Epilepsy

A seizure can be defined as the occurrence of signs and/ or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain.
'Epilepsy' is the tendency to have unprovoked seizures. The lifetime risk of seizure is about 5%, although incidence is highest at the extremes of age.

26.34 Classification of seizures (2010 ILAE Classification)

Generalised seizures

- Tonic–clonic (in any combination)
- Absence
  - Typical
  - Atypical
  - Absence with special features
- Myoclonic absence
- Eyelid myoclonia
- Myoclonic
  - Myoclonic
  - Myoclonic atonic
  - Myoclonic tonic
- Clonic
- Tonic
- Atonic

Focal seizures

- Without impairment of consciousness or awareness (was 'simple partial')
  - Focal motor
  - Focal sensory
- With impairment of consciousness or awareness (was 'complex partial')
- Evolving to a bilateral, convulsive seizure (was 'secondarily generalised seizure')
  - Tonic
  - Clonic
  - Tonic–clonic

Unknown

- Epileptic spasms

Pathophysiology

The inhibitory transmitter gamma-aminobutyric acid (GABA) is particularly important, acting on ion channels to enhance chloride inflow and reduce the chances of action potential formation. Excitatory amino acids (glutamate and aspartate) allow influx of sodium and calcium, producing the opposite effect. It is likely that many seizures result from an imbalance between this excitation and inhibition.
Seizures may be related to a localised disturbance in the cortex, becoming manifest in the first instance as focal seizures.

In seizures that are generalised constitute around 30% of all epilepsy at onset, the abnormal activity probably originates in the central mechanisms controlling cortical activation and spreads rapidly. In humans, many generalized epilepsies will have a genetic basis, and these almost always become apparent before the age of 35.

Clinical features

Seizure type and epilepsy type

Epilepsy that starts in patients beyond their mid-thirties will almost invariably reflect a focal cerebral event. Where activity remains focal , this will be obvious. Occipital onset will cause visual changes (lights and blobs of colour), temporal lobe onset will cause false recognition (déjà vu), sensory strip involvement will cause sensory alteration (burning, tingling), and motor strip involvement will cause jerking.

Trigger factors for seizure:

1. Sleep deprivation
2. Missed doses of anti-epileptic drugs in treated patients
3. Alcohol (particularly withdrawal)
4. Recreational drug misuse
5. Physical and mental exhaustion
6. Flickering lights, including TV and computer screens (generalized epilepsy syndromes only)
7. Intercurrent infections and metabolic disturbances
8. Uncommon: loud noises, music, reading, hot baths.

Focal seizures

They are caused by localised cortical activity. A spreading pattern of seizure may occur, the abnormal sensation spreading much faster (in seconds) than a migrainous focal sensory attack. Awareness may become impaired if spread occurs to the temporal lobes (previously ‘complex partial seizure’). Patients stop and stare blankly, often blinking repetitively, making smacking movements of their lips or displaying other automatisms, such as picking at their clothes. After a few minutes, consciousness returns but the patient may be muddled

and feel drowsy for a period of up to an hour. The age of onset, preceding aura, longer duration and post-ictal symptoms usually make these easy to differentiate from childhood absence seizures.

Seizures arising from the anterior parts of the frontal lobe may produce bizarre behaviour patterns, including limb posturing, sleep walking, or even frenetic ill-directed motor activity with incoherent screaming.

26.36 Causes of focal seizures

Idiopathic

- Benign Rolandic epilepsy of childhood
- Benign occipital epilepsy of childhood

Focal structural lesions

Genetic

- Tuberous sclerosis (p. 1302)
- Autosomal dominant frontal lobe epilepsy
- Autosomal dominant partial epilepsy with auditory features (ADPEAF)
- von Hippel–Lindau disease (p. 1216)
- Neurofibromatosis (p. 1215)
- Cerebral migration abnormalities

Infantile hemiplegia

Dysembryonic

- Cortical dysgenesis
- Sturge–Weber syndrome

Mesial temporal sclerosis (associated with febrile convulsions)

Cerebrovascular disease (Ch. 27)

- Intracerebral haemorrhage
- Cerebral infarction
- Arteriovenous malformation
- Cavernous haemangioma

