CURRENT LITERATURE

RESPONSE TO FIRST AED

Effectiveness of First Antiepileptic Drug

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PURPOSE: To investigate the interaction among efficacy, tolerability, and overall effectiveness of the first antiepileptic drug (AED) in patients with newly diagnosed epilepsy.
METHODS: The 470 patients were diagnosed, treated and followed up from January 1984 at a single center. Outcome was classified as seizure freedom for at least the last year or failure of initial treatment because of inadequate seizure control, adverse events, or for other reasons.
RESULTS: Overall, 47% of patients became seizure free with the first prescribed AED. A higher proportion ($p = 0.025$) of patients with symptomatic or cryptogenic epilepsy changed treatment because of intolerable side effects (17%), and a lower proportion ($p = 0.007$) became seizure free (43.5%) compared with those with idiopathic epilepsy (8.5 and 58%, respectively). Most patients (83%) received carbamazepine (CBZ; $n = 212$), sodium valproate (VPA; $n = 101$), or lamotrigine (LTG; $n = 78$). The majority of seizure-free patients required only a moderate daily AED dose (93.1% with ≤800 mg CBZ, 91.3% with ≤1,500 mg VPA, 93.8% with ≤300 mg LTG), with commonest dose ranges being 400–600 mg for CBZ, 600–1,000 mg for VPA, and 125–200 mg for LTG. Most discontinuations due to poor tolerability also occurred at or below these dose levels (CBZ, 98%; VPA, 100%; LTG, 75%). Patients taking CBZ (27%) had a higher incidence of adverse events necessitating a change of treatment than did those treated with VPA (13%) or LTG (10%), resulting in fewer becoming seizure free (CBZ vs. VPA, $p = 0.02$; CBZ vs. LTG, $p = 0.002$).
CONCLUSIONS: Nearly 50% of newly diagnosed patients became seizure free with the first-ever AED, with >90% doing so at moderate or even modest dosing. Tolerability was as important as efficacy in determining overall effectiveness.

COMMENTARY

The analysis of Kwan and Brodie of the response of patients with newly diagnosed epilepsy to their first antiepileptic drug (AED) is an important data set for clinicians who are struggling with the very thorny issue of choosing the first drug to prescribe for their epilepsy patients. This decision process becomes ever more complex as new AEDs are approved, and the treatment armamentarium grows.

Kwan and Brodie (1,2) analyzed the outcome of treatment in 470 newly diagnosed epilepsy patients in two articles. Taken as a whole, these articles provide several critical pieces of information. Newly diagnosed patients have a 47% chance of seizure remission with their first AED, and a 63% chance of remission over ≤5 years of treatment with the first and subsequent drugs, in monotherapy or polytherapy. If the first drug is tolerated but ineffective at eliminating seizures, the likelihood of remission with subsequent monotherapy or polytherapy trials decreases to 10%. Most patients who became seizure free do so with moderate doses of AEDs. Perhaps surprisingly, in this analysis, the choice of AED did not influence outcome in a significant way. This confirms the results of several randomized comparisons of new and old AEDs in newly diagnosed patients that have demonstrated no difference in efficacy (3–7).

The current article focuses on the response to the first drug administered. The most commonly prescribed drugs were carbamazepine (CBZ), valproic acid (VPA), and lamotrigine (LTG). As might be expected, patients with idiopathic generalized epilepsy fared better with VPA and LTG than with CBZ, and required lower doses of AED than did patients with symptomatic or cryptogenic epilepsy. Overall, CBZ caused more dropouts due to side effects than did the other two AEDs. Rash was the most common side effect leading to discontinuation. Perhaps the most informative data from this study relate to dosages used. Only moderate dosages were required to render patients seizure free in most cases. More than 90% of seizure-free patients were taking (≤800 mg of CBZ, ≤1,500 mg VPA, or ≤300 mg LTG. The authors interpreted these findings as an indication that "pushing to toxicity," a common practice when using AEDs in monotherapy, may not substantially benefit patients. They question whether alternative or combination therapy should be substituted earlier. However, because failure of the first drug is associated with

only a 10% chance of seizure remission with subsequent treatments, it seems reasonable to persist with initial therapy, even with the likelihood of small gains, as long as quality of life is not adversely affected by dose-related side effects. The data presented are very important, however, in defining initial target dosages for newly diagnosed patients. Appropriate initial target dosing would be 400–600 mg of CBZ, 600–1,000 mg of VPA, and/or 125–200 mg of LTG, the doses that were used by the majority of seizure-free patients.

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