Considerations in the Treatment of a First Unprovoked Seizure

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ABSTRACT

Treatment issues following a first unprovoked seizure are discussed, using an approach that emphasizes weighing the relative risks and benefits of the therapeutic decisions. The majority of children and adults who present with a first unprovoked seizure will not experience further seizures. Both seizures and the therapies available carry some risk, and optimal patient care requires careful balancing of these risks and benefits. Treatment with antiepileptic drugs reduces recurrence risk but does not alter long-term prognosis. In general, treatment should be deferred until a second seizure has occurred. Whatever the decision, it should be made jointly by the medical providers and the patient and family after careful discussion, including assessment of risk and impact of seizure recurrence. Providing appropriate education and counseling to patients and families may be the most important aspect of treatment of a first unprovoked seizure.

KEYWORDS: First seizure, unprovoked seizure, recurrence risk

Preventing seizure recurrence is a concern well summarized by Gowers: "The tendency of the disease is to self perpetuation; each attack facilitates the occurrence of another, by increasing the instability of the nerve elements."[1] A significant challenge in addressing the treatment of a first unprovoked seizure is to examine this fear in light of the available evidence about seizure recurrence and long-term outcome. The decision to treat or not to treat the first unprovoked seizure has important implications for health and quality of life. In an era of increasing awareness and concern about medication side effects, the impact of initiating potentially long-term therapy may be substantial. Alternatively, the possibility that each seizure may increase the risk of subsequent seizures and development of epilepsy suggests a mandate of initial aggressive therapy.

This article reviews the clinical decision-making following a first unprovoked seizure, in particular with regard to initiating antiepileptic drugs (AEDs). The risks and benefits of initiating AED therapy are addressed in the context of an individualized therapeutic approach that emphasizes weighing the risks and benefits of drug therapy versus both the statistical risk of another seizure and the consequences of such an event.

FIRST UNPROVOKED SEIZURE: DEFINITION AND RECURRENCE RATE

Approximately one third to one half of children and adults with seizures will present following a single seizure.[2,3] The exploration of the treatment of a first unprovoked seizure requires an understanding of the natural history and prognosis of the disorder in this setting. As defined by the International League Against Epilepsy (ILAE), a first unprovoked seizure is a seizure occurring in a person over 1 month of age with no prior history of unprovoked seizures.[4] The definition excludes neonatal seizures, febrile seizures, or seizures in the

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setting of acute precipitating causes such as head trauma, infection, or metabolic derangements.

In ~10 to 12% of cases, the first unprovoked seizure will be status epilepticus (SE; seizure with duration ≥30 minutes or a series of seizures lasting ≥30 minutes without regaining of consciousness in between).[4–7] A seizure flurry occurring within 24 hours with return to baseline between seizures is typically considered to represent a first seizure, in accordance with ILAE guidelines.[4]

Recurrence Rate

The recurrence rate after a first seizure is reported to range from 27 to 52% in studies that carefully exclude those with prior seizures.[5,7–19] It is very difficult to do prospective population-based studies of first seizures, as many first seizures are unrecognized and/or unwitnessed, and the majority of patients do not present for medical attention unless the first seizure is convulsive. Therefore, many population-based studies rely on retrospective identification, a fact that limits the results. In two meta-analyses, recurrence rates in prospective studies (40% at 2 years) were reported to be lower than retrospective studies (51 to 52% at 2 years).[9,20]

There are now several large prospective Class 2 studies in both children and adults.[5,7,18–24] Studies that are prospective have shown remarkably similar recurrence risks of ~50% without treatment. This is especially true of the more recent prospective studies where many patients were not treated following the first seizure.[23] Recurrence rates are influenced by the duration of follow-up. In one prospective study with long-term follow-up, the cumulative risk of a second seizure was 29%, 37%, 43%, and 46% at 1, 2, 5, and 10 years, respectively.[25] In another study, untreated individuals had recurrence rates of 26%, 39%, 51%, and 52% at 6 months, 2, 5, and 8 years, respectively.[23] In many studies, 50% of recurrences occur within 6 months of the initial seizure,[5,9] and overall, 80% of the 5-year recurrence risk appears to be realized by 2 years after the initial seizure.[9,20]