Tumours (primary and secondary) (p. 1213)

Trauma (including neurosurgery)

Infective (p. 1201)

- Cerebral abscess (pyogenic)
- Toxoplasmosis
- Cysticercosis
- Tuberculoma
- Subdural empyema
- Encephalitis
- Human immunodeficiency virus (HIV)

Inflammatory

- Sarcoidosis
- Vasculitis

Generalised seizures

Tonic–clonic seizures: An initial ‘aura’ may be experienced by the patient, depending on the cortical area from which the seizure originates. The patient then becomes rigid (tonic) and unconscious, falling heavily if standing (‘like a log’) and risking facial injury. During this phase, breathing stops and central cyanosis may occur. As cortical discharges reduce in frequency, the limbs produce jerking (clonic) movements for a variable

time. Afterwards, there is a flaccid state of deep coma, which can persist for some minutes.
The patient may be confused, disorientated and/or amnesic after regaining consciousness. During the attack, urinary incontinence and tongue-biting may occur. A severely bitten, bleeding tongue after an attack of loss of consciousness is pathognomonic of a generalised seizure. Subsequently, the patient usually feels unwell and sleepy, with headache and myalgia.

Absence seizures: Absence seizures (previously 'petit mal') always start in childhood. The attacks are rarely mistaken for focal seizures because of their brevity. They can occur so frequently (20–30 times a day) that they are mistaken for daydreaming or poor concentration in school.
Myoclonic seizures: These are typically brief, jerking movements, predominating in the arms. In epilepsy, they are more marked in the morning or on awakening from sleep, and tend to be provoked by fatigue, alcohol or sleep deprivation.
Atonic seizures: These are seizures involving brief loss of muscle tone, usually resulting in heavy falls with or without loss of consciousness. They only occur in the context of epilepsy syndromes that involve other forms of seizure.
Tonic seizures: These are associated with a generalised increase in tone and an associated loss of awareness. They are usually seen as part of an epilepsy syndrome and are unlikely to be isolated.
Clonic seizures: Clonic seizures are similar to tonic– clonic seizures. The clinical manifestations are similar but without a preceding tonic phase.
Seizures of uncertain generalised or focal nature
Epileptic spasms: They signify widespread cortical disturbance and take the form of marked contractions of the axial musculature, lasting a fraction of a second but recurring in clusters of 5–50, often on awakening.

Epilepsy syndromes

Many patients with epilepsy fall into specific patterns, depending on seizure type(s), age of onset and treatment responsiveness: the so-called electroclinical syndromes. It is anticipated that genetic testing will ultimately demonstrate similarities in molecular pathophysiology.

26.38 Electroclinical epilepsy syndromes

Adolescence to adulthood

- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalised tonic–clonic seizures alone
- Progressive myoclonus epilepsies (PME)
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Less specific age relationship

- Familial focal epilepsy with variable foci (childhood to adult)
- Reflex epilepsies

Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen's syndrome
- Gelastic (from the Greek word for laughter) seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

Epilepsies with structural–metabolic causes

- Malformations of cortical development (hemimegalencephaly, heterotopias etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber etc.)
- Tumour
- Infection
- Trauma
- Angioma
- Perinatal insults
- Stroke etc.

Epilepsies of unknown cause

Conditions with epileptic seizures traditionally not diagnosed

- Benign neonatal seizures (BNS)
- Febrile seizures (FS)

26.39 Common epilepsy syndromes

	Age of onset	Type of seizure	EEG features	Treatment	Prognosis
Childhood absence epilepsy	4–8 yrs	Frequent brief absences	3/sec spike and wave	Ethosuximide Sodium valproate Levetiracetam	40% develop GTCS, 80% remit in adulthood
Juvenile absence epilepsy	10–15 yrs	Less frequent absences than childhood absence	Poly-spike and wave	Sodium valproate Levetiracetam	80% develop GTCS, 80% seizure-free in adulthood
Juvenile myoclonic epilepsy	15–20 yrs	GTCS, absences, morning myoclonus	Poly-spike and wave, photosensitivity	Sodium valproate Levetiracetam	90% remit with AEDs but relapse if AED withdrawn
GTCS on awakening	10–25 yrs	GTCS, sometimes myoclonus	Spike and wave on waking and sleep onset	Sodium valproate Levetiracetam	65% controlled with AEDs but relapse off treatment

(AED = anti-epileptic drug; GTCS = generalised tonic–clonic seizures)

The more common epilepsy syndromes, which are largely of early onset and are sensitive to sleep deprivation, hyperventilation, alcohol and photic stimulation.

