**An evidence-based approach to the first seizure**

*Samuel Wiebe, †José F. Téllez-Zenteno, and †Michelle Shapiro

*Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada; and †Division of Neurology, Department of Medicine, University of Saskatchewan, Saskatoon, Canada

**SUMMARY**

Evidence-based care (EBC) is an explicit approach to applying the best evidence to the care of individual patients. We outline the basic principles of EBC and apply them to various clinical questions pertaining to a patient presenting with a first seizure, providing a summary of the best available evidence for each question. Depending on the question at hand, the evidence derives from retrospective, prospective, and randomized controlled studies in children and adults. There is solid evidence that early seizure recurrence is reduced by early initiation of AEDs. A meta-analysis of six randomized trials revealed an average absolute risk reduction of 34% (95% CI 15–52) with AED therapy. However, the prognosis for the development of epilepsy is not altered by early intervention. EEG epileptiform abnormalities, family history of epilepsy, imaging lesions, and remote symptomatic seizures increase the risk of recurrence, and impact the risk–benefit ratio of treatment after a single event. In the end, clinicians must evaluate patients with a first unprovoked seizure on a case-by-case basis to determine the appropriateness of treatment with a given AED.

**KEY WORDS:** Single seizure, Single unprovoked seizure, Epilepsy, Treatment, Diagnosis.

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**OVERVIEW OF THE EVIDENCE-BASED CARE PROCESS**

The clinical encounter with a patient with a first, unprovoked seizure generates numerous important questions. For example, what is the differential diagnosis? What is the diagnostic and prognostic usefulness of EEG, and imaging? What is the yield of routine blood work? What is the prognosis for recurrence? Should one recommend antiepileptic drug (AED) treatment? What are the implications for work and driving? Clinicians answering these questions must draw on the best available evidence, interpret it in the context of their clinical experience and the problem at hand, and apply it according to the patient’s preferences and values. Evidence-based care (EBC) is an explicit approach to conscientiously and judiciously apply the best external evidence to the management of individual patients. Briefly, EBC entails the following steps: (1) stating the clinical problem at hand in the form of a defined, answerable question; (2) efficiently searching the literature for the best evidence; (3) critically appraising the evidence for its validity and usefulness; and (4) applying the evidence in the context of the patients’ circumstances and values. Here we outline the basic principles of EBC and apply them to various clinical questions pertaining to a patient presenting with a first seizure, providing a summary of the best available evidence for each question. Our aim is to illustrate for clinicians how evidence-based medicine principles can be applied to a common clinical scenario.

**Asking focused questions**

A critical aspect of applying evidence to individual patients entails asking answerable, focused questions. Focused questions allow clinicians to search the literature efficiently and with maximum yield. Experts of the EBC process suggest that answerable questions have four elements that can be used in the literature search strategy to find relevant evidence (Richardson et al., 1995). The four elements are: (1) patient (e.g., basic patient characteristics, including age, type of seizures, and risk factors), (2) intervention (e.g., the passage of time in the case of prognosis, or anticonvulsants in the case of therapy), (3) comparison (e.g., treatment versus placebo or no treatment), and (4) outcome (e.g., seizure recurrence). The mnemonic for this is PICO. For example, if our question is “Should adults presenting with a first seizure receive anticonvulsant therapy?” the focused
Table 1. Elements of scientific validity for articles addressing different clinical questions

<table>
<thead>
<tr>
<th>Question about</th>
<th>Criteria for validity</th>
</tr>
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| Diagnosis      | 1) Spectrum of population in whom diagnosis is in question  
2) Independent (blind) assessment of test and of gold standard  
3) Test and gold standard are applied to all individuals irrespective of results |
| Therapy        | 1) Patients are allocated to treatment groups in a random fashion, and the randomization sequence is concealed  
2) All patients who entered the trial are accounted for  
3) Patients in different groups are similar at baseline |
| Harm           | 1) Patient and control groups are clearly identified, and are similar in all important aspects  
2) Exposures and outcomes are assessed in the same manner and are clearly defined  
3) Follow-up is sufficiently long, and assessment of outcomes is done independently |
| Prognosis      | 1) Population of interest is representative and at a similar, well-defined point in the course of the disease  
2) Follow-up is sufficiently long and complete  
3) Assessment of outcomes is done independently |

Modified from Oxman et al. (1993).