Recurrence Risk after a Seizure Flurry

As discussed above, the ILAE definition of a first unprovoked seizure includes a seizure flurry occurring within 24 hours with return to baseline between seizures.[4] While this decision has been debated,[25–27] the majority of studies have found no difference in recurrence risks in children or adults who present with a cluster of seizures in 1 day compared with those who present with a single seizure. Furthermore, studies of adults with refractory partial epilepsy being evaluated for epilepsy surgery in monitoring units demonstrate that seizure flurries or clusters do not represent independent seizures,[28] thus supporting the concept that a first seizure event presenting as a seizure flurry can be considered a single seizure.

FIRST UNPROVOKED SEIZURE: TO TREAT OR NOT TO TREAT?

Formulating the decision about whether to initiate AED therapy after a first unprovoked seizure requires that the physician integrate aspects of the history and neurological examination with results of testing. Utilizing these features in the framework of available literature, the clinician will be able to present a recommendation that fairly accurately reflects the patient's risk of seizure recurrence.

Risk Factors for Recurrence

It appears clear that certain factors increase the risk of seizure recurrence, particularly etiology, electroencephalogram (EEG) findings, and sleep state at the time of the initial seizure. Other factors, such as age of onset, the duration of the initial seizure in children, and multiple seizures at first seizure presentation, do not confer a higher risk of recurrence.[24]

ETIOLOGY

A remote symptomatic first seizure confers a higher recurrence risk than a cryptogenic first seizure, for both children and adults.[9,14,19,25,29] In fact, a first remote symptomatic seizure is associated with a higher risk of recurrence, a higher risk of multiple recurrences, and a lower probability of long-term remission.[30] The occurrence of a first idiopathic unprovoked seizure, defined as a first seizure associated with a consistently abnormal EEG,[31,32] confers a recurrence risk comparable to the risk following a remote symptomatic first seizure.[25]

EEG

The EEG is an important predictor of recurrence, particularly in cases that are not remote symptomatic and in children.[5,7,9,10,13–15,21,22,25,29,33] All studies of recurrence risk following a first seizure in childhood report that the presence of an abnormal EEG confers a higher recurrence risk than a normal EEG.[5,9,10,14,22,24,25,29,33] Some studies report that only epileptiform abnormalities increased the recurrence risk in children,[10] while in others, any clearly abnormal EEG pattern, including generalized spike and wave, focal spikes, and focal or generalized slowing, increased the risk of recurrence in cases that were not remote symptomatic.[25,33] The risk of seizure recurrence by 24 months for children with an idiopathic/cryptogenic first seizure in our study[25,33] was 25% for those with a normal EEG, 34% for those with nonepileptiform abnormalities, and 54% for those with epileptiform abnormalities.

In adults, most studies find an increased recurrence risk associated with an abnormal EEG,[9,13,34–36] although one study found that only generalized spike and wave patterns, not focal spikes, were predictive of recurrence.[7]

SLEEP STATE

Both sleep state and time of day are associated with differential recurrence risks. For children, being asleep during a first seizure (whether the sleep is a daytime nap or night-time sleep) is associated with a higher recurrence risk.[25,37] In our series, the 2-year recurrence risk was 53% for children whose initial seizure occurred during sleep compared with 30% for those whose initial seizure occurred while they were awake.[25] In adults, seizures that occur at night are associated with a higher recurrence risk than those that occur in the daytime.[22] From a therapeutic point of view, the implication of a seizure in sleep is unclear. While the recurrence risk is higher, recurrences will tend to occur in sleep,[37] which is associated with a lower morbidity than is a daytime seizure.

THE ROLE OF AED THERAPY IN RECURRENCE RISK

Over the past 20 years, the practice of routinely treating with AEDs after a first seizure has evolved to a more empirically based paradigm. In this setting, it has been possible to report on larger numbers of patients who are not treated with AEDs after they present with a seizure. Nonrandomized studies examining both treated and untreated patients have tended to report a higher recurrence risk in the setting of treatment[13,19]; however, the clinical decision to treat may well represent the presence of prognostic factors associated with increased recurrence rates, as discussed here.

