ARTICLE

Antiepileptic drug treatment after an unprovoked first seizure

A decision analysis

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Abstract

Objective

To compare the expected quality-adjusted life-years (QALYs) in adult patients undergoing immediate vs deferred antiepileptic drug (AED) treatment after a first unprovoked seizure.

Methods

We constructed a simulated clinical trial (Markov decision model) to compare immediate vs 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 ≤38.0%, QOL reduction with recurrent seizures ≤0.06, and efficacy of AEDs on lowering seizure recurrence rate ≤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.

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Glossary

AED = antiepileptic drug; **ILAE** = International League Against Epilepsy; **QALY** = quality-adjusted life-year; **QOL** = quality of life.

Current guidelines from the International League Against Epilepsy (ILAE) recommend making a diagnosis of epilepsy if patients meet 1 of the following conditions: at least 2 unprovoked seizures occurring >24 hours apart, 1 unprovoked seizure and a probability of further seizures over the next 10 years ≥60%, or diagnosis of an epilepsy syndrome.[1]

Patients presenting with ≥2 unprovoked seizures are readily diagnosed with epilepsy, and virtually all are prescribed antiepileptic drug (AED) therapy. In contrast, starting vs withholding AED treatment after a single unprovoked seizure has been a long-standing topic of debate. On one hand, several studies show that immediate AED treatment reduces the risk of seizure recurrence by ≈35% over the next 2 years.[2–6] On the other hand, starting AED therapy immediately has had little effect on long-term seizure remission rate and carries risks of substantial adverse effects.[2] Finally, the current 1-size-fits-all threshold of 60% for epilepsy diagnosis and AED treatment overlooks the need to personalize recommendations on the basis of a patient's specific comorbidities and seizure burden and the effects of the decision on the patient's quality of life (QOL). An important unresolved question is, Which patients with a first unprovoked seizure can expect a net benefit from immediate AED treatment, and which patients should begin treatment only after experiencing further seizures?

To address this question, we constructed a Markov decision model to perform a simulated clinical trial, starting from a first unprovoked seizure, to quantitatively determine which treatment option provides greater QOL over a lifetime.

Methods

Model structure and measures

Modeling and statistical analysis were conducted with TreeAge Pro HealthCare software (Williamstown, MA) and Matlab (Natick, MA). In our Markov model, treatment options and possible outcomes from each treatment are modeled as discrete health states. During each cycle (defined as 1 year), an individual can either transition from 1 state to another or remain in the same state. Each state is assigned a utility, and the contribution of this utility to the overall prognosis depends on the number of cycles spent in the state.

The model consists of 2 Markov cycle subtrees, immediate AED treatment and deferred AED treatment, as well as 5 health states (figure 1): (1) no recurrent seizures, no AED treatment; (2) no recurrent seizures, AED treatment, no AED adverse effects; (3) no recurrent seizures, AED treatment, AED adverse effects; (4) recurrent seizures, AED treatment, no AED adverse effects; and (5) recurrent seizures, AED treatment, AED adverse effects.

The utility of each health state was assigned a QOL value based on previous studies (table 1).[6,7] The health states included within each cycle tree, shaded in color by their relative utilities, are diagrammed in figure 1.

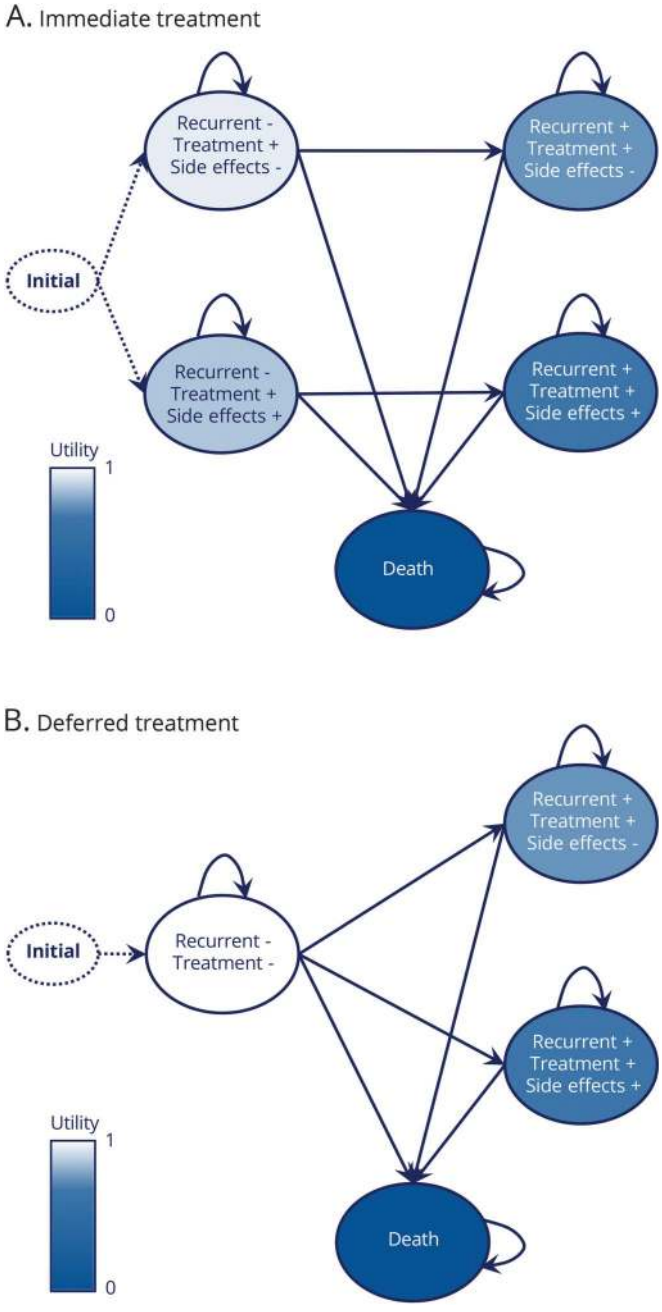
Each Markov cycle tree delineates all possible transitions between states that can occur between cycles (figure 1), as well as their associated probabilities estimated from published clinical data.[2,3,8–13] Data for all transition probabilities are available from Github (table e-1, github.com/erikbao/firstseizure_decisionanalysis). Because studies have shown that the risk of seizure recurrence is highest within the first few years after a first seizure,[14] we stratified the probability of seizure recurrence over 4 time windows: 0 to 2, 2 to 5, 5 to 8, and 8+ years (data available from Github, table e-1, github.com/erikbao/firstseizure_decisionanalysis).[2] The yearly transition probability of seizure recurrence was estimated from retrospective data for each time range, and this probability was decreased by a multiplicative factor if the patient was taking AEDs. For base case 1, this factor was estimated by taking the average fold difference in recurrence probabilities of patients in the presence vs absence of AEDs at the 2- to 5- and 5- to 8-year time frames. Individuals in all Markov states also had a yearly probability of death (death rate) that varied, depending on age and presence of recurrent seizures. More detailed information on the calculation of death rate is available from Github (appendix e-1, github.com/erikbao/firstseizure_decisionanalysis).

