

Epilepsy

What is epilepsy?

Epilepsy is a chronic disorder characterised by recurrent seizures caused by occasional, excessive and disorderly discharges from nerve cells which spread within the brain. Seizures vary from mild 'absences' through to full-scale convulsions and *grand mal* - so-called tonic-clonic seizures. The seizures can be generalised or partial, affecting only part of the brain. In a few people they are caused by brain lesions, such as tumours or blood vessel abnormality, but in most cases there is no obvious organic cause.

Who does epilepsy affect?

The worldwide prevalence of epilepsy is between five and ten cases per 1,000 people. The lifetime prevalence is two to five per cent of the general population. Recent surveys in EU member states indicate that around five people per thousand are treated for epilepsy in a given year. However, there is evidence that epilepsy is under-treated and also that the number of seizures reported by patients is significantly under-reported.

The incidence rates vary between 40 and 70 per 100,000 population. This rate is especially high in the first five years of life and in people over the age of 65. The annual incidence rises by the age of 80-84 to be about twice as high as in the overall population. An estimated seven million people in Europe will have an epileptic seizure at some time during their lives. People with epilepsy number between 40 and 50 million worldwide, and a significant proportion - as many as 30 per cent - have a treatment-refractory form of the condition.

Such individuals are more likely to have a particular variant of the gene for a protein which exports anti-epileptic medicines from cells. Refractory epilepsy brings significant extra morbidity - memory loss, learning difficulties, depression and impaired psychosocial skills.

Epilepsy is a brain condition in which patients have seizures that may be mild or severe. People with epilepsy can feel isolated. In recent years, a better understanding of epilepsy has led to better treatments. Today, people with epilepsy can feel part of society and enjoy everyday life.



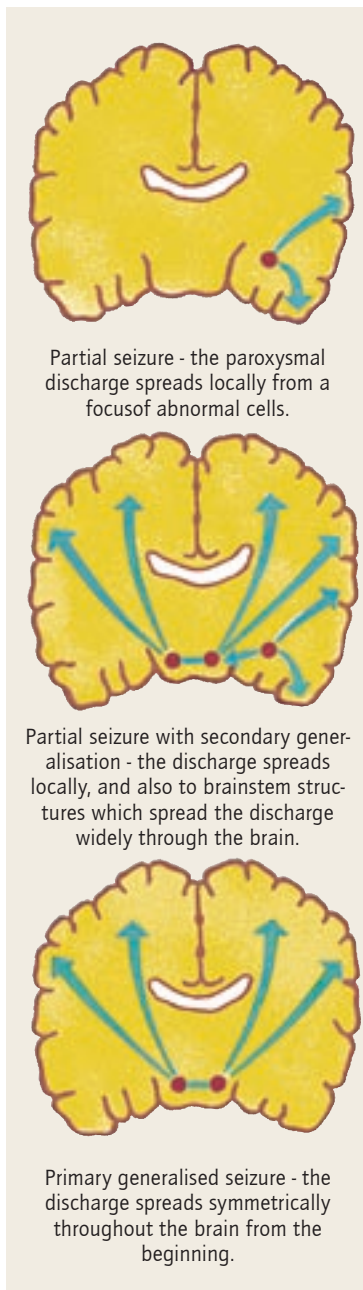


FIGURE 1: Types of brain discharge in epilepsy

Present treatments:

Some people only experience infrequent attacks and medication may not be appropriate, while in others, attacks may be much more frequent and incapacitating. A number of medicines has been available for this group for over 25 years, such as derivatives of carboxamide, succinimide, hydantoine and valproic acid, all of which are still in use. These older therapies control seizures, but almost all cause some drowsiness and other side effects such as nausea and unsteadiness. Brain surgery has a role in people who do not respond to current medication, but it is estimated that only about 10,000 such operations are carried out each year in Europe.

New compounds based on a better understanding of epilepsy have been introduced in the last decade. These are, e.g. derivatives of benzodiazepines, acetames, fatty acids or gamma-amino butyric acid (GABA) and are used either alone or in combination with other medicines. Usual clinical practice is to begin therapy with a single medicine, increasing its dose until the desired control of seizures is achieved. If side effects become intolerable, another medicine is tried instead. Only when two or three such therapies have been tried and failed is it usual to add a second medicine.