Several randomized clinical trials in children and adults have assessed the role of treating a first seizure.[11,12,17,23,38–41] These studies are summarized in Table 1. Across studies, treatment after a first seizure appears to lower the risk of a seizure recurrence by 50%, yet this treatment does not affect the long-term outcome of epilepsy. In the FIRST seizure trial group, where the cumulative risk of seizure recurrence for treated and untreated patients was 25% and 51%, respectively,[17] the number of patients needed to treat to attain one remission would be four.[20] In the more recent Multicentre Trial for Early Epilepsy and Single Seizures (MESS), immediate treatment after a first unprovoked seizure reduced the risk of recurrence from 50 to 25%, but similarly did not provide a measurable effect on long-term outcome. The effect of treating a first seizure reduced the chance of a 2-year remission by 2 years, but this effect was lost by 4 years. In this trial, the number of first seizure subjects needed to treat to attain one remission was 14.[23] In general, the accumulating evidence from these studies indicates that AED therapy is effective in reducing the risk of a recurrent seizure but does not alter the underlying disorder, and therefore does not change long-term prognosis.[42]

Current recommendations tend toward waiting for a second seizure before initiating treatment, particularly in adults.[23,38] A practice parameter was issued from the American Academy of Neurology on AED therapy following a first seizure in children and adolescents.[43] This parameter recommends that: treatment with AEDs is not indicated for the prevention of the development of epilepsy, and treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacological and psychosocial side effects. A practice parameter addressing this issue in adults is currently under development by the American Academy of Neurology.

Risks of Treating

An important consideration in the decision about treating after a first seizure is that AEDs, while effective in controlling seizures, are associated with a variety of significant side effects. Idiosyncratic and acute adverse events sufficient to require discontinuation of the drug occur in 15% or more of patients newly treated with an AED, and must be considered when deciding whether to initiate AED therapy.[44] Chronic toxicity is a further concern in both children and adults, including cognitive and behavioral effects,[45] bone loss,[46] and neuropathy,[47] among others. Furthermore, for women of childbearing age, including adolescents, a discussion of the risks of treatment must include consideration of the potential teratogenicity of these compounds.[48]

A hidden side effect of continued AED treatment is that of being labeled. The person with a single seizure who is off medications is considered to be healthy by both him- or herself and society. That individual can lead a normal life with very few restrictions, and in fact, rarely needs to disclose having had a seizure, unless he or she chooses to. In contrast, even if the patient only had a single seizure, being on AED therapy implies chronic illness to both the patient and those around him or her.[49]

Risks of Not Treating

MEDICAL AND PSYCHOSOCIAL IMPACT

The major risk associated with not treating a first seizure is experiencing a seizure recurrence, as evidence indicates that immediate treatment will reduce the risk of a recurrent seizure by 50% (see above). The potential consequences of the seizure recurrence include both direct consequences, such as injury, and psychosocial impact. Serious injury from a brief seizure is a relatively

Table 1 Randomized Clinical Trials on the Treatment of the First Unprovoked Seizure

Author(s), Year	Setting	Population (N)	Drug and Comparator (N)	12-month Recurrence (%)	1-year Remission (%)	2-year Remission (%)	5-year Remission (%)	Notes
Camfield et al (1989)[11]	Population-based pediatric neurology service	31 children	CBZ 10–20 mg/kg/d (14) No meds (17)	CBZ (14) No meds (53)	—	Treated (80) No meds (88)	—	CBZ stopped for adverse events in 4 patients Somnolence (14%) Rash (14%)
Chandra (1992)[39]	University and private hospitals	228 adults	VPA 1200 mg (115) Placebo (113)	Placebo (4) VPA (56)	—	—	—	VPA adverse events: gastrointestinal (3%); weight gain (4%); hair loss (2%)
FIRST (1993)[17]	University and general hospitals	387 aged 2–70 years	PB 15–40 mg/mL (103)	Treated (17)	Treated (93)	Treated (81)	Treated (64)	Treatment stopped for adverse events in 14 patients
Musicco et al (1997)[38]			CBZ 4–10 mg/mL (63)	No meds (28)	No meds (90)	No meds (78)	No meds (63)	
Leone et al (2006)[41]			VPA 50–100 mg/mL (33) PHT 10–20 mg/mL (5) No meds (193)					
Gilad et al (1996)[40]	Hospital emergency department	91 aged 18–50 years	CBZ 10 mg/kg/d (46) No meds (45)	Treated (13) No meds (59)	—	—	—	20% switched to VPA
Das et al (2000)[12]	Neurology outpatient service	76 children and adults	Treated (36) No meds (40)	Treated (11) No meds (45)	—	—	—	—
Marson et al (2005)[23]	UK and non-UK centers	812 children and adults	CBZ (328) VPA (325) PHT (25) LTG (19)	Treated (27)* No meds (34)*	—	Treated (95) No meds (96)	—	Adverse events: immediate treatment (39%); deferred treatment (35%)

