

# TO TREAT OR NOT TO TREAT...IS IT STILL THE QUESTION?

**Treatment of the First Tonic–Clonic Seizure Does Not Affect Long-Term Remission of Epilepsy.** Leone MA, Solari A, Beghi E; FIRST Group. *Neurology* 2006;67(12):2227–2229. We followed 419 patients with a first, unprovoked, primarily or secondarily generalized tonic–clonic seizure, randomized to immediate antiepileptic treatment or to treatment only in the event of seizure recurrence. The probability of achieving a 2-year remission was 72 versus 57% at 3 months, 84 to 79% at 3 years, and 85 to 86% at 10 years ( $p = \text{NS}$ ). The probability of entering 5-year remission was 47 to 40%, 58 to 58%, and 64 to 64% ( $p = \text{NS}$ ). Early treatment does not affect the long-term prognosis of epilepsy.

## COMMENTARY

The treatment of a first unprovoked epileptic seizure has been and continues to be one of the issues most often debated in epilepsy. In the first major population-based study carried-out more than 20 years ago, Annegers et al. followed 424 patients after an initial first seizure; they found that the risk of recurrence was 36% by one year, 48% by 3 years, and 56% by 5 years (1). Does treatment after a first seizure alter

these statistics? To date, there is a consensus that immediate or delayed treatment after a first seizure does not impact the long-term outcome of the seizure disorder. In contrast, immediate treatment prolongs the time to a first breakthrough seizure and increases the percentage of patients that reach an earlier 2-year remission. These conclusions were obtained from one single-center study (2) and four multicenter, randomized studies (one of which is an earlier study of the article reviewed here) that included both children, aged 2 years and older, and adults, including elderly people aged 60 years and older. (3–5).

Two of these studies, known as the First Seizure Trial Group or FIRST studies, included 397 children and adults.

Among the 204 treated patients, 36 (17.7%) had a breakthrough seizure, while seizures occurred in 75 (39%) of untreated patients, yielding a cumulative risk of seizure recurrence at 24 months of 25 and 51%, respectively (3). However, by 4 years the chance of 2-year remission was of 72 and 67%, respectively, and by 10 years, it was almost identical between the two groups (86 and 85%, respectively) (4). In another study, known as the Multi-Centre Study of Early Epilepsy and Single Seizures or MESS study, patients were randomized to immediate or delayed treatment after a first unprovoked seizure, if the clinician and patients were not sure whether to start treatment (5). Among the 722 patients randomized to immediate treatment 64% achieved an immediate 2-year remission, while this was the case in 52% of patients for whom treatment was delayed. Yet, by 5 (92% in both groups) and 8 years (96 and 95%, respectively) the chance of 2-year remission was almost identical. Furthermore, there was no difference in quality of life between patients who received immediate or delayed treatment.

Yet, while these data may have practical implications for the long-term outcome of patients, they do not provide clinicians with the tools to decide whether to start patients on antiepileptic drugs (AEDs) after a first seizure, since an increased risk of an earlier breakthrough seizure may have negative implications in the life of many patients (e.g., increased risk of self-harm, delay in recovering driving privileges, etc.). Fortunately, several studies have reached a consensus on the variables that increase the risk of seizure recurrence, and these were summarized in a recent review by Haut et al. (6). They include: (1) seizure-type, (2) etiology, (3) EEG data, and (4) sleep state at time of the first seizure. Most of the controversy surrounds the treatment of an initial generalized tonic-clonic seizure, as complex partial seizures are typically associated with an increased risk of recurrent seizures, while myoclonic and absence seizures have already recurred (often for a protracted time period) by the time their existence is brought to medical attention.

An initial remote symptomatic seizure is more likely to be associated with an increased recurrence risk than a cryptogenic seizure, both in pediatric and adult patients. Furthermore, a first unprovoked seizure in which the EEG reveals generalized epileptiform discharges consistent with idiopathic epilepsy is also predictive of an increased recurrence risk and in fact, is comparable to that of remote symptomatic seizures. These two forms of epilepsy differ with respect to their long-term prognosis: idiopathic seizures are likely to enter an early and long-term remission, while remote symptomatic seizures are more likely to have multiple recurrences and are less likely to achieve a long-term remission. Of note, the duration of the first seizure (e.g., status epilepticus as the initial seizure) or a cluster of initial seizures are not predictive of increased recurrence risk in children, but this finding has not been reproduced in adults. Also,

children with status epilepticus as the initial ictal event have an increased risk of status in case of recurrence.

Abnormal EEG findings in adults and children are associated with an increased risk of seizure recurrence. In reviewing the literature, Haut et al. conclude that any electrographic abnormality is sufficient to be considered an increased risk of seizure recurrence in children, while in adults, generalized epileptiform discharges are the only pattern with definite risk (the significance of other abnormalities is still being debated) (5). In addition, studies have clearly established a higher recurrence risk when the first seizure occurs during sleep. In children, this association is significant whether sleep is during day or nighttime, while only the latter applies to adults.

The choice of AED depends not only on the type of epileptic seizure and suspected syndrome but must factor in the age, gender, concomitant medication, and comorbid medical, cognitive, psychiatric, or neurologic disorders of the patient. Clearly, the practice of an intravenous load of phenytoin is proving unnecessary in a large majority of patients with new-onset seizures. Furthermore, studies of patients with new-onset epilepsy have shown that AEDs that require a slow titration (e.g., lamotrigine, topiramate) confer comparable protection to those AEDs with more rapid titration rates (e.g., carbamazepine, phenytoin). In a recent study of patients with new-onset partial and idiopathic or unclassified generalized epilepsy (i.e., the Standard and New Antiepileptic Drugs or SANAD Study), patients were randomized to carbamazepine, lamotrigine, topiramate, and gabapentin for the treatment of partial seizures and to valproic acid, lamotrigine, and topiramate for generalized epilepsy (7,8). In patients with partial seizures, lamotrigine was found to be significantly better for time to treatment failure (either because of lack of efficacy or poor tolerability) than the other three AEDs, while lamotrigine and carbamazepine were comparable for time to 12-month seizure remission. For patients with generalized epilepsy, valproic acid was found to be better tolerated than topiramate and more efficacious than lamotrigine.

How long should patients remain on medication? Seizure recurrence after discontinuation of AEDs has been studied by the Medical Research Council of the United Kingdom in 1013 patients who were randomized to slow taper or continued treatment under double-blind, placebo-controlled conditions (9). Seizure relapse occurred in 22% of patients who remained on medication and 44% of those who discontinued the AED. The variables associated with seizure recurrence included: (1) a long history of seizures before remission, (2) more than one seizure type, (3) presence of structural lesion, (4) abnormal neurologic exam, (5) presence of learning disabilities, (6) relapse following prior remission, and (7) juvenile myoclonic epilepsy. In the absence of these variables, AEDs can be discontinued in children after entering a 2-year seizure-free remission, while in adults, a 4-year seizure-free remission is typically required. In summary,

treatment of a first seizure has an impact on the recurrence risk over a short but not a long-time period. Thus, in the end, there is “the good epilepsy” and “the bad epilepsy.” The former will respond to most appropriate AED, which eventually may be discontinued; the latter will fail to yield seizure remission with any AED.

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