life threatening.	1-15 mg/ kg/day	Acetaminophen over a long period of time may reduce its effectiveness. Tegretol, Phenobarbital, increase its elimination and Dilantin may elimination from the result in slower body. Depakene may result in slower elimination, increasing risk for toxicity.
Topiramate	Broad spectrum. Multiple childhood epilepsy syndromes.	Sedation. Difficulties concentrating and finding words. Reduced appetite. Weight loss. Dizziness. Somnolence. Confusion. Anorexia. Sleep disorders. Nephrolithiasis.	3-6 mg/kg/day	Drugs that are hepatically metabolized. Drug inducers and valproic may accelerate its elimination. It may increase Phenytoin levels and reduce Valproic acid levels.
Tiagabine	Partial and secondary generalized seizures.	Somnolence. Dizziness. Headache.	Beginning with 0.1 mg/kg/day to be titrated upward	Other sedatives may enhance its sedative effects.
Vigabatrin	Partial seizures. Infantile spasm.	Drowsiness. Dizziness. Ataxia. Tremor. Amnesia. Depression. Weight loss. Hyperactivity.	40 mg/kg/day up to 150 mg/kg/day	It may decrease levels of Phenytoin (about 20%).
Oxcarbazepine	Partial seizures.	Nausea. Headache. Dizziness. Diarrhea. Vomiting. Upper respiratory tract infection. Constipation Dyspepsia. Ataxia. Nervousness. Allergic skin reaction.	30-46 mg/kg/day	It may interact with certain drug such as Felodipine and Verapamil.

quality of life, especially for those who experienced failure of traditional therapy.

Behavioral changes seem to be the condition that most directly affects the pediatric dentist. Other collateral effects such as nausea or sedative effects could modify the selection of sedatives for those patients who require pharmacologic behavior management for dental treatment.

Gabapentin (Neurontin), one of the new AEDs, seems to cause more behavioral changes as a collateral effect compared with the other AEDs. Its lack of drug interactions may cause gabapentin to be chosen more often as a drug of choice in the treatment of partial seizures. The pediatric dentist should be aware of behavioral changes, such as aggression, hyperexcitability, tantrums, and somnolence, since gabapentin could interfere with some patients' ability to cooperate with dental treatment.

Due to its broad spectrum, topiramate could become popular in the treatment of childhood seizures. Difficulty staying focused is the most frequent side effect that the pediatric dentist should anticipate while providing dental treatment.

Other new AEDs such as lamotrigine, tiagabine, and vigabatrin, possess side effects that need to be evaluated prior to any conscious sedation for dental operative procedures. Patients being treated with lamotrigine are at risk of developing nausea and somnolence, which can be enhanced with the use of agents such as nitrous oxide when used in the dental setting.

These new drugs represent the most important and relevant advance in the treatment for epilepsy in the last decade. Unfortunately, still many patients continue to experience refractory epilepsy despite the use of these new agents.

Clinicians caring for children who have epilepsy anticipate further advances in the pharmacogenetics of these drugs, leading to individually tailored, effective, and safe therapy.

Conclusions

1. New AEDs have broadened the therapeutic options in treating patients with refractory epilepsy and those who cannot tolerate conventional therapy. Although these drugs are promising, further clinical experience will be necessary to validate the usefulness of these agents.
2. The pediatric dentist should be aware of behavioral changes that can occur as side effects of these new AEDs.

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