CONSENSUS STATEMENT

Prognosis in epilepsy: initiating long-term drug therapy


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Received 12 February 2014; accepted 2 March 2014
Available online 12 June 2015

Keywords
Epilepsy; Evidence-based medicine; Clinical practice guidelines; Prognosis; Onset of long-term treatment; Failure of first antiepileptic drug

Abstract

Introduction: Prognosis in epilepsy refers to the probability of either achieving seizure remission (SR), whether spontaneously or using antiepileptic drugs (AED), or failing to achieve control of epileptic seizures (ES) despite appropriate treatment.

Use of AED is recommended after a second unprovoked ES. For a first episode, the decision of whether or not to start drug treatment depends on the risk of recurrence and the advantages or disadvantages of the antiepileptic drug. The main goal of treatment is achieving absence of ES without adverse effects (AE). AED is selected according to epilepsy type and the demographic and clinical characteristics of the patient.

Development: A PubMed search located articles and recommendations by the most relevant scientific societies and clinical practice guidelines concerning epilepsy prognosis and treatment. Evidence and recommendations are classified according to the prognostic criteria of the Oxford Centre for Evidence-Based Medicine (2001) and the European Federation of Neurological Societies (2004) for therapeutic actions.

Conclusions: Most newly diagnosed epileptic patients achieve good control over their ES. The majority of the AEDs available at present provide effective control over all types of ES, and

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2173-5808/$ - see front matter © 2014 Sociedad Española de Neurología. Published by Elsevier España, S.L.U. All rights reserved.
choice therefore depends on the patient’s individual characteristics. Treatment should be initiated as monotherapy at the lowest effective dose, which in half of all patients provides ES control and is well tolerated. In cases in which the first AED is not effective, alternative therapy should be started, and monotherapy should be employed before combination therapy where possible. The probability of achieving good control over ES decreases with each successive treatment failure.

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Introduction

In epilepsy, prognosis depends on multiple probabilities: the likelihood of achieving remission of epileptic seizures (ES), whether spontaneously or by using antiepileptic drugs (AED); the likelihood of sustaining remission over time, even after discontinuing AEDs; and the likelihood of not achieving seizure control, despite providing appropriate treatment.

This article includes a review of the natural history of epilepsy, the efficacy of AEDs for preventing recurrence of a first ES, and the long-term drug treatments used to manage epilepsy.

Natural history of epilepsy

The natural history of untreated epilepsy can be deduced from door-to-door population studies, but their diagnostic certainty is low. Based exclusively on semiological data, these studies are carried out in less-developed countries with poor access to pharmacological treatment. The probability of long-term seizure remission without treatment in some of these countries has been calculated at 41% to 46%. A Finnish cohort study over a long follow-up time and including a few untreated patients found remission rates of 42% at 10 years and of 52% at 20 years after onset of epilepsy. Population studies have reported spontaneous remission rates ranging between 30% and 50% among patients not receiving treatment (LE 1).1–3

Observational epidemiology studies, whether prospective or retrospective, have been carried out in developed countries in patients of all ages, most of whom receive antiepileptic treatment. These studies report sustained remission rates of between 60% and 76% (LE 1).4–9 Half of the patients who are not treated with AEDs after a first generalised tonic-clonic seizure (GTCS) never experience another (LE 1).6

Hospital-based studies have also found sustained remission among patients with childhood-onset epilepsy, with rates of 68% to 93%, depending on the duration of the remission time examined (LE 1).7,8

Efficacy of antiepileptic drugs in reducing risk of recurrence of a first or subsequent seizure

Treatment with AEDs is recommended for both children and adults who experience a second unprovoked ES. At
Factors associated with a high risk of recurrence include the type and number of ES, symptom aetiology, anomalies detected in the neurological examination, partial seizures (PS), epileptiform anomalies on the electroencephalogram (EEG), and structural changes in neuroradiological studies (LE II). Table 1 lists the grades on the prognostic index of recurrence given by the MESS study.