Investigations

Single seizure

All patients with transient loss of consciousness should have a 12-lead ECG. Where seizure is suspected or definite, patients should have imaging with either CT or MRI, although the yield is low unless focal signs are present. EEG may help to assess prognosis once a firm diagnosis has been made. The recurrence rate after a first seizure is approximately 40%, and most recurrent attacks occur within a month or two of the first.

26.40 Investigation of epilepsy

From where is the epilepsy arising?

- Standard EEG
- Sleep EEG
- EEG with special electrodes (foramen ovale, subdural)

What is the cause of the epilepsy?

Structural lesion?

- CT
- MRI

Metabolic disorder?

- Urea and electrolytes
- Liver function tests
- Blood glucose
- Serum calcium, magnesium

Inflammatory or infective disorder?

- Full blood count, erythrocyte sedimentation rate, C-reactive protein
- Chest X-ray
- Serology for syphilis, HIV, collagen disease
- CSF examination

Are the attacks truly epileptic?

- Ambulatory EEG
- Videotelemetry

Epilepsy

Where more than one seizure has occurred, an EEG may help to establish the type of epilepsy and guide therapy. As imaging becomes more sensitive, focal changes are picked up more often.

Inter-ictal EEG is abnormal in only about 50% of patients with recurrent seizures, so it cannot be used to exclude epilepsy. The sensitivity can be increased to about 85% by prolonging recording time and including a period of natural or drug-induced sleep, but this does not replace a well-taken history. Ambulatory EEG recording or video EEG monitoring may help with differentiation of epilepsy from other attack disorders if these are sufficiently frequent.

26.41 Indications for brain imaging in epilepsy

- Epilepsy starting after the age of 16 yrs
- Seizures having focal features clinically
- EEG showing a focal seizure source
- Control of seizures difficult or deteriorating

Imaging cannot establish a diagnosis of epilepsy but identifies any structural cause. It is not required if a confident diagnosis of a recognised epilepsy syndrome (e.g. juvenile myoclonic epilepsy) can be made. While CT will exclude a major structural cause of epilepsy, MRI is required to demonstrate subtle changes such as hippocampal sclerosis, which may direct or inform surgical intervention.

Management

It should be emphasised that epilepsy is a common disorder that affects 0.5–1% of the population, and that full control of seizures can be expected in approximately 70% of patients.

Immediate care

26.42 How to administer first aid for seizures

- Move person away from danger (fire, water, machinery, furniture)
- After convulsions cease, turn person into 'recovery' position (semi-prone)
- Ensure airway is clear but do **NOT** insert anything in mouth (tongue-biting occurs at seizure onset and cannot be prevented by observers)
- If convulsions continue for more than 5 mins or recur without person regaining consciousness, summon urgent medical attention
- Do not leave person alone until fully recovered (drowsiness and confusion can persist for up to 1 hr)

Anticonvulsant therapy

Anticonvulsant drug treatment (anti-epileptic drugs, or AEDs) should be considered after more than one unprovoked seizure. These agents either increase inhibitory neurotransmission in the brain or alter neuronal sodium channels to prevent abnormally rapid transmission of impulses. In the majority of patients, full control is achieved with a single drug. Dose regimens should be kept as simple as possible.