(PICO) question would be: (1) adults with a first convulsive seizure (P); (2) anticonvulsants (I); (3) no anticonvulsants (C); (4) seizure recurrence (O). Using these four elements in combination increases the chances of finding relevant articles.

Finding the best evidence

The degree to which our clinical question is focused will determine the nature and effectiveness of our literature search. Standardized approaches to searching the literature are widely available. For example, PubMed’s Clinical Queries has a search engine that can focus on clinical questions about therapy, prognosis, etiology, and diagnosis, with options for a broad (sensitive) or narrow (specific) search (http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml - accessed July 25, 2007).

Appraising the evidence for validity and usefulness

For any clinical question, there is a hierarchy of evidence, ranging from the most to the least valid or credible. The most scientifically valid evidence derives from rigorous clinical research with little opportunity for bias or error, while the least valid evidence derives from unsystematic and anecdotal reports. Table 1 provides basic elements of scientific validity for different types of clinical questions (Oxman et al., 1993)

Applying the evidence to the patient at hand

Clinicians must be able to obtain from the literature meaningful summary results that can be applied to individual patients. Examples include risk difference, numbers needed to treat, and relative risks. Bussiere and Wiebe (2005) provide an extensive discussion on how to apply various metrics of outcome to the care of individual patients. In the following sections, we address the broad issues relating to the first seizure using the EBC principles outlined above.

INCIDENCE OF UNPROVOKED SEIZURES

Approximately 10% of the population will have at least one seizure at some point in their life (Berg & Shinnar, 1991). Half of these will occur during childhood and adolescence, and the highest risk is before age 1 year (Pohlmann-Eden et al., 2006). In a classic, retrospective cohort study in Rochester, MN, U.S.A., the incidence of all unprovoked seizures was 63 per 100,000 and the incidence of epilepsy was 48 per 100,000 between 1975 and 1984 (Hauser et al., 1993). In the United Kingdom, a study involving 13 general practice settings between January 1005 and June 1996 found an incidence of all unprovoked seizures of 57 per 100,000, while that of epilepsy was 46 per 100,000, and of a single seizure was 11 per 100,000 (MacDonald et al., 2000). Reports of incidence in children and adult from northern Sweden showed an incidence of all unprovoked seizures was 60 per 100,000 (Forsgren et al., 1996) (Sidenvall et al., 1993). In a recent, well-conducted prospective study in Iceland, the incidence of first unprovoked seizures was 56.8 per 100,000, 23.5 for single unprovoked seizures, and 33.3 per 100,000 for epilepsy (Olafsson et al., 2005). In summary, the incidence of unprovoked seizures ranged from 50 to 70 per 100,000 with higher prevalence in children younger than 1 year and adults older than 65 years.

THE RISK OF A SECOND SEIZURE AND RISK FACTORS

In a meta-analysis of 13 studies involving 1930 patients (Berg & Shinnar, 1991), the recurrence risk for seizures at or near 2 years was 36% and 47% in prospective and retrospective studies, respectively. Abnormalities on examination and on EEG, partial epilepsy predicted a second seizure. The studies had important variation in methodology. However, between 1 and 5 years the rate of recurrence
predictive model, validation is needed in a separate study. Anticonvulsants are not warranted. As with any high risk. Their message is that in patients with low risk recurrence, 2 points score ranges from 0 to 4 points; 0 points = low risk of seizures and can influence the decision to start AEDs. For example, epidemiological data show that most patients with a single unprovoked seizures are between 16 and 60 years old (average 40) (van Donselaar et al., 1992) (Hopkins et al., 1988; Musicco et al., 1997). Thus, patients younger than 12 years and also the elderly could have a higher risk of recurrent seizures. A positive family history, the antecedent of febrile seizures (Hauser et al., 1990; Offringa et al., 1994), the presence of two or more unprovoked seizures, and the initial suspicion of epilepsy are other markers of recurrence (Hauser et al., 1998). Similarly, the presence of an etiology and an initial abnormal exam have been associated with a higher risk of recurrence (Hauser et al., 1998; Shinnar et al., 2000; Kalita et al., 2005). Finally, some studies have not found any risk factors for recurrence (Pohlmann-Eden et al., 1994; Bora et al., 1995).