### Determinants of onset of treatment with antiepileptic drugs

The following risks should be taken into account when contemplating treatment for a first ES:

- Treatment does not prevent future development of epilepsy
- The psychological, social, and legal effects on the patient
- Potential adverse effects of the AED, whether neurotoxic, idiosyncratic, teratogenic, or chronic

Risks must be weighed against the following benefits of treatment:

- Decreased risk of recurrence
- Legal capacity to drive vehicles and engage in certain professional activities
- Psychosocial benefits

The American Academy of Neurology (AAN) states that treatment with AED is not indicated for preventing the development of epilepsy, and that prescribing AED treatment after the first ES requires weighing the benefits of reduced risk of a second ES against the pharmacological and psychosocial risks of treatment (LE IV).

Most authors and Clinical Practice Guidelines (CPGs) recommend starting treatment in the following clinical situations (LE III-IV):

- After 2 or more ES with significant clinical symptoms occurring within a period of 6 to 12 months.
- After the first ES, if the patient is at moderate to high risk of recurrence and wishes to begin treatment.
- After 2 or more ES with minor symptoms occurring within a longer time period if the patient is at moderate to high risk of recurrence and wishes to begin treatment.
- After experiencing status epilepticus (SE), a first GTCS during pregnancy, or unprovoked ES in elderly, disabled, or HIV-positive patients.

Fig. 1 indicates the therapeutic actions after a first ES as recommended by consensus of the authors of the SEN epilepsy group guidelines (GE-SEN).
Onset of long-term pharmacological treatment in adults

The purpose of AED treatment is to achieve absence of ES without adverse events. Doctors must select the most appropriate type of AED according to type of epilepsy and the patient’s characteristics (age, sex, weight, comorbidities, etc.). Although very few studies have compared monotherapy to polytherapy approaches, clinical experience shows that treatment with a single AED provides effective seizure control in most patients, while also promoting compliance and decreasing the likelihood of adverse effects.18–25

Evidence regarding epileptic seizure treatment in adults

We have reviewed LE-based recommendations from the listed medical societies and/or findings from randomised controlled trials (RCTs) or systematic reviews.

Abbreviations of AEDs are listed in Table 2.

- Veterans Affairs Epilepsy Cooperative Study. 1985-1992 (PHT, CBZ, VPA, PB, PRM).18,19
- American Academy of Neurology (AAN) and the American Epilepsy Society. 2004. Initial systematic review of monotherapy (GBP, LTG, TPM, OXC) and treatment of refractory epilepsy (GBP, LTG, TPM, TGB, OXC, LEV, ZNS).21,22
- National Institute for Health and Clinical Excellence. 2012. CPGs for management of the epilepsies in adults and children.25
Variables considered when selecting an AED for patients recently diagnosed with epilepsy should include such drug characteristics as specificity for the type of seizure, efficacy spectrum, tolerability, pharmacokinetics, interactions, types of presentation, titration rate, and number of doses per day. Patient-related variables should include genetic studies, age, comorbidities, and any other treatments.

The first-choice drug is the one with the greatest probability of being effective and the lowest probability of adverse effects; the correct dose is the lowest to achieve ES control without adverse effects.

Table 3 shows the initial doses, temporary dose scaling recommendations, and normal AED maintenance doses.

Patients should first be treated with a single AED (initial monotherapy) at the lowest effective dose to minimise the risk of adverse effects and facilitate treatment compliance. In one prospective observational study, almost half of all patients recently diagnosed with epilepsy at any age, with any type of ES or aetiology, remained seizure-free as a result of the first AED administered; in this group, more than 90% remained seizure-free while on low doses. Among patients who did not respond to the first AED without adverse effects, the probability of seizure control decreased with each successive attempt at treatment (LE II).27

Another prospective observational study of a newly diagnosed patient cohort and their treatment response patterns found that at the time of their most recent outpatient visit, 68% had been seizure-free for more than a year and 62% were being treated with a single AED. Treatment responses were divided into 4 groups: early and sustained seizure freedom (37%); delayed but sustained seizure freedom (22%); fluctuation between periods of seizure freedom and relapse (16%); and seizure freedom never attained (25%) (LE II).28

The initially selected AED should be discontinued if unacceptable adverse effects appear, ES continues, or new ES are provoked by the treatment. In any of these cases, patients should be switched to a different AED with better prospects for a good response.