*Estimated with approximation.
CBZ, carbamazepine; VPA, valproate; PB, phenobarbital; PHT, phenytoin, UK, United Kingdom; LTG, lamotrigine.
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uncommon event usually related to the impairment of consciousness or loss of consciousness that occurred at an inopportune time or place (driving a car or riding a bicycle, swimming, on a stairway, cooking, etc.). These are much less likely to occur in children who are usually in a supervised environment and are not driving, operating heavy machinery, or cooking. In the MESS trial, injuries occurred more frequently in the immediately treated than in the deferred group,[23] implying that treatment with AEDs does not protect against injury. In fact, most reports of serious injuries in patients with epilepsy discuss patients with intractable epilepsy who experience injuries, such as burns, in the context of frequent seizures.[50,51]

Another potential risk of not treating is the risk of SE, particularly in adults who sustain a higher morbidity with SE than children. It should be noted that the risk of SE in the population of patients with a first seizure is low and essentially limited to those who have had it before.[52] Therefore, consideration should be given for initiating AED treatment after a first unprovoked seizure presenting as SE, particularly in adults.

While a seizure may be a dramatic and frightening event, the long-term psychosocial impact of an isolated seizure in children is minimal. In adults, the psychosocial impact can be more serious and include the loss of driving privileges and possible adverse effects on employment.[53,54] The social stigma of seizures is also much more a concern in adolescents and adults.

TREATING TO PREVENT THE DEVELOPMENT OF EPILEPSY

The theoretical risk of not treating a first seizure is the possibility that each seizure may contribute a progressive epileptogenic process. However, there is no convincing evidence that a brief seizure causes brain damage.[43,55,56] Furthermore, current epidemiological data and data from controlled clinical trials indicate that treating a first seizure does not alter the long-term prognosis of epilepsy.[17,23,38,43,56–58] Most recently, the 5-year outcome in the MESS trial was not different for the immediate versus delayed treatment group.[23] Prognosis is primarily a function of the underlying epilepsy syndrome, and while treatment with AEDs does reduce the risk of subsequent seizures, it does not appear to alter the long-term prognosis for seizure control and remission.[15,38,43,58,59]

Treatment after Two Seizures

The issue of treatment after two seizures in adults is fairly straightforward. In an early adult study,[7] the 70% recurrence risk after a second seizure led to the conclusion that treatment with AEDs is appropriate once a second seizure has occurred. In children,[24] the overall recurrence risk of ~70% after a second seizure was higher in those with a remote symptomatic etiology and in those whose second seizure occurred within 6 months of the first. Once the second seizure had occurred, EEG abnormalities and sleep state at the time of the seizure were no longer associated with a differential risk of further seizures. However, many children have idiopathic self-limited syndromes, such as benign rolandic epilepsy, in which the need for treatment has been questioned.[55,60,61] Thus, the decision to treat children with cryptogenic/idiopathic seizures who have a second attack must consider whether a benign self-limited syndrome is present, as well as the frequency of the seizures and the relative risks and benefits of therapy.

