An immediate antiepileptic drug regimen reduced short-term (2-y) recurrence of seizures more than a deferred regimen


Clinical impact ratings: Emergency Med ★★★★★✩✩✩ GIM/FP/GP ★★★★★✩✩✩ Neurology ★★★★★★★★

**Question**
In patients with few or infrequent seizures, is an immediate antiepileptic drug (AED) regimen more effective than a deferred AED regimen for reducing recurrence of seizures?

**Methods**
Design: Randomized controlled trial.  
Allocation: Concealed.*  
Blinding: Unblinded.*  
Follow-up period: 2 and 5 years.  
Setting: Centers in the United Kingdom, India, Chile, Hungary, Italy, the Netherlands, Poland, Portugal, Slovakia, and Yugoslavia.  
Patients: 1443 patients ≥ 1 month of age (mean age 25 y, 57% men) with documented history of ≥ 1 clinically definite, spontaneous, unprovoked epileptic seizure (excluding febrile convulsions or acute symptomatic seizures) who, along with their clinicians, were uncertain whether to proceed with AED treatment. Exclusion criteria were current receipt of AEDs other than a short-acting drug to treat serial seizures or status, previous prophylactic treatment for acute symptomatic seizures, or progressive disease.  
Intervention: Patients were stratified by center and number of seizures at baseline (single or ≥ 2 seizures) and allocated to an immediate AED regimen (type, dose, and duration of AED was chosen according to the clinician’s usual practice) (n = 722) or a deferred AED regimen (no AED drugs until both clinician and patient agreed that treatment was necessary) (n = 721).  

**Outcomes for immediate vs deferred antiepileptic drug (AED) regimen at 2 and 5 years†**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Follow-up (y)</th>
<th>Immediate AED</th>
<th>Deferred AED</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First seizure</td>
<td>2</td>
<td>37%</td>
<td>48%</td>
<td>23% (13 to 32)</td>
<td>10 (6 to 17)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>48%</td>
<td>58%</td>
<td>17% (9 to 25)</td>
<td>10 (7 to 23)</td>
</tr>
<tr>
<td>First tonic–clonic seizure</td>
<td>2</td>
<td>27%</td>
<td>38%</td>
<td>29% (17 to 39)</td>
<td>10 (6 to 16)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>37%</td>
<td>48%</td>
<td>23% (13 to 32)</td>
<td>9 (6 to 17)</td>
</tr>
<tr>
<td>≥ 1 adverse event</td>
<td>At any follow-up</td>
<td>37%</td>
<td>30%</td>
<td>26% (9 to 46)</td>
<td>13 (8 to 36)</td>
</tr>
</tbody>
</table>

‡Abbreviations defined in Glossary; RRR, RBI, RR, NNT, NNH, and CI calculated from data in article. Outcome event rates determined from time-to-event data.

**Commentary**
In a very diverse group of patients, with equally diverse risks for seizure recurrence, Marson and colleagues compared early and deferred AED treatment after a first seizure or an early diagnosis of epilepsy. Immediate treatment (within 1 wk to 3 mo) with carbamazepine and valproate (92% of patients) delayed seizure recurrence, but side effects were increased and the early benefit was lost by 5 years. Interestingly, by the 6th year, about 45% of patients in each group were taking AEDs. The reasons for stopping AEDs are not given, but important questions are raised about the possible role of adherence to, and side effects of, the AEDs used in the study.

We would benefit from additional information. Why were participating clinicians uncertain about starting AEDs? What proportion of patients actually taking (and not taking) AEDs were seizure free? After how many seizures were AEDs started in the deferred-treatment group? What was the effect of AEDs in relevant subgroups of patients (e.g., idiopathic vs symptomatic or cryptogenic epilepsy)? Were patients in the early therapy group whose seizures recurred more likely to express uncertainty about their assigned treatment in the trial? The more common occurrence of status epilepticus (9 vs 2 patients) and deaths (31 vs 23 patients) in the early-treatment group is unexplained and paradoxical. However, the relatively infrequent occurrence precludes drawing valid statistical inferences. The possibility of somewhat sicker patients in the early-treatment group comes to mind, but chance alone could explain this finding.

In the end, the effect of an early AED policy seems to be one of trade-offs: fewer seizures initially, but more side effects, and no difference in the long term. Previous studies have identified variables that increase seizure recurrence risk (e.g., neurologic abnormalities and abnormal electroencephalogram results) (1), and the authors promise a predictive model based on their data. Having seen the big picture, clinicians and individual patients now need to consider more specific information to make a decision about starting AEDs or waiting until further seizures occur.

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**Reference**