Cumulative QOL over a lifetime was quantified in terms of quality-adjusted life-years (QALYs), calculated as QALYs = QOL × number of years, representing a measure of life expectancy factoring in changes in QOL due to medical conditions.[15] QALYs were used as the primary outcome in our study for 2 reasons: the QALY is a widely recognized analytic index with important clinical, economic, and policy implications, being valued at $50,000 to $100,000 per QALY,[16–18] and it serves as a marker to determine the critical sensitivity thresholds for other clinical variables.

Calculation of utility

Utility estimates for each health state of the Markov model were obtained from previously published data on QOL (table 1). The utility discount rate accounts for the fact that costs or benefits occurring immediately are valued more highly than those occurring in the future, and a default value of 0.03 was used for this analysis.

Figure 1 Markov model for immediate and deferred AED treatment



Markov cycle trees for (A) immediate antiepileptic drug (AED) treatment and (B) deferred AED treatment showing different states in the disease course and possible transitions between them. Colors are weighted by the utility (quality-adjusted life-years) associated with each state. Recurrent = recurrent seizure.

The utility of AED adverse effects, *uSe*, was estimated to be 0.9 by extrapolation from a clinical study that compared Liverpool Adverse Effects Profile scores between patients with a first seizure who had taken AEDs and those who had not.[19] A more detailed derivation of this utility data is available from Github (appendix e-1, github.com/erikbao/firstseizure_decisionanalysis).

The overall utility of each health state was then calculated as the product of utility measures. For example, the utility of health state 3, no recurrent seizures with AED treatment and with adverse side effects, was calculated as $uRx \times uSe = 0.864$, where *uRx* is the utility of AED treatment and *uSe* is the utility of AED adverse effects.

Base cases

To study the relative importance of recurrent seizure risk, effect of recurrent seizures on QOL, and risk of experiencing adverse events from AEDs, we constructed 3 base cases based on clinical scenarios commonly seen in patients with a first seizure. The base cases are described in qualitative terms below; numerical details of the models are provided in table 2.

Table 1 QOL value

Model health states	Utility (QOL)
No recurrent seizures	
Without AED treatment	1.00
AED treatment without adverse side effects	0.96[7]
AED treatment with adverse side effects	0.864[7,19]
Recurrent seizures	
AED treatment without adverse side effects	0.75[7]
AED treatment with adverse side effects	0.675[7,19]
Death	0

Abbreviations: AED = antiepileptic drug; QOL = quality of life.

Case 1 (risk of recurrent seizures: low; change in QOL due to recurrence: substantial)

A 30-year-old man with no identifiable neurologic conditions, history of seizures, AED use, depression, anxiety, or comorbidities presents with a single unprovoked seizure. His MRI and EEG are normal. The absence of any other identifiable risk factors for recurrent seizure suggests a low risk for recurrent seizures.[14,20] If seizures do recur, they are expected to have a substantial reduction in QOL. This patient does not meet the ILAE definition of epilepsy (10-year recurrence risk is not >60%).

Case 2 (risk of recurrent seizures: high; change in QOL due to recurrence: substantial)

A 30-year-old woman presents with a first unprovoked seizure. MRI shows hippocampal atrophy, consistent with mesial temporal sclerosis as a focal cause of epilepsy. The positive MRI result establishes a high risk (>60%) of experiencing recurrent seizures if not prescribed an AED.[14] If seizures do recur, they are expected to have a substantial reduction in QOL. This patient meets the ILAE definition of epilepsy.

