

## TREATMENT OF NEW ONSET SEIZURES: PREDICTING LONG-TERM OUTCOME

### Prediction of Risk of Seizure Recurrence after a Single Seizure and Early Epilepsy: Further Results from the MESS Trial

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**BACKGROUND:** The MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) showed a reduced risk of further seizures in patients, for whom treatment with antiepileptic drugs was uncertain, who were randomly assigned immediate treatment compared with delayed treatment. However, there was no evidence of long-term remission rates. This study was undertaken to assess the role of patient characteristics and treatment in the prediction of seizure recurrence. This will enable decision making on the basis of the perceived risk of treatment compared with the benefit of reducing the risk of further seizures in the initial years after diagnosis.

**METHODS:** A prognostic model was developed based on individual patient data from MESS to enable identification of patients at low, medium, or high risk of seizure recurrence. A split-sample approach was used in which the

model was developed on a subsample of the full data and validated on the remainder of the sample. Distinction of the prognostic groups and predictive accuracy of the model were assessed.

**FINDINGS:** Number of seizures of all types at presentation, presence of a neurological disorder, and an abnormal electroencephalogram (EEG) were significant factors in indicating future seizures. Individuals with two or three seizures, a neurological disorder, or an abnormal EEG were identified as the medium-risk group, those with two of these features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group.

**INTERPRETATION:** The model shows that there is little benefit to immediate treatment in patients at low risk of seizure recurrence, but potentially worthwhile benefits are seen in those at medium and high risk.

### COMMENTARY

When the first epileptic seizure occurs, it heralds a new life for the patient, with tough decisions to be made. The decision of when to start a drug or whether to treat at all is not an easy one. If only one or two complex partial seizures and not a generalized tonic-clonic seizure has occurred, many clinicians prefer to wait and see if a next seizure will occur instead of starting the patient on an antiepileptic drug (AED), with all its potential constraints and side effects. The dilemma is difficult to confront without solid evidence on which to base the decision of whether to treat or not. A large, multicenter (13 countries), randomized trial was undertaken to answer the question: Should treatment be started or deferred until further seizures have occurred?

The first findings from this study were published in June 2005 (1). In this report, 722 patients with newly diagnosed epilepsy were randomly assigned to immediate treatment with an AED, which the physician selected. The dose also varied,

depending on what the physician felt was adequate. Another group, consisting of 721 patients, deferred their treatment until a further seizure had occurred. The study found that immediate treatment increased the time to the first and second complex partial seizures as well as to the first generalized tonic-clonic seizure, and it reduced the time to achieve 2-year remission. In other words, immediate treatment reduced the number of seizures within the first 2 years. Interestingly, however, immediate treatment with an AED did not prevent recurrences between 3 and 5 years; no difference was demonstrated between the two groups.

In the current study, the authors further analyzed patient characteristics and treatment results from the MESS trial in order to predict who would be at high, medium, or low risk for additional seizures. The idea was to be able to predict who could defer treatment and who should be advised to begin medical treatment immediately. The authors developed a prognostic model in which half of the patient group was used to construct the model and the other half was used to validate it. Patient characteristics that were judged to have potential prognostic value were: (i) number of seizures before randomization; (ii) presence of a neurological disorder; (iii) abnormal EEG;

(iv) epilepsy syndrome and randomization; (v) men/women; (vi) febrile convulsions; and (vii) family history. Among these, the most important factors in predicting whether treatment should be immediate or could be deferred (irrespective of what type of abnormality was found) were the existence of a neurological disorder, total number of seizures prior to randomization, and abnormal EEG. An estimate of the probability of seizures by 1, 3, and 5 years was calculated. For the low-risk group, the probability of seizures at 5 years was no different between the delayed and immediate groups. For patients with a medium or high risk, contrary to the conclusion drawn from the 2005 trial, a deferred treatment resulted in a worse outcome at 1, 3, and 5 years. Thus, estimating the patient's risk group will determine whether or not treatment can safely be deferred.

Is there a practical value to this information for clinicians in daily practice? Concerned about the application to clinical practice, the authors performed the needed calculations and simplified the rating procedure, resulting in a prognostic index of one to four. Thus, if a person has had only one seizure, their number would be 0, with 2 to 3 seizures, the number would be 1, and more than 3 seizures, the number is 2. A score of 1 is added if there is a neurological deficit, learning disability, or developmental delay present. Another point is added if there is an abnormal EEG, irrespective of what the abnormality is. It did not make a difference in the calculation whether or not the EEG contained spikes or spike-waves. Low-risk patients received a score of 0, medium-risk a score of 1, and high-risk a score of over 2. A closer look at the data reveals information about treatment issues. According to the results, a high-risk patient will have a greater than 50% chance of a seizure recurrence within 3–5 years if a drug is started immediately and a 65% chance after 5 years if treatment is deferred. A medium-risk patient given immediate treatment will have a 35–39% chance of recurrence at 3 and 5 years but with deferred treatment it is 50–56% risk. A low-risk patient will have a 30–39% increase in risk in both groups.

In certain circumstances, such as a planned pregnancy, a medium-risk patient might want to defer AED treatment, which would eliminate the possibility of adverse reactions of the AED on the fetus. The results from this study could help the patient make an informed decision. The article also confirms the concern that delaying treatment might increase the risk for further seizures and eventual intractability, lending support to the old idea that “seizures beget seizures.” When undecided, patients with higher risk factors than 1 should be encouraged to take medication. By estimating the probability of seizure recurrence, the patient can be a partner in the decision to treat or not. In other words, the study helps make complex decisions somewhat less complicated.

A key feature of this study is that it supports the practice of not using AEDs after the first seizure if there are no

other risk factors (many physicians would not even give a diagnosis of epilepsy at this point). However, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy have introduced a new classification stating that a single seizure is indeed epilepsy, if it is accompanied by “enduring epileptogenic abnormality” (2). The statement implies that one seizure should be treated yet does not specify what “enduring” means—an issue that has concerned other experts in epilepsy as well (3). In contrast, the MESS study simplifies the decision of when to treat a single seizure and whether to call it epilepsy.

There are some weaknesses to this study. A detailed seizure semiology was not done, except to divide into categories of tonic-clonic and complex partial seizures. Knowing the syndrome would also help in predicting seizure recurrence. This information was not available from the MESS study. However, in many cases a clear diagnosis is not possible in spite of access to MRIs and EEGs. In addition, the choice of AED could have been a factor contributing to the end result but was not assessed. As mentioned, no specific AED was stipulated and drug choice was at the clinician's discretion. In fact, 40% of the patients were started with carbamazepine, 43% with valproate, 6% with phenytoin, and 5% with lamotrigine. No other AED was chosen for more than 3 patients. The drugs used in the study are known not to have neuroprotective effects; while animal studies suggest that some of the newer AEDs may be neuroprotective (4), especially topiramate and levetiracetam and possibly zonisamide. Would patients on these drugs have done better than the others? This question remains unanswered, but there was a golden opportunity missed here to compare the new drugs and long-term seizure control. Hopefully, further studies will answer this question.

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## References

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