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The Cost of the Second Seizure: Rethinking the Treatment Decision

Antiepileptic Drug Treatment After an Unprovoked First Seizure: A Decision Analysis

Bao EL, Chao LY, Ni P, et al. *Neurology*. 2018;91(15):e1429-e1439. doi:10.1212/WNL.0000000000006319

Objective: To compare the expected quality-adjusted life-years (QALYs) in adult patients undergoing immediate versus deferred antiepileptic drug (AED) treatment after a first unprovoked seizure. Methods: We constructed a simulated clinical trial (Markov decision model) to compare immediate versus deferred AED treatment after a first unprovoked seizure in adults. Three base cases were considered, representing patients with varying degrees of seizure recurrence risk and effect of seizures on quality of life (QOL). Cohort simulation was performed to determine which treatment strategy would maximize the patient's expected QALYs. Sensitivity analyses were guided by clinical data to define decision thresholds across plausible measurement ranges, including seizure recurrence rate, effect of seizure recurrence on QOL, and efficacy of AEDs. Results: For patients with a moderate risk of recurrent seizures (52.0% over 10 years after first seizure), immediate AED treatment maximized QALYs compared to deferred treatment. Sensitivity analyses showed that for the preferred choice to change to deferred AED treatment, key clinical measures needed to reach implausible values were 10-year seizure recurrence rate $\leq$38.0%, QOL reduction with recurrent seizures $\leq$0.06, and efficacy of AEDs on lowering seizure recurrence rate $\leq$16.3%. Conclusion: Our model determined that immediate AED treatment is preferable to deferred treatment in adult first-seizure patients over a wide and clinically relevant range of variables. Furthermore, our analysis suggests that the 10-year seizure recurrence rate that justifies AED treatment (38.0%) is substantially lower than the 60% threshold used in the current definition of epilepsy.

Commentary

The major conclusion of this article is that immediate drug treatment after a first seizure is the best choice in many cases, even if the International League Against Epilepsy (ILAE) definition of epilepsy is not met. Bao and coauthors have attempted to place this crucial decision on a more quantitative basis and have integrated a vast amount of data to construct a mathematical model. The variables to be considered are well known: history of remote neurological events, seizure type, results of EEG, neuroimaging, and physical examination. There are good data quantifying the effects of each on the likelihood of seizure recurrence.[1] We are also accustomed to considering qualitative factors such as age, occupation, and patient preference. But it is difficult to consider all of the variables in a quantitative way for an individual patient. Bao et al have used published data to model the results of treating versus not treating the first seizure with anti-seizure drugs (ASDs). They considered seizure recurrence rate, drug adverse effect rate, and mortality. They went one step further, estimating the effects on quality of life (QOL) for each outcome, then factoring this into the initial decision to treat or not to treat.

Their method was a Markov decision process. This is a mathematical exercise which starts with a condition (a seizure occurred), followed by a set of possible actions (treat or not treat), a calculation of the likely results of each of the actions (probability of recurrent seizure and/or medication side effects), and then most importantly, assignment of a value to each possible result.[2] The value metric selected for this simulation was quality-adjusted life-years (QALY). The QALY is a standard concept, which is used in a variety of clinical and economic analyses.

The first steps in this process were based on published data, such as the likelihood of seizure recurrence with and without treatment.[3] However, each subsequent step involved progressively more qualitative assumptions, though each is reasonable based on what we know about epilepsy. A very helpful feature of this article is the inclusion of 3 theoretical patient scenarios. These cases highlight the degree of objectivity of each part of the sequence. The key outcome was the effect of a recurrent seizure on QOL. The impact was judged to be worse in their example of a healthy 30-year-old (QOL: 0.75 compared to a baseline of 1.0). The detrimental effect was judged to be less on

their example of a 60-year-old wheelchair-bound person with focal motor seizures (QOL: 0.90). The assignment of negative value was partly subjective but is plausible and is supported by previous data relating QOL to seizures.[4]