Based on data from a large, pragmatic randomized trial (Marson et al., 2005) of treatment of patients with a first seizure and newly diagnosed epilepsy, Kim et al. (2006) reported prediction rule to identify patients with various probabilities for seizure recurrence after a single unprovoked seizure. The index takes into account the past history of seizures (one seizure prior to presentation = 0 points, two or three seizures = 1 point, four or more = 2 points), the presence of neurological deficit, learning disability, or developmental delay (1 point for each of these characteristics) and abnormalities in the EEG (1 point). The final score ranges from 0 to 4 points; 0 points = low risk of recurrence, 2 points = medium risk, and 2–4 points = high risk. Their message is that in patients with low risk (0 points), anticonvulsants are not warranted. As with any predictive model, validation is needed in a separate study.

**Definition and Diagnosis of Seizures**

A distinction must be made between provoked and unprovoked seizures, since this has implications for treatment and prognosis. Provoked seizures are those that result from some immediately recognizable stimulus or cause, e.g., hypoglycemia, hyponatremia, and fever. Provoked seizures typically only recur in the presence of the acute cause and thus do not constitute epilepsy (Herman, 2004). In contrast, unprovoked seizures usually do not require an immediate precipitating event. The occurrence of an unprovoked seizure suggests the possibility of an underlying neurological disorder that may predispose patients to recurrent seizures (Herman, 2004). Unprovoked seizures have been classified as cryptogenic (no known cause), remote symptomatic (related to brain injuries or lesions), or idiopathic (probably genetic) (Commission on Epidemiology and Prognosis: International League Against Epilepsy, 1993).

The differential diagnosis of a single seizure includes psychogenic nonepileptic events, cardiac and neurogenic syncope, transient ischemic attacks, sleep disorders, panic attacks, complicated migraines, and rarely movement disorders (Raj & Sheldon, 2002; Alsaadi & Marquez 2005; Ebll, 2006). The role of laboratory investigations and imaging is addressed below.

The definition of epilepsy is being revised (Fisher et al., 2005) to extend to those patients with only one seizure in the presence of any factor that can predispose to future seizures. However, clinicians dealing with first seizure patients still need to decide whether such predisposing factors exist, and what the risk of recurrence is. Therefore, the concept of a single unprovoked seizure is most relevant to our discussion.

**Etiology, Imaging, and Risk of Recurrence**

Many studies have found a greater risk of seizure recurrence in patients with remote symptomatic seizures than in those with idiopathic seizures (Camfield et al., 1989; Berg & Shinnar 1991; Musicco et al., 1997). In the quantitative review of Berg (Berg & Shinnar, 1991), the lowest seizure recurrence risk was in the idiopathic group with normal EEGs (24%, 95% CI 19–29) and the highest risk was in the group with remote symptomatic seizures and abnormal EEGs (65%, 95% CI 55–76). In their randomized study, Musicco et al. noted that remote symptomatic and secondarily generalized seizures increased seizure recurrences over 1 or 2 years (Musicco et al., 1997).

In a first practice parameter published in 1996, imaging was considered as a part of the evaluation of patients with single unprovoked seizures (Quality Standards Subcommittee & American Academy of Neurology, 1996). This information contrasted with a second practice parameter for children with first unprovoked seizures where imaging was not recommended as standard of management (Hirtz et al., 2003). Studies that evaluate the role of CT or MRI in patients with single unprovoked seizures have shown various rates of abnormalities. Abnormal findings were reported in 17% (Das et al., 2000), 4% (Edmondstone, 1995), 47% (Forsgren et al., 1996), 1% (Hopkins et al., 1988), 11% (Hui et al., 2001), 29% (Schoenenberger & Heim, 1994), and 3% (van Donselaar et al., 1992). On average, these studies found clinically relevant abnormalities in approximately 10% of cases. The high rate of lesions identified in the cohorts of Forsgren and Schoenenberger (Schoenenberger & Heim, 1994; Forsgren et al., 1996) could be explained because of the prospective character of these studies. Additionally, Forsgren et al. (1996) used MRI to...
evaluate patients. MRI in the first seizure needs more exploration, although in selected cases and in nonemergent situations, MRI could be more sensitive than CT scan to detect abnormalities in patients with single unprovoked seizures (Greenberg et al., 1996; Hirtz et al., 2003; ACEP 2004).

