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

Marson A, Jacoby A, Johnson A, et al. **Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial.** Lancet. 2005;365:2007-13.

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: First seizure of any type, first tonic–clinic seizure, 2-year remission of seizures, and adverse effects.
Patient follow-up: 86% (intention-to-treat analysis).

MAIN RESULTS

693 patients (48%) had a seizure. 332 patients (46%) in the deferred group started on an AED regimen. AEDs were carbamazepine, valproate, phenytoin, and lamotrigine. The immediate AED regimen increased the time to first seizure and time to first tonic–clonic seizure more than the deferred regimen at 2 and 5 years (Table). At 2 years, more patients in the immediate AED group were seizure-free (2-y remission) than those in the deferred AED group (Table). 2-year remission did not differ between groups at 5 years of follow-up. More patients in the immediate group had ≥ 1 adverse event (Table).

CONCLUSION

In patients with few or infrequent seizures, immediate antiepileptic drug treatment reduced short-term (2-y) but not long-term (5-y) recurrence of seizures.

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*See Glossary.

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

Outcomes	Follow-up (y)	Immediate AED	Deferred AED	RRR (95% CI)	NNT (CI)
First seizure	2	37%	48%	23% (13 to 32)	10 (6 to 17)
	5	48%	58%	17% (9 to 25)	10 (7 to 23)
First tonic–clonic seizure	2	27%	38%	29% (17 to 39)	10 (6 to 16)
	5	37%	48%	23% (13 to 32)	9 (6 to 17)
				RBI (CI)	
2-y remission	2	64%	52%	23% (13 to 35)	9 (6 to 15)
	5	92%	90%	2.1% (–1.1 to 5.6)	Not significant
				RRI (CI)	NNH (CI)
≥ 1 adverse event	At any follow-up	37%	30%	26% (9 to 46)	13 (8 to 36)

†Abbreviations defined in Glossary; RRR, RBI, RRI, 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 unexpected 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 longer 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

1. **Berg AT, Shinnar S.** The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology. 1991;41:965-72.