Case 3 (risk of recurrent seizures: high; change in QOL due to recurrence: modest)

A 60-year-old woman who presents with a first unprovoked seizure is wheelchair bound (indicating a lower fall risk, so there is lower risk of injury in the event of a seizure) and has focal motor seizures (e.g., right arm twitching) rather than generalized convulsions. This patient has a high risk (>60%) for recurrent seizures and meets the ILAE definition of epilepsy, but she also has a high risk of adverse effects from AED

Table 2 Base case numerical details

Base case	Age, y	Risk of recurrent seizure, % (years after first seizure)	QOL for recurrent seizures	Recurrent seizure mortality ratio	Probability of AED adverse events, %	QOL for AED adverse events
Patient 1	30	21.9 (0–2)	0.75	5.4	22	0.90
		7.04 (2–5)				
		0.68 (5–8)				
		0.010 (8+)				
Patient 2	30	65.7 (0–2)	0.75	5.4	22	0.90
		21.12 (2–5)				
		4.08 (5–8)				
		0.030 (8+)				
Patient 3	60	65.7 (0–2)	0.90	1.5	80	0.80
		21.12 (2–5)				
		4.08 (5–8)				
		0.030 (8+)				

Abbreviations: AED = antiepileptic drug; QOL = quality of life.

treatment, a greater reduction in QOL from AED adverse events, and a smaller expected reduction in QOL if further seizures occur.

Model assumptions

This model embodies several simplifying but reasonable assumptions. We assume that if a patient experiences a recurrent seizure at any time, the patient will be diagnosed with epilepsy and prescribed AEDs. We also assume that if a patient starts taking AEDs, the patient will continue AED therapy for the remainder of his/her lifetime. In addition, if a patient develops AED-related side effects, we assume that he/she will continue having side effects for the remainder of life, whereas if a patient does not have initial adverse effects to AEDs, he/she will remain free of adverse effects at all later times. We also assume that a patient's risk of AED-related side effects is independent of seizure recurrence. These assumptions affect the possible transitions between different Markov health states (figure 1).

Cohort simulation

A cohort simulation was performed to calculate which treatment maximizes the expected QOL over a lifetime (QALYs) for each base case. The simulation considers an initial cohort of patients distributed among baseline health states. For immediate AED treatment, the initial cohort was divided into 2 groups, those with and those without side effects, based on the estimated probability of side effects (data available from Github, table e-1, github.com/erikbao/firstseizure_decisionanalysis). For each cycle, the fraction of the cohort initially in each health state is partitioned according to transition probabilities specified by the model. The QALYs accrued for a given cycle are the sum of the QOL in each state multiplied by the fraction of the cohort in that state. The simulation ends after 90 cycles, and the measured outcome is the total QALYs accrued over all cycles.

Of note, because this simulation is strictly determined by the transition probabilities and QOL estimates of the model, it is nonstochastic and independent of sample size. To account for uncertainty in the variables of the model, we performed sensitivity analyses.

Sensitivity analysis

Base case 1 represents an adult patient with a common age range and seizure history presenting with a first unprovoked seizure, as indicated by epidemiologic studies.[21] Sensitivity analyses were performed on measures of interest to define specific ranges over which a certain treatment option is favored.

We performed 1-way sensitivity analyses for the following clinical variables of interest: effect of recurrent seizures on QOL, severity of AED side effects, seizure recurrence rate, efficacy of AEDs in reducing seizure recurrence rate, and influence of recurrent seizures on mortality rate. We also performed 2-way (effect of seizures on QOL and increase in mortality, risk of AED side effects and risk of recurrent seizures without treatment) and 3-way (seizure recurrence rate, impact of seizure on QOL, and efficacy of AEDs) sensitivity analyses to determine what related multivariate combinations would favor deferred vs immediate AED treatment.

Data availability

All supplemental data and TreeAge analysis files are available at github.com/erikbao/firstseizure_decisionanalysis. Additional raw data and code used in preparation of the figures and tables are available on request.

