AEDs under the microscope

In the past 100 years, the development of new and better tolerated anti-epileptic drugs (AEDs) has led to seizure freedom for as many as 70 per cent of people with epilepsy. But AEDs only treat the symptoms of epilepsy and many have unpleasant side effects. Professor Ley Sander discusses the need to look at the natural progress of untreated epilepsy while Professor Tony Marson underlines the need for better evidence to support the newer drugs. And on page 18 we ask you, are you taking your tablets?

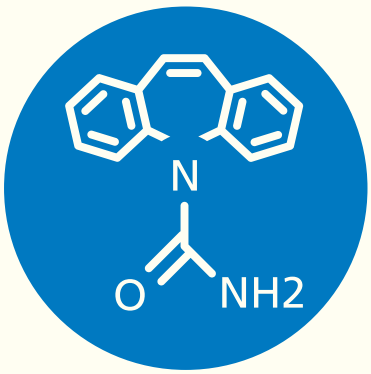
In 1912, the story goes, a young physician Alfred Hauptmann was allocated accommodation above the epilepsy ward at a hospital in Freiburg, Germany. Disturbed by the sound of patients having seizures and himself unable to sleep, Hauptmann sedated the patients below him with the latest hypnotic drug on the market – phenobarbital, or Luminal as it was branded.

He quickly observed that not only was he finally able to enjoy an uninterrupted night's sleep, but that the patients showed a dramatic reduction in both daytime and sleep seizures. Phenobarbital, it seemed, was not just a useful sedative, it also had anti-epileptic properties. Overnight, Hauptmann had ushered in a therapeutic treatment that was to revolutionise the world of epilepsy, until then largely dependent on bromide.

One hundred years later the number of anti-epileptic drugs (AEDs) available has increased dramatically and Hauptmann's wonder drug has been overshadowed by better tolerated medication with fewer side effects though efficacy varies from person to person.

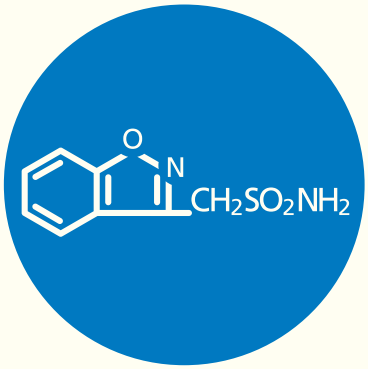
But 100 years of AEDs has also had an unwitting side effect. While bringing seizures under control or at least reducing their frequency and severity, AEDs have also masked our knowledge of the natural history of the untreated condition.

When a person has had two or more unprovoked seizures, a diagnosis of epilepsy may be made and AED treatment



carbamazepine

is started. And the role of the medication is critical. Seizures are not benign events and the importance of bringing them under control cannot be overemphasised. We treat seizures to reduce the risk of people injuring themselves, for example



zonisamide

by falling into the road, or burning themselves with hot liquids or food. The dangers are very real.

With expert treatment up to 70 per cent of seizures are brought under control and the impact of this on quality of life is huge with people able to work, drive and support both themselves and their families. For many people, AEDs mean that seizures are a short-lived phenomenon.

But the exact role of AEDs in this good outcome remains open to debate. They can suppress seizures for many but they do not alter epilepsy as an underlying condition. We do not know whether the seizures stop because of the drugs prescribed or because, at some point, the generating trigger has itself gone into spontaneous remission.

While for many people seizure freedom means a lifetime of taking AEDs, we know that some people remain seizure free even when drugs are withdrawn under medical supervision. These people tend to be those who show a good prognosis – they have one seizure type that is quickly brought under control by medication, have no structural abnormalities in the brain and no irregular activity on an EEG. But we do not know whether their seizures remit spontaneously or because the drugs have helped them over time.

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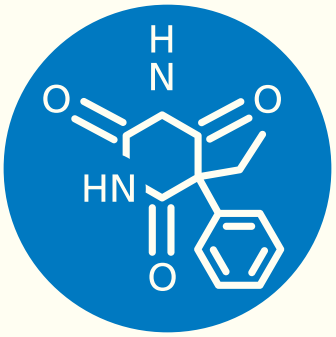
AED treatment is usually started at the point of diagnosis in the developed world, and long-term outcome studies in the last century have consequently focused on the prognosis of treated epilepsy. It is only by turning our attentions to resource-poor countries where as many as 85 per cent of people with epilepsy do not receive anti-epileptic drug treatment, that we can begin to shed important light on the course of untreated epilepsy.

A survey in northern Ecuador in the late 1980s identified 1,029 people with a probable or definite history of epilepsy. Among the 643 people who had never received AED treatment, 49 per cent had been seizure free for at least the previous 12 months. This meant 31 per cent of the whole patient population had entered remission spontaneously. A similar study commissioned by the World Health Organization in rural China showed that in a group of 387 epilepsy patients, 41 per cent of those with a history of epilepsy but not on medication or having seizures, had never been treated.

