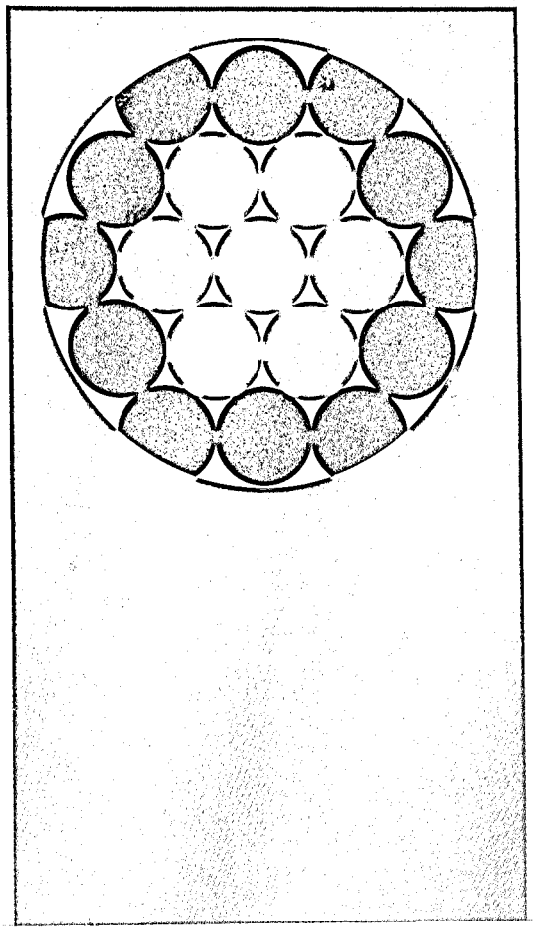
Clinical Neuropharmacology



A Journal of Reviews and Original Investigations in the Pharmacology of Central Nervous System Dysfunction

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REVIEWS

Manuscripts should be sent to: Christopher G. Goetz, M.D., Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison, Chicago, IL 60612, U.S.A. [For editorial assistance or questions contact Bernadette Gillard at Rush-Presbyterian-St. Luke's Medical Center, telephone (312) 942-8010.]

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Clinical Pharmacology of Antiepileptic Drugs

Carl W. Bazil and Timothy A. Pedley

The Comprehensive Epilepsy Center, The Neurological Institute of New York, Columbia University, New York, New York, USA

Antiepileptic drugs (AEDs) are the mainstay of treatment for the majority of patients with epilepsy. However, not all patients with seizures require treatment with AEDs, and many patients with some forms of epilepsy, especially children, need only 1 or 2 years of drug therapy (1). Thus, important questions for the treating physician to have in mind are "When to start AEDs?" and "When can AEDs be safely withdrawn?"

Nonetheless, it is safe to say that, as a group, patients with epilepsy typically receive one or more drugs, usually for many years. Therefore, it is essential that physicians have a good understanding of the clinical pharmacology of these agents, including their mechanisms of action, utilization patterns, and potential for interactions with other therapeutic agents.

SELECTION OF ANTIEPILEPTIC DRUGS

Table 1 lists the drugs currently used to manage different types of seizures. Table 2 gives the usual dosage, effective plasma concentration, half-life, and common side effects for the most commonly used of these agents (2).

Carbamazepine, phenytoin, primidone, and phenobarbital are equally effective for partial and secondarily generalized seizures, although one may be effective when another is not (3). Valproate is also as effective for secondarily generalized seizures but is somewhat less effective than carbamazepine (and, presumably, phenytoin) in managing simple or complex partial seizures (4). Despite relatively equal antiepileptic potency, however, these drugs differ substantially in terms of side effects, pharmacokinetic properties, and cost. Similar comparative data are generally lacking for AEDs introduced after 1994. Phenytoin, with its relatively long half-life, which usually allows the drug to be given once or twice daily after midadolescence, has traditionally been preferred to drugs with shorter half-lives (5). However, concern about phenytoin's occasional undesirable cosmetic effects (gingival hypertrophy, hirsutism, and coarsening of facial features) and other adverse consequences associated with long-term therapy have led to the preferential use of carbamazepine or one of the newer drugs (*e.g.*, lamotrigine, topiramate, zonisamide) as initial treatment in many patients today. Carbamazepine, despite its short half-life, can be given twice daily if an extended-release formulation (*e.g.*, Tegretol-XR, Carbatrol) is used. Phenobarbital and primidone are rarely used now, except in special circumstances, because of the high incidence of sedation and cognitive side effects at therapeutic doses and plasma concentrations (3).

As a group, generalized-onset seizures respond best to valproate (6). Valproate can be used effectively as monotherapy in about 80% of patients, even when several types of generalized-onset seizure coexist. Lamotrigine and topiramate are appropriate alternatives when valproate fails (7). A growing number of neurologists prefer lamotrigine to valproate because of a more favorable adverse effect profile. Phenytoin and carbamazepine are also effective against generalized tonic–clonic seizures, but the response is less reliable than with valproate (2). However, they are ineffective against absence or myoclonic seizures, which commonly coexist with generalized tonic–clonic seizures, which means another drug (*e.g.*, ethosuximide, clonazepam) must be used. Furthermore, phenytoin, gabapentin, and especially carbamazepine can actually aggravate nonconvulsive generalized-onset seizures (7).

MONOTHERAPY OR POLYTHERAPY?

Medical treatment of epilepsy in adults is generally less satisfactory than in children, especially when confronted with partial and secondarily generalized seizures. Fewer than 50% of such patients with recurrent seizures remain seizure free for more than 12 consecu-

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Address correspondence and reprint requests to Dr. Timothy A. Pedley, 710 W. 168th St., The Neurological Institute of New York, Columbia University, New York, NY 10032, USA; E-mail: tap2@columbia.edu.

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