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Efficacy and Adverse Effects of Established and New Antiepileptic Drugs*

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Summary: Antiepileptic drug (AED) selection is based primarily on efficacy for specific seizure types and epileptic syndromes. However, efficacy is often similar for the different AEDs, and other properties such as adverse effects, pharmacokinetic properties, and cost may also be of importance. For idiopathic generalized epilepsies with absence, tonic–clonic, and myoclonic seizures, the AED of choice is valproate (VPA). Secondarily generalized epilepsies with tonic, atonic, and other seizure types are difficult to treat with any single AED or combination of AEDs. The AEDs of choice for absence seizures are ethosuximide (ESM) and VPA. For control of primary generalized tonic–clonic seizures, any of the other major AEDs can be effective. If VPA cannot be prescribed, carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), or primidone (PRM) may be effective, but ESM or a benzodiazepine (BZD) must be added to control associated absence or myoclonic seizures. The AEDs of first choice for partial epilepsies with partial and secondarily generalized tonic–clonic seizures are CBZ and PHT. Increasing evidence suggests that VPA is a good alternative when CBZ and PHT fail. PB and PRM are second-choice selections because of adverse effects. A combination of two of the five standard AEDs may be necessary to treat intractable seizures, but no studies have been done to indicate an optimal combination. Other epilepsy syndromes such as neonatal and infantile epilepsies, febrile epilepsy, alcoholic epilepsy, and status epilepticus require specific AED treatment. Ultimately, AED selection must be individualized. No "drug of choice" can be named for all patients. The expected efficacy for the seizure type, the importance of the expected adverse effects, the pharmacokinetics, and the cost of the AEDs all must be weighed and discussed with the patient before a choice is made. A number of new AEDs with unique mechanisms of action, pharmacokinetic properties, and fewer adverse effects hold important promise of improved epilepsy treatment. **Key Words:** Epilepsy—Seizures—Anticonvulsants—Adverse effects—Neurologic diagnosis.

With the recent or anticipated introduction of five new antiepileptic drugs [AEDs; felbamate (FBM), gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OCBZ), and vigabatrin (VGB)], a wide array of medications is now available to prevent the recurrence or decrease the severity of convulsive or nonconvulsive seizures. Converging evidence from many studies has made increasingly clear the advantages and disadvantages of the well-established AEDs, including carbamazepine (CBZ), ethosuximide (ESM), phenobarbital (PB), phenytoin (PHT), primidone (PRM), and valproate (VPA). The role of the new AEDs is less clear. Most of the new AEDs are different from the older ones in their mechanisms of action, pharmacokinetics, and adverse effects, which may mean that they eventually will find an important place in the treatment of epilepsy. However, the relative efficacy of these AEDs has not been established, their safety for long-term use is not yet proven, and they will cost more than the standard AEDs. It is expected that the standard AEDs will be used until they fail to provide good treatment or until cumulative evidence from controlled clinical trials suggests that one of the newer compounds should be the AED of first choice.

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EFFICACY AS A SELECTION FACTOR

The selection of an AED is based primarily on its efficacy for specific types of seizures and epilepsy. Certain epileptic syndromes can be recognized on the basis of a constellation of characteristics, including not only types of seizures but also, for example, age at onset, electroencephalographic (EEG) findings, and etiology. Classifications of seizure types (Table 1) and epileptic syndromes (Table 2) have been proposed by the International League Against Epilepsy (Commission, 1981, 1989). Al-

seizure control after the dosage is increased to the point of causing side effects. For more difficult problems, a combination of the two AEDs may provide better control (Rowan et al., 1983). Several other AEDs provide variable success in control of absence seizures and are most often used in patients who are unable to tolerate ESM or VPA because of adverse effects. Acetazolamide (AZM) is moderately efficacious, although no controlled trials are available. Its side effects are minimal, but evidence of tolerance limits its efficacy in long-term administration (Lombroso and Forsythe, 1960). Similarly, the benzodiazepines (BZDs), including diazepam (DZP), clonazepam (CZP), and nitrazepam (NZP), provide good control but may lose efficacy after several months of administration (Browne, 1976). BZDs usually produce much more sedation than ESM or VPA. The oxazolidinediones [trimethadione (TMO) and paradione (PMO)] are used infrequently. These compounds have more frequent and serious side effects than the AEDs currently available. Because the teratogenic risk of TMO is especially high, it should not be administered to fertile women (Yerby, 1992). The other commonly prescribed AEDs have little efficacy in the treatment of absence seizures, and there is some evidence that CBZ may increase the frequency of attacks (Shields and Saslow, 1983; Snead and Hosey, 1985).