**LABORATORY STUDIES IN SINGLE UNPROVOKED SEIZURES**

The information about laboratory investigations is conflicting. Traditionally some centers have recommended screening for uremia, hypoglycemia, drug intoxications, and electrolyte disorders. Importantly, these studies derive from emergency departments where the frequency of unprovoked seizures may be lower and that of acute provoked seizures may be higher, e.g., alcohol withdrawal, acute stroke, tumors, and electrolyte abnormalities (Turnbull et al., 1990; Sempere et al., 1992; Henneman et al., 1994; Tardy et al., 1995).

On the other hand, studies done outside of the emergency room setting question the utility of laboratory tests (Hopkins et al., 1988; Edmondstone, 1995). In these studies, the prevalence of abnormalities ranged from 0% to 15%, but rarely were they of clinical significance. An important empirical question that remains unanswered is the threshold at which the prevalence of an abnormality justifies routine performance of the test.

In summary, laboratory studies are useful in patients whose clinical features suggest underlying problems, e.g., persistent alteration of level of consciousness, fever, or focal neurological symptoms (Edmondstone, 1995). Specifically, patients from emergency departments should be tested, considering the higher prevalence of provoked seizures (Tardy et al., 1995).

**LUMBAR PUNCTURE AND TOXICOLOGICAL PROFILE**

Few studies have explored the utility of the lumbar puncture in single unprovoked seizures (Sempere et al., 1992; Henneman et al., 1994). These studies come from emergency departments in which lumbar punctures were done in patients with a potential infectious etiology (i.e., provoked seizures). In these studies, abnormalities were reported in up to 8% of studies. The information is scanty, and there is no evidence to support CSF examinations routinely in unprovoked seizures.

Seizures are reported as a consequence of drug intoxication, for example, secondary to tricyclic antidepressants, cocaine and other stimulants (Zaccara et al., 1990; Olson et al., 1993). Although some studies support performing a toxicological screen in patients with first seizures (Olson et al., 1993), no prospective well-conducted studies have been performed in this regard. Accordingly, a recent policy paper from the American Academy of Emergency Physicians does not recommend routine toxicological screening in the management of adult patients with seizures (ACEP, 2004). As a whole, the evidence does not support routine toxicological examinations for single unprovoked seizures.

**EEG AND RECURRENTCE RISK**

Epileptiform abnormalities in the EEG increase the chance of seizure recurrence. In the systematic review of Berg & Shinnar (1991), EEG abnormalities increased the relative risk of subsequent seizures by anywhere from 1.2 to 4.1 (15 studies). This result was nonsignificant in one study (Hopkins et al., 1988). The pooled relative risk of epileptiform abnormalities for recurrence was 2.0 (95% CI 1.6–2.6), while the relative risk of nonepileptiform abnormalities was 1.3 (95% CI 0.9–1.8). Hauser et al. (1990) found that only generalized spike-wave in the idiopathic group increased seizure recurrence. Finally, in randomized trials, Gilad et al. (1996) found no correlation between EEG abnormalities and seizure recurrence risk (p = 0.26 treated and p = 0.34 untreated). However, Muscicco et al. (1997) found that patients with epileptiform EEG abnormalities had more relapses but did not alter the probability of remaining seizure free for 1 or 2 years. Finally, Das et al. (2000) found that EEG abnormalities were predictive of subsequent seizures (p < 0.001).

**TREATMENT AFTER A SINGLE UNPROVOKED SEIZURE**

Patients with two unprovoked seizures, and hence a diagnosis of epilepsy, are routinely treated with antiepileptic drugs (AEDs). The decision to treat a patient with a single unprovoked seizure is more complicated. In this case, a number of factors need to be taken into account including the likely risk of seizure recurrence, patient age, occupation, need to drive, personal preference, and the potential side effects of AEDs.