The other important outcome was the presence or absence of medication side effects, with assignment of a QOL value for each. The authors assigned a value of 1.0 to the case of no side effects, and assigned a value of 0.9 for adverse effects in the example of the healthy 30-year-old, and 0.8 for the example of the 60-year-old impaired patient. This clearly involves some subjectivity and does not take into account the nature or severity of the side effects. Since most adverse effects are seen at drug initiation or are dose related, this calculation may be biased toward the first cycle of the Markov process (the first year). The authors use the simplifying assumptions that, once started, a patient will stay on medication for life, that ASD adverse effects will continue for life, and that no new ASDs will appear—for life expectancy or to 90 years! As they acknowledge, this is an oversimplification. Nevertheless, we have some idea of QOL related to various adverse effects of ASDs. Another possible outcome in the Markov trees was death. Although small, this risk was factored into the comparison between treatment and no treatment. Existing data suggest that not taking medication increases the risk of death in persons with epilepsy.

Since assignment of values to the likelihood of transition from one state to another in the Markov process (eg, transition from no recurrent seizures to recurrent seizures) depends critically upon the reliability of the published data, the authors performed a sensitivity analysis, varying the values of probabilities. They varied the risk of seizure recurrence without drug treatment, with drug treatment (expected drug efficacy), and the effects of seizure recurrence on QOL. This analysis led to the major conclusion of the article that changes in the values of the data to "clinically implausible" levels would be required to favor the decision not to treat after the first seizure. For example, the probability of seizure recurrence would have to be as low as 9% in the case of the 30-year-old to favor deferred treatment and would rise only to 30% even if there were a 100% chance of adverse drug effects.

The authors hammer the point that these values are much, much lower than the 60% recurrence risk specified by the ILAE for the diagnosis of epilepsy.[5] A diagnosis of epilepsy by ILAE criteria is assumed to be sufficient for commencement of ASD therapy, which of course is almost always true. The authors state that the "decision to administer antiepileptic drug therapy is intrinsically tied to the operational definition of epilepsy." The unstated implication is that the ILAE criterion of 60% recurrence risk of the diagnosis should be changed.

However, I suggest a different conclusion that the decision to treat can be divorced from the diagnosis of epilepsy. Labeling a patient as having epilepsy is not a benign action. It can have consequences for employment, for insurance, and for self-esteem. Simply being prescribed an ASD does not equal having epilepsy. I do not suggest sugarcoating the situation of having had a seizure, but for many persons a definite diagnosis should be deferred even if a medication is prescribed. Embarking on ASD treatment after a first seizure is in effect a therapeutic trial which may aid in the diagnosis but does not in itself constitute a diagnosis.

A counterargument is that persons receiving antihypertensive medications but with a normal blood pressure are still considered to have hypertension and that persons receiving insulin are still considered to have diabetes even with normal blood sugars. But epilepsy is fundamentally different because of the existential and practical consequences of receiving this diagnosis.

There is another reason to favor ASD treatment after the first seizure: the dread of having another seizure. How much does this affect QOL? I suspect quite a bit. In a recent study, 55% of patients listed worry about seizures as their first concern, though this included all categories of seizure patients.[6] It would be interesting to know the extent of this concern after a first seizure. Patients need to be told that ASDs do not eliminate the possibility of recurrence, but it is surely wrong to say that they do not reduce it. Dread may be reduced by the prescription more than is warranted but that is not necessarily a bad thing.

Anti-seizure drug treatment is often assumed to mean adequate treatment. But most of the published data on rates of seizure recurrence and adverse effects are based on studies of older drugs, and drug dose is not always considered. We have all seen patients who are started on the minimal effective dose who then have a second seizure within the first year. Perhaps they should be started on the median effective dose, with reduction only if unacceptable side effects occur. But that is an argument for another day.

The bottom line is that QALYs are higher for many patients if immediate ASD treatment is chosen, though usually only by a couple of years. This is a complex issue, and the authors acknowledge that their model does not take into account many variables involved in the clinical decision to treat or not to treat after a first unprovoked seizure. They also make the necessary assumption that a first seizure was really a seizure. Less than 100% certainty may influence the choice. However, these variables, as they become known more precisely, can be included in future iterations of the model. Bao et al have taken an important step toward rationalizing this critical clinical decision.

By Edward Faught

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