Many anti-epilepsy medications need to be taken at least twice a day and side effects such as drowsiness, dizziness, headache and gastrointestinal symptoms such as nausea are common initially, even with the newer medicines. Recent surveys have shown that only 30-40 per cent of people with epilepsy persist with the prescribed medication for more than five years and while good seizure control is achieved in 70-80 per cent, the seizures become intractable in 20-25 per cent.

What's in the development pipeline?

The brain chemistry of epilepsy is complex and despite the importance of the inhibitory neurotransmitter GABA in 'damping down' spontaneous nerve firing that might otherwise trigger an epileptic cascade, a variety of mechanisms of action appear to be exploitable for anti-epileptic compounds.

Some new molecules appear to work in completely new ways. These include the interaction with potassium channels in the cell membrane and may also affect the response to GABA. Other compounds appear to affect sodium channels, and early clinical trials have shown that they can reduce treatment-resistant partial seizures. Sodium channels are crucial for the normal electrical activity of the brain, and subtle alterations in sodium channels can cause enhanced excitability and epilepsy. At least three approved medicines appear to act as sodium channel blockers and two further compounds of this type are in development. Further new therapeutic approaches include the inhibition of one kind of glutamate receptor. Another compound is a steroid that interacts with GABA receptors.

A study in newborn rats showed that seizures can be blocked by a commonly used diuretic compound that inhibits the effects of GABA release. While these results are preliminary, they suggest that this substance or related medicines might be a new way of treating seizures in young children. A compound at an advanced clinical stage is a successor to the established derivative of GABA. There is another new molecule which acts both as a potassium channel opener and as an enhancer of GABA by increasing its production. Molecules of the family of acetams are thought to act by preventing neurotransmitter release and also by lowering calcium levels between brain cells.

Also in advanced clinical development is a specific inhibitor of the receptor for AMPA and kainate - two 'excitatory' amino acids that can act to stimulate spontaneous nerve discharge. This compound has shown activity in people with intractable epilepsy resistant to other medications and may also be of value in multiple sclerosis and Parkinson's disease. And there is a second AMPA receptor antagonist in clinical research in Europe. Still at an early stage is a peptide isolated from marine Cone snail

venom which inhibits receptors for NMDA, a third excitatory amino acid. It may also have applications in other neurological disorders.

In addition to the development of new chemical substances, progress may also come from using existing medications more effectively. Thus, there are several projects underway at the preclinical stage to develop extended release formulations of established anti-epilepsy treatments that may improve the continuation rates seen in chronic disease. The introduction of a pro-drug of valproic acid may lead in the same direction.

The longer-term future:

Exploring new mechanisms of action is likely to lead to further promising new medicines for epilepsy, as the complexity of the neurochemical events occurring in the brain before and during an epileptic seizure is unravelled. For centuries it has been observed that epilepsy tends to run in families, leading scientists to presume that inherited genetic mutations contribute to the development of seizures.

But single-gene, inherited epilepsy is rare. Most common epilepsies are probably the result of environmental factors acting in combination with genes. This explains the multitude of epilepsy syndromes and may also explain why epilepsy is often associated with other disorders. Meanwhile, researchers have identified specific epilepsy genes in patients with rare epilepsy syndromes. For example, some types of childhood absence epilepsy have been linked to a gene that codes for a GABA receptor, while a type of nocturnal frontal lobe epilepsy is caused by a gene that affects responses to the neurotransmitter acetylcholine.

A significant new finding that underlines the importance of a second GABA receptor type - the GABA_B receptor - involved in the disease has been detected by research groups in neurology and psychiatry centres and may open up leads to new compounds. A GABA_C receptor is also known to exist, but has not so far been developed for therapy.

Another challenge for epilepsy research will be the development of new animal models. While there is still no model that truly mimics human epilepsy, studying animal models can help to answer questions about how epilepsy develops and how repeated seizures affect brain structure and function. In the past decade, researchers have developed several models for childhood seizures and epilepsy. Research is also ongoing to create models that mimic nerve toxin exposure. Progress has also been achieved in developing models of medicine-resistant epilepsy.

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