26.45 Guidelines for anticonvulsant therapy

- Start with one first-line drug (see Box 26.46)
- Start at a low dose; gradually increase dose until effective control of seizures is achieved or side-effects develop (drug levels may be helpful)
- Optimise compliance (use minimum number of doses per day)
- If first drug fails (seizures continue or side-effects develop), start second first-line drug, followed if possible by gradual withdrawal of first
- If second drug fails (seizures continue or side-effects develop), start second-line drug in combination with preferred first-line drug at maximum tolerated dose (beware interactions)
- If this combination fails (seizures continue or side-effects develop), replace second-line drug with alternative second-line drug
- If this combination fails, check compliance and reconsider diagnosis (Are events seizures? Occult lesion? Treatment compliance/alcohol/drugs confounding response?)
- Consider alternative, non-drug treatments (e.g. epilepsy surgery, vagal nerve stimulation)
- Use minimum number of drugs in combination at any one time

26.46 Guidelines for choice of anti-epileptic drug

Epilepsy type	First-line	Second-line	Third-line
Focal onset and/or secondary GTCS	Lamotrigine	Carbamazepine Levetiracetam Sodium valproate Topiramate Zonisamide Lacosamide	Clobazam Gabapentin Oxcarbazepine Phenobarbital Phenytoin Pregabalin Primidone Tiagabine
GTCS	Sodium valproate Levetiracetam	Lamotrigine Topiramate Zonisamide	Carbamazepine Phenytoin Primidone Phenobarbital Acetazolamide
Absence	Ethosuximide	Sodium valproate	Lamotrigine Clonazepam
Myoclonic	Sodium valproate	Levetiracetam Clonazepam	Lamotrigine Phenobarbital

N.B. Use as few drugs as possible at the lowest possible dose.

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Epilepsy surgery

Some patients with drug-resistant epilepsy benefit from surgical resection of epileptogenic brain tissue. Less invasive treatments, including vagal nerve stimulation or deep brain stimulation, may also be helpful in some patients. All those who continue to experience seizures despite appropriate drug treatment should be considered for surgical treatment. Planning such interventions will require intensive specialist assessment and investigation to identify the site of seizure onset and the dispensability of any targets for resection, i.e. whether the area of brain involved is necessary for a critical function such as vision or motor function.

Withdrawing anticonvulsant therapy

Withdrawal of medication may be considered after a patient has been seizure-free for more than 2 years.

Childhood-onset epilepsy, particularly classical absence seizures, carries the best prognosis for successful drug withdrawal. Other epilepsy syndromes, such as juvenile myoclonic epilepsy, have a marked tendency to recur after drug withdrawal.

Seizures that begin in adult life, particularly those with partial features, are also likely to recur, especially if there is an identified structural lesion. Overall, the recurrence rate after drug withdrawal depends on the individual's epilepsy history.

Contraception

Some AEDs induce hepatic enzymes that metabolise synthetic hormones, increasing the risk of contraceptive failure. This is most marked with carbamazepine, phenytoin and barbiturates, but clinically significant effects can be seen with lamotrigine and topiramate. If the AED cannot be changed, this can be overcome by giving higher-dose preparations of the oral contraceptive. Sodium valproate and levetiracetam have no interaction with hormonal contraception.

Pregnancy and reproduction

There is usually great concern about teratogenesis associated with AEDs.

26.47 Epilepsy in pregnancy

- **Provision of pre-conception counselling is best practice**: start folic acid 5 mg daily for 2 mths before conception to reduce the risk of fetal malformations.
- **Fetal malformation**: risk is minimised if a single drug is used.
  Carbamazepine and lamotrigine have the lowest incidence of major fetal malformations.
  The risk with sodium valproate is higher but should be carefully balanced against its benefits.
  Levetiracetam may be safe, but avoid other newer drugs if possible.
- **Learning difficulties in children**: IQ may be lower when children are exposed to valproate in utero, so its use should always be considered carefully.
- **Haemorrhagic disease of the newborn**: anticonvulsants increase risk. Give oral vitamin K 20 mg daily to the mother during the last month of pregnancy and give IM vitamin K 1 mg to the infant at birth.
- **Increased frequency of seizures**: where breakthrough seizures occur, monitor anticonvulsant levels and adjust the dose regimen accordingly.
- **Pharmacokinetic effects of pregnancy**: carbamazepine levels may fall in the third trimester. Lamotrigine and levetiracetam levels may fall early in pregnancy. Some advocate monitoring of levels.