**EVIDENCE FROM RANDOMIZED TRIALS**

In total, 6 randomized studies have looked at immediate versus delayed treatment in patients with a single unprovoked seizure (Camfield et al., 1989; Chandra, 1992; First Seizure Trial Group, 1993; Gilad et al., 1996; Das et al., 2000; Marson et al., 2005) (Table 2). Only one of these studies was double blind and placebo controlled (Chandra, 1992). Two of the studies assessed only generalized seizures (First Seizure Trial Group, 1993; Gilad et al., 1996), and one (Camfield et al., 1989) only children. Neonates were included in a single trial (Das et al., 2000). Marson et al. (2005) randomized patients with single or
Table 2. Randomized clinical trials exploring the treatment of patients with single unprovoked seizures

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Randomized/ blinded</th>
<th>Treated/ untreated</th>
<th>Ages</th>
<th>Seizure types (unprovoked)</th>
<th>Medications used</th>
<th>Seizure recurrence treated</th>
<th>Seizure recurrence untreated</th>
<th>Difference</th>
<th>Follow-up time</th>
<th>Side effects on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camfield et al. (1989)</td>
<td>Yes/no</td>
<td>14/17</td>
<td>Children</td>
<td>GTCS, 2° GTCS, tonic, clonic, S or CP</td>
<td>CBZ</td>
<td>14.3%</td>
<td>52.9%</td>
<td>38.6%</td>
<td>1 year</td>
<td>2 children on CBZ had somnolence and 2 had an allergic rash</td>
</tr>
<tr>
<td>Chandra (1992)</td>
<td>Yes/yes</td>
<td>115/113</td>
<td>16–79 years</td>
<td>GTCS, 2° GTCS, S or CP</td>
<td>VPA</td>
<td>4.3%</td>
<td>55.7%</td>
<td>51.4%</td>
<td>9 months to 5 years</td>
<td>2.6% GI upset 4.3% weight gain 1.7% hair loss</td>
</tr>
<tr>
<td>Gilad et al. (1996)</td>
<td>Yes/no</td>
<td>46/45</td>
<td>18–50 years</td>
<td>GTCS</td>
<td>CBZ (80%), VPA (20%)</td>
<td>22%</td>
<td>71%</td>
<td>49%</td>
<td>Up to 3 years</td>
<td>All were started on CBZ, 20% were switched to VPA because of side effects</td>
</tr>
<tr>
<td>FIRST (1993)</td>
<td>Yes/no</td>
<td>204/193</td>
<td>70%&gt;60 years</td>
<td>GTCS or 2° GTCS</td>
<td>PB (47%), CBZ (30%), VPA (16%), PHT (2%)</td>
<td>18%</td>
<td>39%</td>
<td>21%</td>
<td>Up to 2 years</td>
<td>7% in total discontinued treatment due to side effects</td>
</tr>
<tr>
<td>Das et al. (2000)</td>
<td>Yes/no</td>
<td>40/36</td>
<td>0–50 years</td>
<td>GS</td>
<td>Not stated</td>
<td>11.1%</td>
<td>45%</td>
<td>33.9%</td>
<td>1–2 years</td>
<td>Not stated</td>
</tr>
<tr>
<td>Marson et al. (2005)</td>
<td>Yes/no</td>
<td>722/721</td>
<td>1 month to &gt; 70</td>
<td>GTCS, 2° GTCS, tonic, clonic, S or CP, myoclonic, and absence</td>
<td>Not stated</td>
<td>6 months: 18%</td>
<td>6 months: 26%</td>
<td>6 months: 8%</td>
<td>6 months to 8 years</td>
<td>Higher levels of depression, GI symptoms, tiredness, HA, rash and poor mastery, etc. in patients on treatment</td>
</tr>
</tbody>
</table>

GTCS, generalized tonic clonic seizure; 2° GTCS, secondarily generalized tonic–clonic seizure; S or CP, simple or complex partial seizure; GS, generalized seizure; CBZ, carbamazepine; VPA, valproic acid; PB, phenobarbital; PHT, phenytoin; LTG, lamotrigine; HA, headache.
multiple seizures, but reported results for these two groups separately.