Results

Cohort simulations

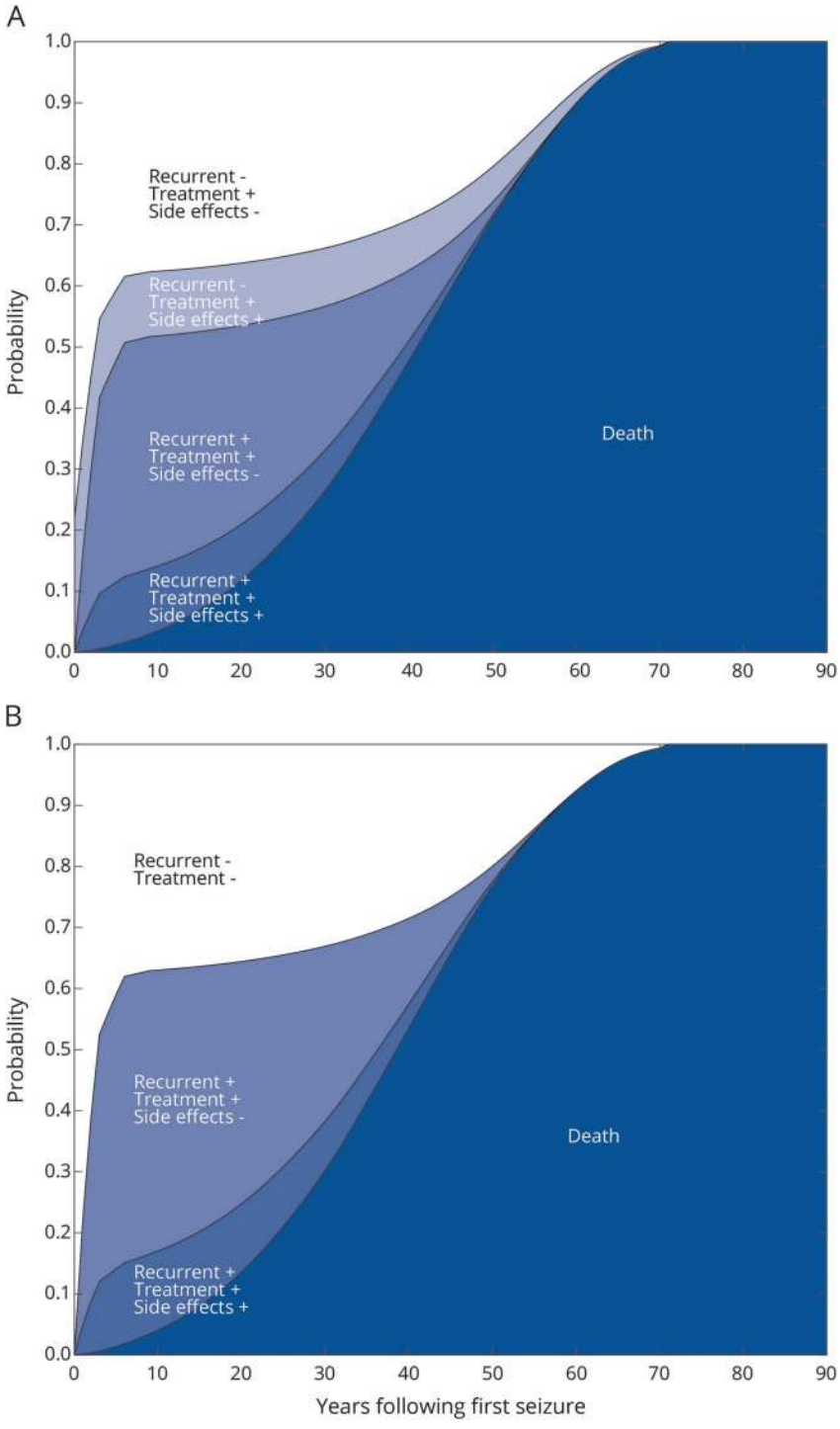
To assess the expected effect on QALYs for each treatment strategy, we performed cohort simulations on the decisions of immediate vs deferred AED therapy, starting from immediately after a first seizure and extending over a duration of 90 years to reach equilibrium for all 3 base cases. The simulated clinical trial for base case 1, a common type of adult patient with a first seizure,[21] is shown in figure 2, and results for all 3 base cases are shown in table 3. Compared to deferred AED treatment (figure 2B), immediate AED treatment for base case 1 (figure 2A) had a much lower rise in the proportion of individuals with recurrent seizures. For example, at year 10, 51.8% of individuals in the immediate AED cohort had experienced recurrent seizures compared to 63.0% in the deferred AED simulation. The progression of individuals transitioning to death exhibited a sigmoidal shape in both cohorts, but the proportion dead in the deferred AED cohort increased at a faster rate than in the immediate AED cohort.

Immediate AED treatment was preferred for base case 1: immediate AED treatment resulted in 19.04 QALYs, whereas deferred AED treatment yielded 18.65 QALYs (table 3). In dollar values, using the conservative approximation of $50,000 per QALY gained,[16] this difference in treatment outcomes would amount to $19,500 gained per individual. Although this patient had no identifiable risk factors for recurrent seizures beyond having had a first seizure (normal EEG, MRI, and neurologic examination) and thus failed to meet the ILAE definition of epilepsy, our model favored immediate AED treatment.

For base case 2, the model also favored immediate AED treatment to maximize QALYs (immediate AED treatment = 15.23 QALYs, deferred AED treatment = 14.75 QALYs; table 3). This result was expected because the patient had a positive MRI establishing increased recurrent seizure risk and thus met the ILAE definition of epilepsy. Therefore, under current guidelines, this patient would be prescribed AEDs on initial presentation.

For base case 3, cohort simulation favored deferred AED treatment over immediate AED treatment, albeit by a small margin (immediate AED treatment = 10.89 QALYs,

Figure 2 Cohort proportions over time for immediate vs deferred AED treatment



Both cohort simulations start at year 0 immediately after a first seizure. (A) In the immediate treatment model, individuals begin in the 2 states of receiving antiepileptic drug (AED) treatment with or without side effects (22% with side effects, 78% without). (B) In the deferred treatment model, all individuals begin in the state of no recurrent seizure and no AED treatment. In subsequent cycles, varying proportions of individuals remain in the same cohort or progress to another state involving recurrent seizures or death. All individuals are in the death cohort by the end of each simulation (year 90).

deferred AED treatment = 10.79 QALYs; table 3). This patient also met the ILAE definition for epilepsy because of her high risk for recurrent seizures (>60%), similar to base case 2, but deferred treatment was favored in this case because of the patient's minimal expected decrease in QOL from recurrent focal seizures and a high risk of AED adverse effects (table 2).