Myoclonic seizures

Myoclonic seizures are associated with many epileptic syndromes. Successful seizure control is more often associated with the epileptic syndrome than with the seizure type. Myoclonic seizures occurring in generalized idiopathic epilepsy, such as juvenile myoclonic epilepsy, can be fully controlled in 75–90% of patients (Delgado-Escueta and Enrile-Bascal, 1984; Bourgeois et al., 1987; Chadwick, 1987). Myoclonic seizures occurring with degenerative central nervous system disease or postanoxic encephalopathy may be refractory to any form of therapy. Despite the variable probability of good control with treatment, VPA is the AED of choice in most cases. ESM is less effective, but methsuximide (MSM) has been tried with some success in patients unresponsive to other AEDs. The BZDs are quite effective but cause sedative side effects, and in many patients some loss of efficacy is noted after several months of treatment.

Primary generalized tonic–clonic seizures

Tonic–clonic or clonic–tonic–clonic seizures associated with generalized idiopathic epilepsy occur alone or with absence and/or myoclonic seizures. Their response to treatment is excellent. Seizures in 75–85% of patients can be completely controlled with VPA monotherapy. Some studies did not clearly distinguish between primary and secondarily generalized tonic–clonic seizures, but the response was especially favorable in patients with generalized idiopathic epilepsy (Bourgeois et al., 1987; Chadwick, 1987). Control was the same or better than that obtained with administration of PHT or CBZ (Shakir et al., 1981; Convanis et al., 1982; Wilder et al., 1983; Turnbull et al., 1985; Chadwick, 1987). Half of the patients in the study of Bourgeois et al. (1987) were not controlled with other AEDs, including CBZ, PB, or PHT alone or in combination with other AEDs. In refractory patients with generalized idiopathic epilepsy, we were able to obtain complete seizure control with VPA monotherapy in 80% of patients who had not responded to CBZ, PB, PHT, or a combination of these AEDs, in addition to ESM or BZDs. This high success rate was achieved only after a lengthy crossover and high dosages of VPA initially (Mattson and Cramer, 1988). No entirely satisfactory controlled clinical trial has yet been done to compare all available AEDs for this seizure type. Earlier studies suggest that PB and PRM are as effective as CBZ and PHT for control of tonic–clonic seizures and could be used as alternative drugs for this seizure type if VPA is ineffective or not tolerated because of adverse effects.

Secondary epilepsies (symptomatic)

West syndrome

West syndrome is characterized by myoclonic seizures (infantile spasms), a hypsarrhythmic EEG pattern and, in most cases, mental retardation. The seizures begin in the first 2 years of life, particularly between 4 and 6 months of age. Adrenocorticotropic hormone (ACTH) or corticosteroids are usually considered the treatment of choice (Hrachovy et al., 1983; Lombroso, 1983; Aicardi, 1986). Controversy continues as to whether ACTH or corticosteroids have a better effect on the long-term outcome than AEDs such as VPA. In a prospective study of high-dosage VPA treatment (associated with a high mean plasma VPA concentration of 113 μg/ml), 20 of 22 patients achieved total seizure control after 6 months, an outcome comparable to that achieved with ACTH treatment and with less adverse effects (Siemes et al., 1988). This result is somewhat better than that found with NZP or other BZDs (Lacy and Penry, 1976). However, VPA carries an increased risk for idiosyncratic metabolic hepatotoxicity in this age group. Some early evidence (Chiron et al., 1991) suggests that VGB may be helpful in this syn-

TABLE 1. *International classification of epileptic seizures*

I. Partial (focal, local) seizures
  A. Simple partial seizures
  B. Complex partial seizures
    1. With impairment of consciousness at onset
    2. Simple partial onset followed by impairment of consciousness
  C. Partial seizures evolving to generalized tonic–clonic seizures (GTCS)
    1. Simple partial seizures evolving to GTCS
    2. Complex partial seizures evolving to GTCS, including those with simple partial onset
II. Generalized seizures (convulsive or nonconvulsive)
  A. Absence seizures
  B. Atypical absence seizures
  C. Myoclonic seizures
  D. Clonic seizures
  E. Tonic seizures
  F. Tonic–clonic seizures
  G. Atonic seizures
III. Unclassified epileptic seizures, including some neonatal seizures

Modified and adapted from Commission (1981).

though admittedly imperfect, these classifications provide our best current understanding and serve as a frame of reference for communication.

GENERALIZED EPILEPSIES AND EPILEPTIC SYNDROMES

The generalized epilepsies and epileptic syndromes comprise in part the idiopathic epilepsies with age-related onset and the secondary (idiopathic or symptomatic) epilepsies, such as infantile spasms (West syndrome) and Lennox–Gastaut syndrome. This classification also includes symptomatic epilepsies with a nonspecific etiology, such as early myoclonic encephalopathy, and epileptic syndromes associated with some diseases, such as Ramsay–Hunt syndrome.