All randomized controlled trials showed that immediate treatment with an AED reduced the risk of a subsequent seizure in the short-term, but none showed that long-term AED treatment altered long-term outcomes. However, this statement is problematic because patients did not remain on their initial treatment group on the long term. That is, by 2 or 3 years, many patients in the untreated group were receiving treatment, and many in the treated group had stopped their treatment. Marson et al.’s study (Marson et al., 2005) had the longest follow-up (8 years). They looked at both time to first seizure and time to first tonic-clonic seizure. The largest differences occurred at 5 years, when 42% of treated and 51% of untreated patients experienced a second seizure, while 35% of treated and 44% of untreated patients experienced a tonic–clonic seizure. Two-year remission rates were identical (92%) for both groups at 5 years, and almost identical (95% vs 96%) at 8 years. Thus, long-term prognosis was not altered with early intervention. An important aspect of Marson et al.’s study (Marson et al., 2005) is that participation of multiple centers allows for a broader, perhaps more representative population. The FIRST study had similar results (First Seizure Trial Group, 1993). The overall risk of seizure recurrence was 50% lower in treated patients at 2 years (adjusted RR = 0.5, 95% CI 0.3–0.6). However, there was no significant difference between the groups in achieving a 1- or 2-year seizure-free period (RR 2-year remission 0.82, 95% CI 0.64–1.03) (Musicco et al., 1997), and both had a 64% chance of 5-year remission at 10 years (Leone et al., 2006).

In the only double blind and placebo-controlled trial, Chandra (Chandra, 1992) showed a dramatic difference in seizure recurrence in those treated with valproic acid (4.3%) versus those receiving placebo (55.7%). Time of follow-up was variable though, and remission was not assessed. Gilad et al. (1996) found that treated men (<40% treated vs 90% untreated p < 0.001) were less likely to have recurrent seizures than were treated women (45% treated vs 70% untreated p = 0.03). They also noticed that in a 3-year study, the highest rate of recurrence was in the first year, when untreated patients had 3 times as many seizures as treated patients. Finally, the two smaller trials cited here (Camfield et al., 1989; Das et al., 2000) did not assess long-term outcomes, but showed a significant reduction in seizure recurrence in treated patients in the short term. Das et al. (2000) had a follow-up of 1–2 years and found 11.1% seizure recurrence in treated versus 45% in untreated patients (p < 0.002). Camfield et al. (1989) followed children for a year and found 14.3% seizure recurrence in treated versus 52.9% in untreated patients (p = 0.0295).

A meta-analysis of all six randomized trials (Fig. 1) reveals absolute risk reductions ranging from 8% to 51%. Because of substantial heterogeneity, a random effects meta-analysis was performed, yielding an absolute reduction in the risk of seizure recurrence of 34% (95% CI 15–52) with AED therapy. Interestingly, the two studies with the lowest effect size, 21% (First Seizure Trial Group, 1993) and 8% (Marson et al., 2005), were also the largest trials. These trials were also responsible for the heterogeneity of the meta-analysis (Fig. 1).
CONCLUSIONS

The American Academy of Neurology has published a practice parameter for the treatment of children with a first unprovoked seizure (Hirtz et al., 2003). The recommendations state that “treatment with AED is not indicated for the prevention of the development of epilepsy (Level B)” and “treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects (Level B).”

Retrospective, prospective, and randomized controlled studies in children and adults provide good evidence that early seizure recurrence is reduced by early initiation of AED treatment. However, the prognosis for the development of epilepsy is not altered through early intervention, taking into account the caveats stated above about this statement. Epileptiform abnormalities, remote symptomatic seizures, family history of epilepsy, and abnormal imaging all increase the risk of recurrence, and therefore the likelihood of treatment after a single event. In the end, clinicians must evaluate patients with a first unprovoked seizure on a case-by-case basis to determine the appropriateness of treatment with a given AED.

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