Current challenges in the treatment of epilepsy

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Article abstract—Significant progress in the classification, diagnosis, and pharmacologic management of epilepti seizures has occurred over the past two decades, but epilepsy remains a therapeutic challenge. Clinical studies sho that most patients with epilepsy can have complete or almost complete seizure control with optimally managed monothe apy that employs a traditional antiepileptic drug (AED). About half of the remaining patients can obtain improved seizu control with combination antiepileptic drug therapy, but usually with more adverse effects. In the other half, seizures re main refractory to treatment with available antiepileptic drugs, or treatment remains problematic because of drug to tolerance. Advances in understanding the pathogenesis of epilepsy and the mechanisms of action of antiepileptic drugs hav provided a basis for the development of new AEDs that hold promise for difficult-to-treat patients. In this decade, a num ber of new AEDs that may overcome some of the disadvantages of traditional AEDs and offer clinicians and patients added therapeutic options will become clinically available. These will be more fully evaluated for their clinical potentia to meet existing challenges of epilepsy treatment.

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Substantial progress in the classification, diagnosis, and pharmacologic management of epileptic seizures has been made during the past two decades, but epilepsy remains a significant therapeutic challenge. Symptomatic localization-related (partial) epilepsies continue to be more difficult to treat successfully than absence, myoclonic, and tonic-clonic seizures of generalized onset that occur in a variety of idiopathic epilepsy syndromes. Partial seizures also are more difficult to treat effectively than secondarily generalized tonic-clonic seizures. Although traditional antiepileptic drugs (AEDs) allow for successful treatment of many patients,[1-3] a significant number of patients with epilepsy either have seizures that are refractory to therapy with these agents or do not tolerate them well.[2-5]

Advances in the understanding of the pathogenesis of epilepsy and the mechanisms of action of AEDs have enabled the development of AEDs that appear promising for this difficult-to-treat patient group. In this decade, a number of new AEDs will become clinically available that may overcome some of the recognized shortcomings of traditional AEDs and offer clinicians and patients added therapeutic options.[5-8]

of AED clinical trials that had been conducted to date.[9] Despite a large volume of reports, it was clear that relatively few comparative studies had been published and that there was an insufficient scientific basis to justify the recommendation of a single AED for a specific seizure type in adults. Even fewer studies attempted to correlate efficacy with toxicity limitations.

Selection of an AED for an individual patient was usually based on the clinician's personal bias and anticipated or perceived risk of toxicity rather than documented efficacy or specific intolerance. Despite experimental evidence that the most commonly used AEDs exhibited considerable pharmacologic differences, studies that had been performed to date failed to indicate any clear differences in the clinical efficacy or relative toxicities of these agents, emphasizing the need for further critical clinical evaluation and a new approach to the comparative evaluation of AEDs.

Of the 27 comparative clinical studies published from 1920 to 1970, which involved the four major AEDs, only two had a double-blind design to control for bias. We identified at least 10 principal inadequacies and limitations of the AED clinical trials re-

several subsequent major clinical studies also was described.[11] It was conceivable that, with greater attention to clinical subclassification of partial and generalized seizures and other clinical factors, variation of responsiveness to specific AEDs might become apparent for each seizure type and allow rational and optimal AED selection.

Even with recognized shortcomings in the evaluation of traditional AEDs, it was evident that new AEDs were needed, and substantial efforts were directed to this goal.[5,7,12] By the mid-1980s, many new AEDs had reached the clinical phase of development worldwide, and the need to provide updated guidelines for the clinical evaluation of AEDs was widely recognized to be of paramount importance.[13] Although some new AEDs had become available outside the United States, no new AEDs had been pending marketing approval in the United States since the approval of valproic acid in 1978, and none had been approved in over a decade (table 1).

Several new AEDs—felbamate, gabapentin, lamotrigine, and vigabatrin—that are now, or will soon be, available are the result of significant research and development efforts in the last decade. The extensive clinical use of these AEDs with the resultant evaluation of their ultimate efficacy and impact on AED therapy has been widely anticipated.

Efficacy of AEDs. In the context of the emerging AEDs and the decades of inconclusive clinical trials and reports with the traditional AEDs, it is worth reviewing the available data on the efficacy of the major AEDs. Relatively few trials comparing AED monotherapy for the treatment of partial or secondarily generalized tonic-clonic seizures have been performed.[2,3,14-23] Most of the studies have found no significant differences in efficacy among carbamazepine, phenytoin, and valproate, but because of the inadequacies of clinical trials mentioned above, the results of these studies were difficult to evaluate comparatively.