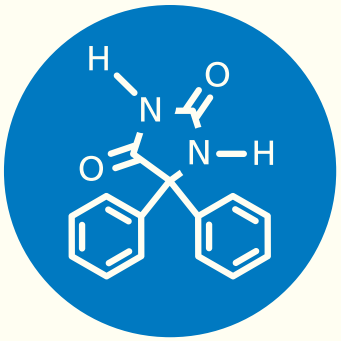
These figures of course must be viewed against the higher mortality rate in many developing countries.



phenobarbital

The possibility of spontaneous remission has attracted relatively little attention from researchers in the developed world. Ethical concerns surround conducting a scientific study that randomly assigns newly diagnosed patients to treatment or no treatment. Such a protocol is difficult to justify when effective treatment has been available since the introduction of bromide as a therapy in 1857.

However a small-scale Finnish study has shown that spontaneous remission of epilepsy has also been observed in developed countries. Thirty-three patients were retrospectively identified at a hospital with each of them having reported two or more unprovoked seizures that had not been treated with AEDs. Ten years after onset, 42 per cent had entered a two-year remission.



phenytoin

The Finnish study was limited by its small sample size and the likely bias that in developed countries where treatment is readily available, it is only those with mild epilepsy who are likely to reject treatment. Similarly studies in resource-poor countries only provide circumstantial evidence from uncontrolled surveys which may not conform to international guidelines.

For these reasons, we cannot draw firm conclusions from such studies. What they do underline is the need to gain greater insight into the natural history of untreated epilepsy and to develop disease-modifying drugs as well as those which suppress seizures.

We need to compare the long-term prognosis of patients who receive the

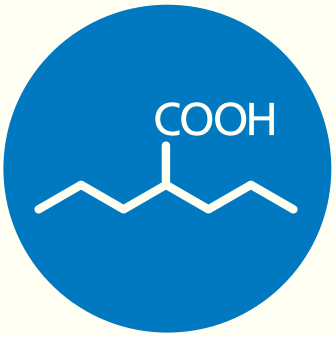
present clinical practice of treatment after a second seizure and those who receive delayed treatment. This second group could only apply to those without poor prognostic factors such as structural brain abnormality, multiple seizures or abnormal EEG findings.

But the question remains 'can we afford not to treat seizures?' I think the answer has to be 'no'. Even if the long-term outcome is good in a newly diagnosed patient, seizures are not benign events and in the wrong place at the wrong time could pose substantial danger. The role of AEDs is considerable and the patient perspective is paramount.

As one gentleman put it so succinctly: 'I would love to try coming off my AEDs but I can't afford to take a sabbatical.'

Yet still the need to explore the natural history of epilepsy remains. Alfred Hauptmann was able to sleep easy in his bed, but can today's epilepsy specialists?

Professor Ley Sander is interim medical director of Epilepsy Society. His global interests include the management of epilepsy in resource-poor countries.



valproic acid

A closer look at AEDs

A nationwide study is setting out to assess the safety and effectiveness of some of the newer anti-epileptic drugs. Professor Tony Marson writes

For many people with epilepsy anti-epileptic drugs (AEDs) are the mainstay of treatment and may have to be taken for life. The ultimate goal of treatment is to maximise quality of life by eliminating seizures at drug doses that do not cause side effects. However, often there is a necessary trade-off between effective seizure control and side effects which can diminish quality of life.

It is important that we have reliable evidence about which drugs are the most effective and safe, as well as evidence about value for money. And a new trial, SANAD II – Standard And New Anti-epileptic Drugs – will set out to provide this.

Over the past 20 years a number of new drugs have become available for the treatment of epilepsy. These have been approved for NHS use on the basis of information from short-term trials. But they do not provide information about the longer term outcomes which inform decisions made by doctors and patients, nor do they provide any useful health economic data.

In 1999 the Epilepsy Research Group at the University of Liverpool began a long-term trial – SANAD I – comparing the effectiveness and cost effectiveness of standard and new treatments available at the time. SANAD I made two important findings. It identified lamotrigine (a new drug) as an effective and cost-effective first-line treatment for patients with focal epilepsy. It also confirmed that valproate (a standard treatment) should remain a first-line drug for patients with generalised epilepsy or seizures that clinicians find difficult to classify.

The findings of SANAD I triggered the recent update of the NICE guideline for the treatment of epilepsy.

Since SANAD I, a number of newer treatments have become available, the most promising of which are levetiracetam and zonisamide. We now need to assess whether these drugs should become first-line treatments. In SANAD II, we propose to assess the longer term effectiveness of these drugs.

The trial, run over seven years, will recruit more than 1,500 newly diagnosed patients aged five and over at 100 sites in the UK. It is being funded through the National Institute for Health Research (NIHR) Health Technology Assessment programme (project no. 09/144/09) and is sponsored by the University of Liverpool and the Walton Centre NHS Foundation Trust.

SANAD-II will be undertaken in conjunction with the Medicines for Children Research Network, the Wales Epilepsy Research Network, and the UK Epilepsy Research Network.

Professor Tony Marson is director of the UK Epilepsy Research Network and deputy director of the Medical Research Council North West Hub for Trials Methodology Research.

The views and opinions expressed here are those of the author and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.