One-way sensitivity analyses

Decision analysis outcomes are intrinsically dependent on the measurement values used in the model. Thus, to assess the robustness of these decisions to changes in clinical variables, we performed 1-, 2, and 3-way sensitivity analyses of our model for base case 1. Because base case 1 represents a common scenario of a patient with a first seizure and base cases 2

Table 3 Results for base cases

Base case	Meeting ILAE definition for epilepsy	Immediate AED treatment outcome (QALYs)	Deferred AED treatment outcome (QALYs)	Preferred decision
Patient 1	No	19.04	18.65	Immediate AED treatment
Patient 2	Yes	15.23	14.75	Immediate AED treatment
Patient 3	Yes	10.79	10.89	Deferred AED treatment

Abbreviations: AED = antiepileptic drug; ILAE = International League Against Epilepsy; QALY = quality-adjust life-years.

and 3 can be simulated by scaling various measures of base case 1 to more extreme values, we limited our sensitivity analyses to base case 1 to avoid redundancy.

Because recurrent seizures may decrease QOL to varying degrees, depending on patient occupation or lifestyle, we examined the effects of changing the QOL reduction of recurrent seizures on favored management strategy (figure 3C). For base case 1, immediate AED treatment is favored at our estimated recurrent seizure utility of 0.75 (compared to 1.0 for a state of normal health), and this decision holds until the utility of recurrent seizures becomes >0.94. In other words, deferred treatment is favored only when recurrent seizures are estimated to reduce QOL by ≤0.06.

We also performed 1-way sensitivity analyses by varying the seizure recurrence rate, efficacy of AEDs on reducing seizure recurrence risk, QOL reduction of AED side effects, and excess mortality rate associated with recurrent seizures (figure 3, A, B, D, and E). Note that when sensitivity analysis is performed on seizure recurrence rate, we ensured that recurrent seizure rates for different time windows are all modified by the same multiplicative factor. With this in mind, from this point on, seizure recurrence rate will be denoted by the yearly recurrence rate for years 0 to 2 after the first seizure but has equal effects on recurrence rates in later time windows as well.

For base case 1, for deferred AED treatment to switch to the preferred decision, key measures needed to reach extreme, clinically implausible values: seizure recurrence rate ≤14.7%, efficacy of AED in lowering recurrent seizure risk ≤16.3%, QOL reduction with recurrent seizures ≤0.06, QOL reduction with AED adverse side effects ≥0.26, and effect of recurrent seizures on mortality ≤1.44 (figure 3). Notably, the threshold seizure recurrence rate of 14.7% needed to favor deferred AED therapy translates into a 10-year cumulative recurrence rate of 38.0%, substantially lower than the threshold of 60% used by the current ILAE definition for epilepsy in patients after 1 unprovoked seizure.

Two-way sensitivity analysis

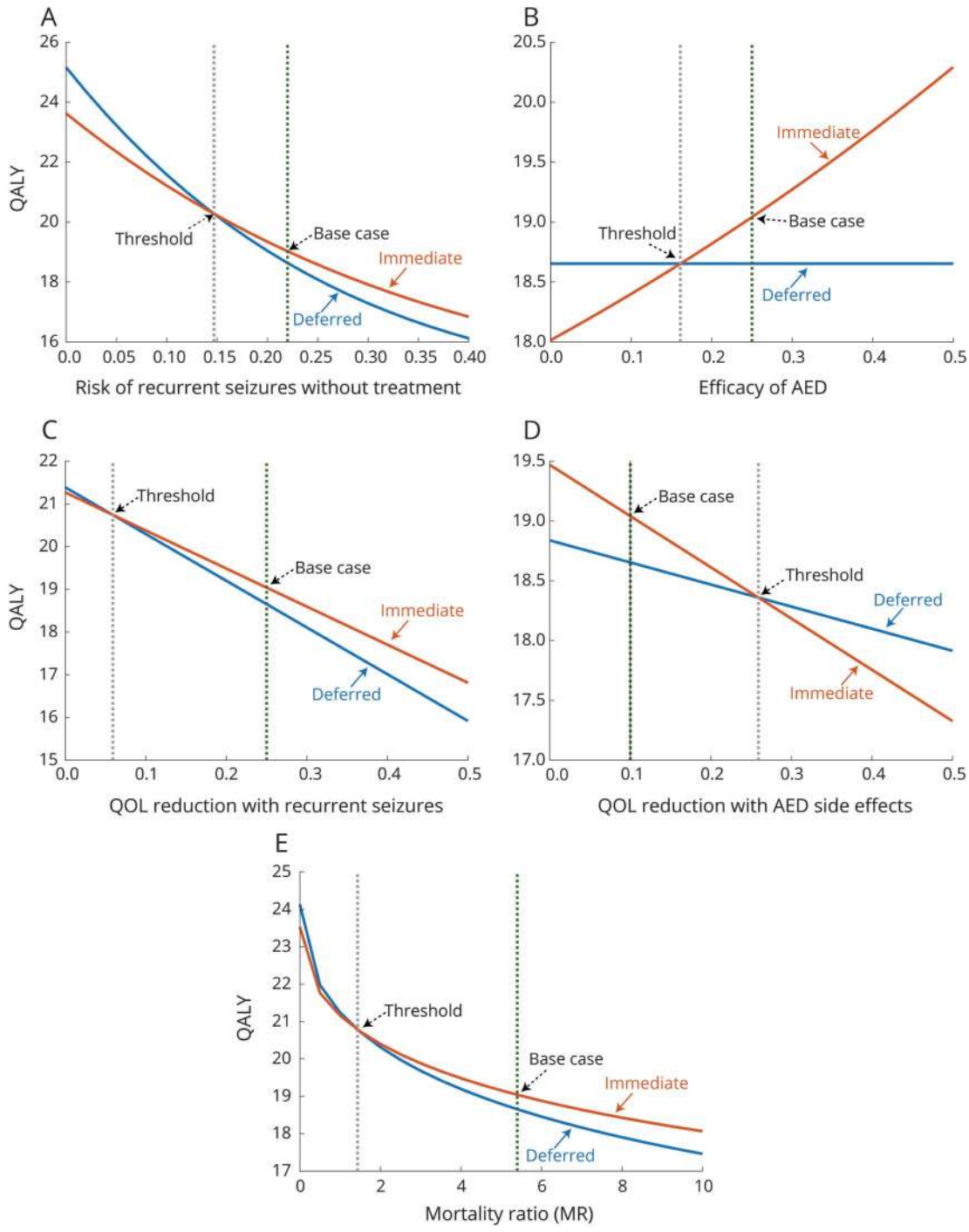
Recurrent seizures exert a deleterious effect on QALYs in 2 different ways: through reducing QOL and by increasing overall mortality. Because there is wide individual variation in QOL and the extent to which seizures increase mortality, we performed a 2-way sensitivity analysis of these paired variables to determine what combination would lead to favoring deferred vs immediate AED treatment (figure 4A). This analysis demonstrates that factors that lower the increased mortality associated with seizures or decrease the effect of recurrent seizures on QOL shift the decision toward favoring deferred AED treatment. However, for base case 1, both measures must be considerably changed for the model to favor deferred AED treatment. Specifically, when both the seizure-associated mortality ratio and the QOL reduction with recurrent seizures are scaled toward 0 at equal rates, the seizure-associated mortality ratio needs to reach 3.24 (vs base case 1 estimate of 5.4) and the QOL reduction needs to reach 0.15 (vs base case 1 estimate of 0.25), a 40% decrease in both values, to start favoring deferred AED treatment. These thresholds, to the best of our knowledge, are lower than any estimates of these measures obtained from clinical data, indicating that immediate AED treatment is favored over a wide range of recurrent seizure severities in patients similar to base case 1.