In many of the trials, the number of patients was too small to detect modest differences in antiepileptic effects; however, two large monotherapy trials have been performed by the Veterans Administration Epilepsy Cooperative Study Group in the United States[17] and by several collaborating groups in the United Kingdom.[15,16,21]

In the Veterans Administration study of partial epilepsy, 622 patients were randomized to receive carbamazepine, phenobarbital, phenytoin, or primi-

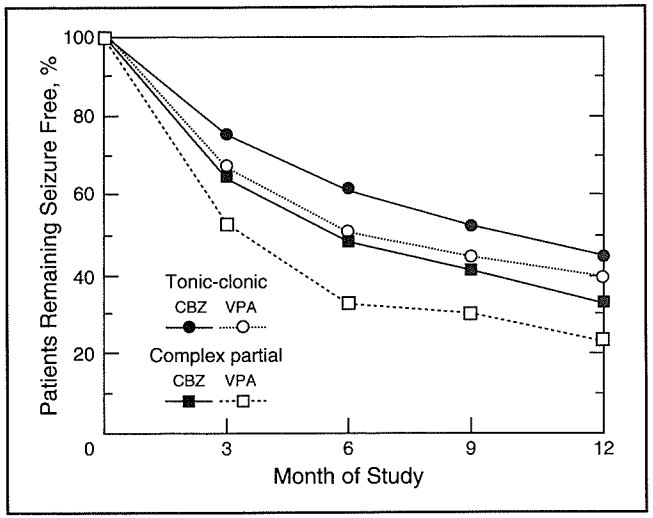

Figure 2. Percentage of patients remaining seizure-free (time to the first seizure). During the 12-month period, patients in the group with complex partial seizures who were taking valproate (VPA) had recurrences earlier than those who were taking carbamazepine (CBZ) ($p < 0.02$). When the patients in both seizure groups were combined, seizures of any type were still found to recur significantly earlier in those taking VPA ($p < 0.03$). There were no significant differences between the VPA and the CBZ recipients in the group with generalized tonic-clonic seizures, according to the life-table analysis. A total of 395 patients could be evaluated at 3 months, 235 at 6 months, 162 at 9 months, and 74 at 12 months.[18] (Adapted from Mattson et al.[18])

drugs were shown to be comparably effective for the treatment of generalized tonic-clonic seizures, but by several measures carbamazepine provided better control of complex partial seizures. Carbamazepine was associated with more acute, but fewer, long-term adverse effects.

As in the first Veterans Administration study, approximately 70 to 80% of patients were adequately managed for 12 months of therapy, but only about 40% of patients on either drug remained seizure-free after 12 months of treatment (figure 2).[18] Of those patients who had seizures during the first 6 months, however, many entered remissions and had no further seizures, so that at 12 months an average of 63% of patients in both studies were under control. The results of these two major trials indicate that (1) most patients can be adequately controlled with monotherapy, but the degree of complete seizure control is unsatisfactory, and (2) about one third of patients will

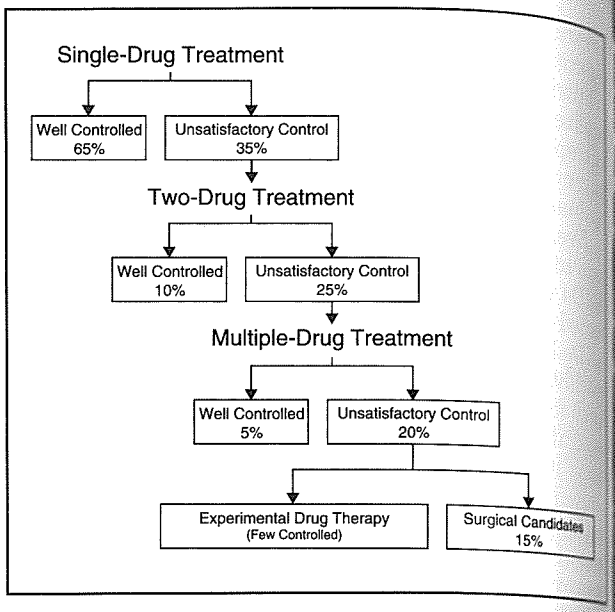

Figure 3. Expected outcome of AED treatment in adults with new-onset localization-related epilepsy. (Modified with permission from Mattson.[2])

some patients.[3,6,27-30] In the first Veterans Administration study, 32 of 82 (39%) patients inadequately treated with monotherapy improved with two-drug therapy, but only nine patients (11%) remained seizure-free.[17] The degree of increased seizure control often was counterbalanced by an increase in adverse effects.