TREATMENT STRATEGIES FOLLOWING A FIRST UNPROVOKED SEIZURE

Assess Measurable Risk of Recurrence

As discussed above, recurrence risk can be estimated based on known features. Several studies have combined risk factor analysis to present risk allocation models for seizure recurrence, including Camfield and colleagues,[10] who utilized EEG, abnormal neurologic examination, and seizure classification, and the MESS trial[23] researchers, who included etiology, total number of seizures at time of randomization, and the presence of an abnormal EEG in their regression modeling. Even without utilizing these models, a clinician can assess that the risk of recurrence is significantly higher in the setting of brain dysfunction as evidenced by history, physical examination, and EEG, than in the setting of an idiopathic seizure.

Integrate Additional Considerations

Certain additional considerations may affect the treatment decisions. For example, a first episode of SE in an adult may warrant immediate treatment, as the potential benefit of reducing the risk of even a single recurrence is high. Patients whose employment will be affected by a second seizure, for example, those whose jobs involve driving and for whom the "clock" restarts with every seizure, may also be candidates for early treatment. Furthermore, certain patients or families have a very low risk tolerance, either for medication initiation or for seizure, and these personal preferences will need to be addressed.

Counsel Patients and Families

Once the clinician has arrived at a recommendation, the most important work begins. Treatment of a first unprovoked seizure must include appropriate education and counseling to patients and families, as both seizures and AED therapy are associated with some risks. Education assists the patient and family in making an

Table 2 Counseling Discussion Topics after a First Unprovoked Seizure

Recurrence risk
Risks versus benefits of antiepileptic drug initiation
Injury prevention/first aid
Driving restrictions
School/employment considerations
Recreational activity

informed decision, helps them to fully participate in the plan of care, and prepares them to deal with the psychosocial consequences of the diagnosis. The discussion must be comprehensive, including first aid measures in case of a recurrence, potential adverse effects of AEDs, risks of recurrence, impact of delaying therapy until after a second seizure on long-term prognosis, and restrictions on activity that will occur with or without therapy. This discussion is best accomplished in the outpatient setting, and preferably when key information on recurrence risks, such as the results of EEG and imaging studies, are available.

Patients and families need to be reassured that the risk of a serious injury or death from an isolated seizure is low. They also need to be counseled about appropriate first aid for seizures and safety information. For adults, a particular challenge is risks in the workplace, including jobs that involve heavy machinery, stoves, or working at heights. Places of employment may or may not be accommodating to the person at risk for a seizure. Adults and adolescents will also need specific instructions regarding driving. When treating children, a discussion of possible restrictions of activities is also important. Most of the child's activities can be continued, although some, such as swimming, may need closer supervision. Counseling often allays fears and educates the patient and family on safety precautions. Educational programs are available for school personnel—teachers, nurses, and students—and information for babysitters is also readily available. Note that, in the case of the child or adult with a first seizure, this discussion is equally applicable whether or not one decides to initiate AED therapy, as therapy reduces but does not eliminate the risk of seizure recurrence.

Patients and families will usually be interested in information that will help them manage the illness or specific problems. While more time-consuming than issuing a prescription, this counseling is necessary for both informed decision-making and for favorable long-term outcomes. A list of recommended topics for discussion is provided in Table 2.

CONCLUSIONS

Well-designed prospective studies of the recurrence risk after a first unprovoked seizure in children and adults show recurrence risks in the 40 to 50% range. Risk factors for recurrence appear consistent across study populations, including children and adults. These risks include seizure etiology, with highest recurrence risk associated with remote symptomatic or idiopathic etiology, and EEG abnormalities of any type, though the impact of an abnormal EEG may be higher in children. It is now clear that treatment following a first unprovoked seizure, while reducing recurrence risk, does not alter prognosis and as a result is usually not indicated. Therefore, given the consequences of long-term drug therapy and its lack of effect on long-term prognosis following a first seizure, the authors generally do not recommend treatment following a first unprovoked seizure in either children or adults.

The approach presented in this article emphasizes that both seizures and the therapies available carry some risk, and that optimal patient care requires careful balancing of these risks and benefits. Assessment of risk requires not only ascertaining the statistical risk of a seizure recurrence or of an adverse event, but also the consequences of such an event. Individual patients and clinicians place different values on different outcomes and on the acceptability of certain risks. Whatever the decision, it should be made jointly by the medical providers and the patient and family after careful discussion.

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