We also performed a 2-way sensitivity analysis to assess how the risk of AED side effects and risk of recurrent seizures without treatment jointly influence the preferred treatment option (figure 4B). This analysis revealed that the decision of the model to favor immediate treatment is robust to changes in the risk of AED side effects but is more heavily dependent on recurrent seizure risk. When the risk of recurrent seizures falls below 0.088, deferred treatment is favored regardless of the risk of AED adverse effects, and conversely, when the risk of recurrent seizures rises above 0.30, immediate treatment is favored even when the risk of AED adverse effects is 100%. These findings suggest that the decision to favor immediate AED treatment may hold true for different medications across a broad spectrum of side effect profiles, whereas it is more sensitive to an individual's recurrent seizure risk.

Three-way sensitivity analysis

Finally, we performed a 3-way sensitivity analysis by varying the seizure recurrence rate, effect of seizures on QOL, and efficacy of AEDs on reducing seizure recurrence (figure 4C). This analysis shows that when AEDs are less effective at reducing recurrent seizure risk, deferred AED therapy becomes the preferred decision over a much wider range of seizure recurrence rates and seizure severity. Therefore, the decision of this model is relatively sensitive to differences in AED

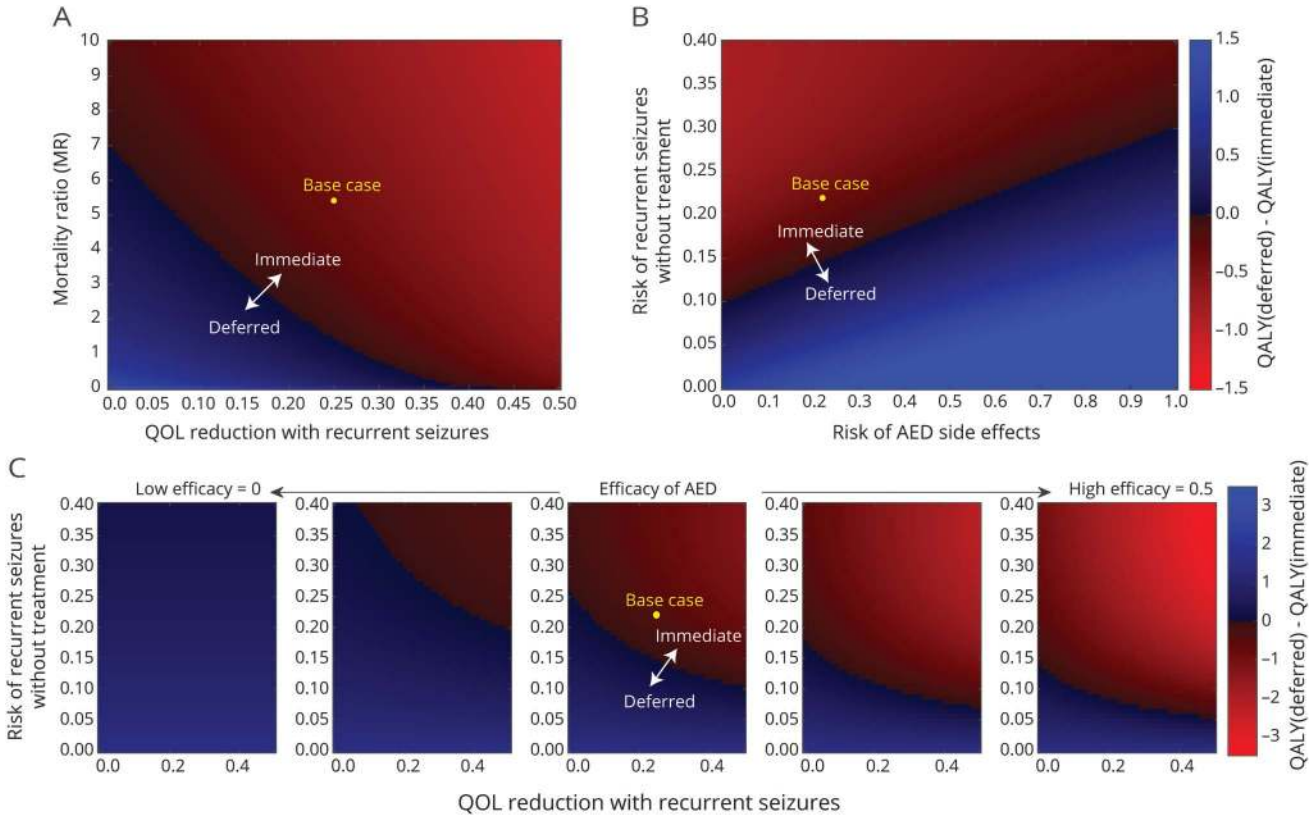
Figure 3 One-way sensitivity analyses



One-way sensitivity analyses of quality-adjusted life-years (QALYs) for (A) QOL reduction with recurrent seizures, (B) QOL reduction with antiepileptic drug (AED) side effects, (C) annual risk of recurrent seizures without treatment, (D) efficacy of AED, and (E) mortality ratio. Blue and red solid lines indicate how QALY varies with the measurement of interest in patients undergoing the deferred vs immediate AED treatment, respectively, with all other measures held fixed. The green dashed line indicates the measure for base case 1, and the gray dashed line indicates the threshold at which deferred and immediate treatments are equally preferred.

efficacy. These results also highlight the importance of considering QOL reduction from recurrent seizures: for base case 1, if recurrent seizures reduce QOL by only 0.1 and AED efficacy is kept constant at 0.75 (third box in figure 4C), a recurrent seizure risk of 20.0% is needed to favor immediate AED treatment, whereas if the QOL reduction with recurrent seizures is increased to 0.5, recurrent seizure risk needs to be only 9.6% to favor immediate AED treatment. These translate into 10-year seizure recurrence rates of 48.64% and 26.35%, respectively, both of which still fall below the current ILAE guideline of 60% for diagnosis of epilepsy in patients after a first unprovoked seizure.

Figure 4 Two- and 3-way sensitivity analyses