Nevertheless, one RCT in a randomised sample of patients with cryptogenic or symptomatic partial epilepsy treated in monotherapy with an alternative AED, or in bitherapy with a second AED, found no differences between the two groups regarding either ES control or adverse effects during one year of follow-up.29 If the initial monotherapy is not effective, most authors and CPGs recommend trying an alternative drug in monotherapy prior to starting bitherapy.

If ES remain uncontrolled after trying two drugs in monotherapy, authors recommend trying combinations of FAEs with proved efficacy for the type of ES and which are unlikely to cause adverse effects. Fig. 2 lists therapeutic actions for possible responses to initial drug treatment according to consensus among authors of the GE-SEN guidelines.

Adjusting treatment to the patient’s individual characteristics, whether or not that treatment follows published recommendations, is a prerogative that doctors should not sacrifice.30
Figure 2  Therapeutic actions corresponding to potential responses to the initial drug treatment

General list of evidence and recommendations on long-term pharmacological treatment of epilepsy in adults

<table>
<thead>
<tr>
<th>Evidence for partial seizures</th>
<th>Level</th>
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<tbody>
<tr>
<td>CBZ, GBP, LEV, LTG, OXC, PB, PHT, TPM, VPA, and ZNS are effective for initial treatment in</td>
<td>I</td>
</tr>
<tr>
<td>monotherapy</td>
<td></td>
</tr>
<tr>
<td>CBZ and PHT are as effective as PB, but better tolerated than that drug</td>
<td>I</td>
</tr>
<tr>
<td>PHT is similar in efficacy and tolerability to either CBZ or VPA</td>
<td>I</td>
</tr>
<tr>
<td>CBZ is more effective than VPA and displays similar tolerability</td>
<td>I</td>
</tr>
<tr>
<td>OXC is as effective as CBZ and PHT but also better tolerated</td>
<td>I</td>
</tr>
<tr>
<td>LTG is as effective as CBZ and also better tolerated</td>
<td>I</td>
</tr>
<tr>
<td>LTG and OXC are more effective than CBZ, GBP, and TPM</td>
<td>III</td>
</tr>
<tr>
<td>LEV and ZNS are as effective as slow-release CBZ</td>
<td>I</td>
</tr>
<tr>
<td>CLB, GBP, LTG, TGB, TPM, OXC, LEV, ZNS, PGB, LCM, ESL, and PER are effective as adjunct</td>
<td>I</td>
</tr>
<tr>
<td>therapy for refractory PS</td>
<td></td>
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<tr>
<th>Evidence in generalised seizures</th>
<th>Level</th>
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<tbody>
<tr>
<td>CBZ, LTG, OXC, PB, PHT, TPM, and VPA are effective for treating GTCS</td>
<td>I—I</td>
</tr>
<tr>
<td>ESM, LTG, and VPA are effective for treating absence seizures. It is not known which is the</td>
<td>III</td>
</tr>
<tr>
<td>most effective</td>
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</tr>
<tr>
<td>ESM is not effective against GTCS</td>
<td>IV</td>
</tr>
<tr>
<td>CZP, LEV, LTG, TPM, VPA, and ZNS may constitute effective treatment for myoclonic ES</td>
<td>IV</td>
</tr>
<tr>
<td>VPA is more effective than LTG and better tolerated than TPM, against generalised epilepsy</td>
<td>III</td>
</tr>
<tr>
<td>with different types of ES</td>
<td></td>
</tr>
<tr>
<td>CBZ, GBP, OXC, PGB, TGB, VGB, PHT, and LTG may exacerbate absence or myoclonic seizures</td>
<td>IV</td>
</tr>
</tbody>
</table>

| Recommendations for initial AEDs                                                               |       |
| In focal onset ES with or without secondary generalisation:                                  | GE-SEN|
| LTG, OXC, LEV, and ZNS                                                                        |       |
| In primary GTCS: VPA, LTG                                                                     | GE-SEN|
| In absence seizures: VPA, ESM, LTG                                                            | GE-SEN|
| In myoclonic seizures: VPA, LEV                                                                | GE-SEN|
| Juvenile myoclonic epilepsy: VPA                                                                | C     |
| Alternatives in women of childbearing age: LTG                                                 | GE-SEN|
Conflicts of interest

The authors have no conflicts of interest to declare.

References