Evidence is unclear whether three- or four-drug combinations can provide additional benefit.[3] Approximately 10 to 15% of patients become well controlled with add-on therapy.[28] Thus, despite optimal management with multiple-drug therapy, approximately 15 to 20% of patients cannot be adequately treated with currently available AEDs, in part because of inadequate efficacy but also because of intolerance associated with low therapeutic indices. Clearly, the need for new AEDs continues. Not only are sizable numbers of patients inadequately controlled, but, in addition, many who obtain control must tolerate some adverse effects and other drawbacks that result from complex pharmacokinetic drug properties, including interactions with other drugs and limited formulations for administration.

AED desirable properties and selection criteria. Despite the progress in understanding the

guidance of treatment for individual patients.[1,3,5,6,8]

Efficacy. For a specific type of epilepsy, most cli
ical studies to date have failed to identify significa
differences in efficacy between AEDs. Although mo
patients' seizures can be adequately controlled wi
traditional AEDs, there is continued need to increa
the degree of seizure control and to provide ther
peutic options for patients whose seizures remain r
fractory to treatment or who are unable to tolera
therapy with existing AEDs. Desirable properties
a new AED include a mechanism of action that wou
provide a rational basis for a new degree or duratio
of control, an increased spectrum of efficacy, or one
more of these effects when the agent is used in com
bination therapy.

Currently used AEDs, as well as some of the emer
ing AEDs, are known to act primarily at three ne
rotransmitter-receptor or ion channels (voltage-d
pendent sodium or calcium channels and $GABA_A$ r
ceptor channels).[31] Although the mechanisms of actio
of felbamate, gabapentin, and lamotrigine are u
clear, gabapentin and felbamate may at least hav
novel mechanisms of action, which may in part a
count for their efficacy when used as add-on therap

Wider use and study of these new AEDs may pr
vide new insights. Advances in research at the ce
lular and molecular levels are likely to aid in the de
sign of new AEDs that act more specifically at know
or different receptors or channels and offer new o
enhanced efficacy.

Adverse effects. Increased tolerability, preferabl
associated with an increased therapeutic inde
clearly is a desirable property of a new AED. Toxicit
of traditional AEDs often has been dose limiting or
major consideration in selection of a specific agen
In the first Veterans Administration study, treat
ment failures were found to occur principally in th
first 6 months of therapy and to result equally fro
systemic toxicity, neurotoxicity, and seizures that o
curred at dosages resulting in adverse effects.[17,25] Th
data suggest that a population of patients exists wh
are susceptible to systemic toxicity for each drug sep
arately. These results underscore the significance o
toxicity in the individual response to traditional AED
and their clinical use.

Although serious adverse effects occur infrequentl
with traditional AEDs, they often occur in the acut
phase of therapy.[1,3,17,25] A minimal risk of serious ad
verse effects would therefore be desirable for new
AEDs. Serious adverse reactions associated with tra

Table 2. Summary of desirable AED properties

Selection criteria	Desirable properties
Efficacy	Selective for seizure type Additive or synergistic with other AEDs Sustained Novel mechanism of action
Adverse effects	Increased therapeutic index Lack of serious or chronic adverse effects Acute effects, if present, are mild and transient Lack of teratogenic potential
Pharmaceutics	Multiple dosage formulations Administered by multiple routes (water soluble)
Pharmacokinetics	Simple profile Not protein bound Not metabolized Does not induce hepatic enzymes Does not inhibit metabolism of other drugs Does not interact with other AEDs or other drugs

AED Antiepileptic drug.

dosing considerations. Because of their metabolic pathways, effects on each other's metabolism, and high degrees of protein binding, traditional AEDs frequently interact among themselves and with other drugs, resulting in considerable toxicity and clinical difficulties.[8,33,34]

Carbamazepine causes autoinduction, phenytoin exhibits saturable metabolism, and valproate has concentration-dependent protein binding. Carbamazepine, phenobarbital, phenytoin, and valproate are oxidatively metabolized. Phenobarbital and phenytoin also induce hepatic enzymes, and carbamazepine and valproate can inhibit the metabolism of other AEDs and other drugs. Ideally, new AEDs would not be protein-bound or metabolized, and they would not induce hepatic enzymes or inhibit the metabolism of other drugs. By their not interacting with other AEDs or other drugs, these new AEDs perhaps would simplify treatment, minimize the need for extensive monitoring and dosage adjustments, and maximize concomitant drug therapy (eg, in eling patients can achieve improved seizure contro with combination AED therapy, but usually with more adverse effects. The other half remain difficult to treat with available AEDs.

New AEDs are becoming available as a result of considerable research and development efforts and may overcome some of the disadvantages of traditional AEDs. The desirable properties of new AEDs have been reviewed and are summarized in table 2. In this decade, a number of new AEDs will be more fully evaluated for their clinical potential to meet the existing challenges of epilepsy treatment.

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