(A) Two-way sensitivity analysis indicating the favored decision for patients with differing levels of quality of life (QOL) reduction from recurrent seizures (x-axis) and seizure-associated mortality ratios (y-axis). In all panels, the yellow point marks base case 1, and the blue and red regions delimit the combinations resulting in greater quality-adjusted life-years (QALYs) with deferred vs immediate antiepileptic drug (AED) treatment, respectively. (B) Two-way sensitivity analysis indicating the favored decision for patients with varying risk of AED side effects (x-axis) and risk of recurrent seizures without AED treatment (y-axis). (C) Three-way sensitivity analysis indicating the favored treatment for patients with differing seizure recurrence rate (y-axis), level of QOL reduction from recurrent seizures (individual x-axes within each subplot), and AED efficacy (x-axis spanning all subplots).

Discussion

Decision analysis is a principled framework for identifying the optimal intervention among competing alternatives and determining which measures contribute most to decision outcomes. The decision to begin AED therapy after a first seizure depends on at least 4 overarching considerations: (1) the probability of further seizures without AED treatment, as ascertained by neuroimaging, EEG, and medical history; (2) the effectiveness of AED treatment at preventing recurrent seizures; (3) the probability and degree of harm expected if seizures do recur; and (4) the probability and degree of harm expected from AED-related side effects. While most physicians consider these factors when deciding whether to prescribe AEDs after a first seizure, without an explicit guiding framework, decision making remains qualitative and subject to cognitive biases.[22,23]

We hypothesized that the seizure recurrence threshold above which immediate AED therapy provides a net expected benefit is in many cases substantially below the current ILAE-recommended threshold of 60% over 10 years. To test this hypothesis, we constructed a Markov decision model to perform a simulated clinical trial over the lifetime of 3 base cases, starting from a first unprovoked seizure.

Our analysis centered on 3 base cases representing patients with a first seizure across a spectrum of seizure risk, effect of recurrence on QOL, and risk of AED side effects. Base case 2 represented a scenario in which immediate AED therapy would currently be strongly recommended as a result of a high risk of recurrent seizures, and our simulation favors immediate AED therapy, consistent with expectations. Base case 3 represented a scenario in which current definitions would operationally classify as epilepsy, but immediate AED therapy would be intuitively discouraged because of the patient's high risk of AED adverse effects and a minimal expected increase in QOL; our model is again consistent with this expectation, favoring deferred AED treatment. For base case 1, representing a typical patient with a first seizure with no particular risk factors for recurrent seizure other than having had a first seizure, our model favors immediate AED therapy, even though this patient fails to meet the ILAE current definition of epilepsy.