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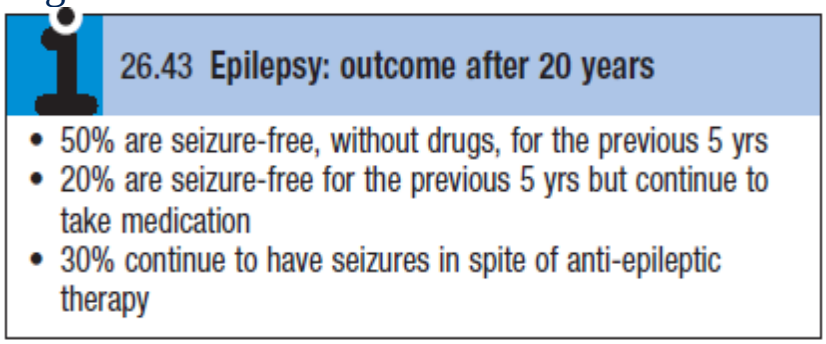
It is important to recognise that the background risk of severe fetal malformation in the population is around 2–3%. The modern AED most associated with teratogenesis is sodium valproate, which, at high dose, increases the risk to around 6-7%.

Seizures may become more frequent during pregnancy, particularly if pharmacokinetic changes decrease serum levels of AEDs.

Menstrual irregularities and reduced fertility are more common in women with epilepsy, and are also increased by sodium valproate. Patients with epilepsy are at greater risk of osteoporosis, almost independently of the drug used. Some centres advocate vitamin D supplementation in any patient with epilepsy, but the higher female risk of osteoporosis makes this most important in women.

Prognosis



26.43 Epilepsy: outcome after 20 years

- 50% are seizure-free, without drugs, for the previous 5 yrs
- 20% are seizure-free for the previous 5 yrs but continue to take medication
- 30% continue to have seizures in spite of anti-epileptic therapy

Status epilepticus

26.14 Management of status epilepticus

Initial

- Ensure airway is patent; give oxygen to prevent cerebral hypoxia
- Check pulse, blood pressure, BM stix® and respiratory rate
- Secure intravenous access
- Send blood for:
  - Glucose, urea and electrolytes, calcium and magnesium, liver function, anti-epileptic drug levels
  - Full blood count and clotting screen
  - Storing a sample for future analysis (e.g. drug misuse)
- If seizures continue for > 5 mins: give diazepam 10 mg IV (or rectally) *or* lorazepam 4 mg IV; repeat *once only* after 15 mins
- Correct any metabolic trigger, e.g. hypoglycaemia

Ongoing

If seizures continue after 30 mins

- IV infusion (with cardiac monitoring) with one of:
  - Phenytoin: 15 mg/kg at 50 mg/min
  - Fosphenytoin: 15 mg/kg at 100 mg/min
  - Phenobarbital: 10 mg/kg at 100 mg/min
- Cardiac monitor and pulse oximetry
  - Monitor neurological condition, blood pressure, respiration; check blood gases

If seizures still continue after 30–60 mins

- Transfer to intensive care
  - Start treatment for refractory status with intubation, ventilation and general anaesthesia using propofol or thiopental
  - EEG monitor

Once status controlled

- Commence longer-term anticonvulsant medication with one of:
  - Sodium valproate 10 mg/kg IV over 3–5 mins, then 800–2000 mg/day
  - Phenytoin: give loading dose (if not already used as above) of 15 mg/kg, infuse at < 50 mg/min, then 300 mg/day
  - Carbamazepine 400 mg by nasogastric tube, then 400–1200 mg/day
- Investigate cause

While generalised status epilepticus is most easily recognised, non-convulsive status may be less dramatic and less easily diagnosed. It may cause only altered awareness, confusion or wandering with automatisms. In an intensive care unit setting,

EEG monitoring is essential to ensure that diagnosis and treatment are optimised.

Non-epileptic attack disorder

The Most Useful/Specific Semiologic (Ictal) Features Suggestive of Psychogenic Nonepileptic Events

1. Pseudo sleep
2. Discontinuous (stop-and-go) activity
3. Irregular or asynchronous (out-of-phase) activity including side-to-side head movement
4. Nonclonic shaking with variable rhythm and direction
5. Pelvic thrusting
6. Opisthotonic posturing
7. Stuttering
8. Weeping
9. Preserved awareness during bilateral motor activity
10. Ictal eye closure
11. Prolonged immobile unresponsiveness with eyes closed (pseudo syncope)
12. Postictal whispering or other partial motor responses