Idiopathic epilepsies

The generalized idiopathic epilepsies usually begin in childhood, but some, including juvenile myoclonic epilepsy, may not appear until adolescence. It is unusual for these epileptic syndromes to begin after the second decade of life, although preexisting absence or myoclonic seizures may not be medically documented until tonic–clonic seizures occur in adulthood. The generalized epilepsies sometimes remit, but many patients continue to be susceptible to recurrent seizures throughout most or all of their adult lives. No specific etiology is known for this group of disorders, other than a significant genetic factor associated with some syndromes. Evidence for other brain dysfunction or disease is not found, except coincidentally. The electroencephalographic (EEG) pattern associated with these epilepsies is generalized spike-and-wave or polyspike-and-wave discharges. These epilepsies are manifested by absence, myoclonic, and tonic–clonic seizures.

VPA is usually the drug of choice for the generalized idiopathic epilepsies. Its efficacy is equal to or greater than that of CBZ or PHT for tonic–clonic seizures (Convanis et al., 1982; Callaghan et al., 1985; Bourgeois et al., 1987; Chadwick, 1987; Mattson and Cramer, 1988) and equal to that of ESM for absence seizures (Sato et al., 1982; Kaneko et al., 1988). VPA is the only AED that can control all seizure types when patients have combinations of tonic–clonic, absence, and/or myoclonic seizures. Low to moderate dosages and blood VPA levels often suffice (Bourgeois et al., 1987). Because modest doses of VPA can be administered, few neurologic or systemic side effects, except perhaps weight gain, are evident with long-term use (Dinesen et al., 1984; Bourgeois et al., 1987; Herranz et al., 1988; Mattson et al., 1992).

Absence seizures

Absence seizures respond well to both ESM and VPA. Controlled clinical trials indicate that either AED can effect marked or virtually complete seizure control in 70% to 90% of patients (Suzuki et al., 1972; Sherwin et al., 1973; Sato et al., 1982; Bourgeois et al., 1987). Although efficacy is comparable between the two AEDs, ESM is usually selected for patients with pure childhood absence epilepsy (pyknolepsy) because side effects are usually fewer or less serious than those of VPA. A trial of VPA is indicated when ESM provides inadequate

TABLE 2. *International classification of epilepsies and epileptic syndromes*

I. Localization-related (focal, local, partial) epilepsies and epileptic syndromes
  A. Idiopathic with age-related onset
    1. Benign childhood epilepsy with centrotemporal spikes
    2. Childhood epilepsy with occipital paroxysms
  B. Symptomatic
II. Generalized epilepsies and epileptic syndromes
  A. Idiopathic with age-related onset
    1. Benign neonatal epilepsy
    2. Childhood absence epilepsy (pyknolepsy)
    3. Juvenile myoclonic epilepsy (impulsive petit mal)
    4. Juvenile absence epilepsy with generalized tonic–clonic seizures on awakening
  B. Secondary (idiopathic or symptomatic)
    1. West syndrome (infantile spasms)
    2. Lennox–Gastaut syndrome
  C. Symptomatic
    1. Nonspecific etiology (early myoclonic encephalopathy)
    2. Specific syndromes (epileptic seizures that may complicate many diseases, e.g., Ramsay–Hunt syndrome, Unverricht's disease)

Modified and abbreviated from Commission (1989).

seizure control after the dosage is increased to the point of causing side effects. For more difficult problems, a combination of the two AEDs may provide better control (Rowan et al., 1983). Several other AEDs provide variable success in control of absence seizures and are most often used in patients who are unable to tolerate ESM or VPA because of adverse effects. Acetazolamide (AZM) is moderately efficacious, although no controlled trials are available. Its side effects are minimal, but evidence of tolerance limits its efficacy in long-term administration (Lombroso and Forsythe, 1960). Similarly, the benzodiazepines (BZDs), including diazepam (DZP), clonazepam (CZP), and nitrazepam (NZP), provide good control but may lose efficacy after several months of administration (Browne, 1976). BZDs usually produce much more sedation than ESM or VPA. The oxazolidinediones [trimethadione (TMO) and paradione (PMO)] are used infrequently. These compounds have more frequent and serious side effects than the AEDs currently available. Because the teratogenic risk of TMO is especially high, it should not be administered to fertile women (Yerby, 1992). The other commonly prescribed AEDs have little efficacy in the treatment of absence seizures, and there is some evidence that CBZ may increase the frequency of attacks (Shields and Saslow, 1983; Snead and Hosey, 1985).

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