Together, these data suggest that the current ILAE definition of epilepsy, which relies on baseline recurrent seizure risk

alone to define epilepsy after a first unprovoked seizure, is too simplistic for deciding whether to start or withhold AED treatment. Our decision analysis shows that immediate AED treatment may provide a net benefit to patients after a first unprovoked seizure even if they have relatively low risk for recurrent seizure (base case 1) and that a high baseline risk for recurrent seizures does not by itself always favor immediate AED treatment (base case 3). Therefore, a more precise and patient-personalized definition of epilepsy should encompass not only seizure recurrence probability but also a multitude of other risks and benefits associated with AED treatment.

Because the decision to administer AED therapy is intrinsically tied to the operational definition of epilepsy, we closely examined the factors leading to the current definition of epilepsy. In 1991, a seminal report defined epilepsy as a clinical manifestation requiring 2 unprovoked seizures occurring at least 24 hours apart.[24] However, the ILAE found this definition inadequate in several clinical cases and revised it in 2013 to allow a diagnosis of epilepsy after a single unprovoked seizure if the risk for recurrent seizure is at least 60% over the next 10 years. This 60% threshold was obtained from a 1998 study estimating multiseizure recurrence rates over 5 years.[25]

Since the formulation of the ILAE definition of epilepsy, however, several studies have offered new insights into various factors surrounding epilepsy treatment and epidemiology.[2,6,7] Our analysis applied these data to evaluate the decision to prescribe AED therapy from a more holistic perspective, taking into account not only seizure recurrence risk but also the effects of recurrent seizures, AED therapy, and AED adverse effects on patient QOL. Factoring in these additional variables, we find that even in a patient with a low risk of recurrent seizures (base case 1), immediate AED therapy is favored to produce greater QALYs over a wide range of clinical measures. The current ILAE guideline of a 60% 10-year seizure recurrence rate for epilepsy diagnosis in patients with a first seizure is >1.5 times higher than the threshold recurrence rate (38.0%) that our model predicts to favor immediate AED therapy.

Our model assumes that a patient will remain on AEDs once started, even if the patient experiences adverse effects. Taking AEDs and experiencing AED adverse effects come with QOL costs (table 1), so patients who have gone many years without seizure recurrence may discontinue AEDs to eliminate this burden of medication. Therefore, our assumption of lifetime AEDs likely overestimates the cumulative QOL cost of immediate treatment. However, even with this conservative assumption, our model still predicts higher QALYs for immediate AED treatment for base case 1. This further strengthens our finding that immediate treatment is preferable to deferred AED treatment for patients similar to base case 1 in a practical clinical setting.

A major limitation of our study is that we did not directly derive primary estimates for our model measures but instead obtained them from previously published clinical data.[2,6,7] For example, most of our estimates for QOL were adapted from a single study that obtained preference-based QOL values acquired from patient interviews.[7] In addition, our calculation of the utility of AED adverse effects was derived from a study comparing AED adverse effects in patients over a 3-month period, which may not be fully generalizable to the side effects of longer-term AED use. Despite accounting for measurement uncertainty via sensitivity analyses, we acknowledge that there is still substantial interindividual variation in QOL perceptions that can exceed our measured sensitivity thresholds, and this must be considered when our analytic framework is applied to any specific patient.

Inaccurate estimates of recurrent seizure probabilities may also bias the results of the model. However, sensitivity analyses for this variable showed that immediate AED treatment would be favored for patient 1 until the 10-year cumulative seizure recurrence rate drops below 38.0%, which is lower than most epidemiologic observations.[2,15,25] Furthermore, the estimates of AED efficacy of our model were based on a previous study that reported data from patients who took primarily carbamazepine or valproate.[2] We anticipate that as newer US Food and Drug Administration–approved AEDs offer improved efficacy and reduced adverse effects tailored to different patient populations, the threshold for immediate AED treatment after a first seizure will decrease even further from that of our current model.

Going forward, our model can be improved by incorporating how AED efficacy, adverse side effects, patient depression, and other variables alter AED adherence, which have been shown to have effects on seizure-associated mortality.[26–28] With additional epidemiologic and imaging data available in the future, our model could also be further personalized with variables for different types of seizures (e.g., generalized tonic-clonic, generalized absence, focal simple partial) and choice of AED (including polytherapy).[29,30] Finally, our model can be adjusted to account for additional patient factors that could influence choice of intervention such as genetic profiling,[31,32] machine learning–driven treatment outcome prediction,[33] treatment affordability,[34] and pregnancy planning.[35] Overall, the base model presented here is customizable and can be adapted to a wide range of clinical cases in the future, offering the potential to inform personalized therapies for epilepsy.

Using a decision model with measures constructed from retrospective clinical data, we provide quantitative evidence favoring the use of immediate AED therapy in adult patients after a first unprovoked seizure over a wide, clinically relevant range of pertinent clinical factors. This finding may have important therapeutic implications for seizure management.

Author contributions

Erik L. Bao, Ling-Ya Chao, and Peiyun Ni: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis. Lidia M.V.R. Moura, Andrew J. Cole, Sydney S. Cash, and Daniel B. Hoch: critical revision of

manuscript for intellectual content. Matt T. Bianchi and M. Brandon Westover: study concept and design, critical revision of manuscript for intellectual content.

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Disclosure

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