Epilepsy

Epileptic seizure = paroxysmal, stereotyped, finite event apparent to the subject or an observer, resulting from sudden synchronised discharge of cerebral neurones
Epilepsy = continuing tendency to have unprovoked seizures; can make diagnosis after two typical seizures

Background

Prevalence
Affects about 0.5% of the population
1,000 UK deaths/year (roughly 50% accidents, 50% SUDEP)

Types
- Focal/partial
  - Simple
  - Complex
  - Secondary generalisation
  - Temporal lobe epilepsy: hallucinations, déja vu, fear, automatisms, rising sensation in abdomen
  - Focal motor (Jacksonian) epilepsy: march, then Todd’s paralysis
- Generalised
  - Tonic-clonic (grand mal)
  - Tonic
  - Myoclonic
  - Absence (petit mal): characteristic EEG: 3 Hz symmetrical spike-wave complexes, 5% risk of adult epilepsy
  - Akinetic
  - Febrile convulsions: 6m-6y, 1:3 further attack, 1% subsequent epilepsy
  - West syndrome: salaam attack esp. on waking, progressive mental handicap, characteristic EEG: hypsarrhythmia
  - Juvenile myoclonic (Janz syndrome): rare generalised seizures esp. on waking, daytime absences, myoclonus esp. in mornings (‘Kellogg’s epilepsy’), linked to chr. 6, EEG: polyspike-wave complexes, photosensitivity; Rx: lamotrigine, topiramate, levetiracetam, zonisamide

Aetiology
- Primary
- Secondary
  - TINV
  - Metabolic: e.g. hypo, electrolyte derangements, drugs (antibiotics, antidepressants, antipsychotics, L-dopa, theophylline, thiazides)

Ix
- Bloods: glu, electrolytes
- Electrical: EEG ± sleep deprivation/photic stimulation/hyperventilation ± videotelemetry
- Imaging: CT ± MRI

Rx
- Treat secondary causes, incl. rare surgical intervention (e.g. TLE)
- Conservative: avoid EtOH/flickering lights
- Medical: anticonvulsants (usually the mainstay)
  - Educate patient regarding
    - Nature of the disease and drug therapy
    - Importance of compliance
    - Importance of never suddenly stopping treatment

Mechanism
- Neuronal discharge (paroxysmal depolarising shift) may remain localised (focal/partial epilepsy) or spread (generalised epilepsy)
- Due to excessive activity of excitatory amino acids and/or reduced activity of inhibitory amino acids
All anti-epileptic agents thus prevent depolarisation of neurones
- Blockade of excitatory amino acid or induced sodium channel activity
- Stimulation of inhibitory neurotransmitters (GABA)
- Other mechanisms?
  - E.g. blockade of T-type calcium channels

**Principles of drug therapy**

**Initiation of therapy**
- Use drug with proven efficacy in type of epilepsy seen
- Aim for monotherapy (possible in 70%)
- Start with low dose and escalate over ca. 1m (enzyme induction), up to MTD if necessary
  - Assist dose selection by TDM
- Ca. 3 months’ treatment with any given agent is necessary to determine efficacy
- Observe seizure diary for diurnal variation and adjust dosing times to give peak concentrations at that time of day

If unable to achieve control
- Confirm compliance by trough level monitoring
- Change to new agent of different class or add a second agent of a different class

Disadvantages of polytherapy
- Interactions via hepatic metabolism is largely unpredictable – need therapeutic monitoring
- Enhanced toxicity

**Therapeutic drug monitoring**

**Indications**
- 2-4w after commencing therapy to guide dosing
- Failure on standard dose of drug
  - Inadequate dosing for that individual
  - Failure of compliance
- Adverse effects
- Valproate
  - When valproate added to another drug
  - When another drug is withdrawn in the presence of valproate
- Pregnancy
- Hepatic or renal disease

**Duration and withdrawal of therapy**

80% are fit-free 1y after withdrawal, if epilepsy is primary

**Advantages**
- Avoid SEs
- Avoid potential effects on cognition
cognition
development in children

**Disadvantages**
- 20% relapse in 1y, another 20% in 5y, then rare
  - More likely if severe, slow to control, multdrug Rx (MRC trial, 1995)
- Potential effect on driving (type 1 license: need to be fit-free for 1y)

Consider withdrawal if fit-free for 3-4y, proceeding over months. One agent at a time, if polytherapy. If a fit recurs then need to reintroduce previous maximal therapy.

**OCP**

Induction of steroid metabolising enzymes can impair efficacy of OCP → use high oestrogen preparations or alternative method.

**Pregnancy**

Consider wide differential other than epilepsy
- Eclampsia
- Venous sinus thrombosis
• CVA, ICH, SAH
• TTP
• Other differentials not specific to pregnancy

A first seizure that cannot readily be attributed to eclampsia or epilepsy warrants CT or MRI.

All anticonvulsants are potentially teratogenic
• Cleft lip and palate
• Cardiac defects
• NTDs due to altered folate metabolism with most drugs

Risk greater with polytherapy
Risk of seizure outweighs risk of anticonvulsant
Counselling, specialist referral, 5mg pre-conceptual folic acid, antenatal screening (AFP + second trimester USS), vitamin K before delivery

**Carbamazepine** is drug of choice for women of child bearing potential
Requires careful monitoring
  • Change in plasma protein binding
  • Change in hepatic drug metabolism

**Breastfeeding**
Drugs are excreted in small quantities into breast milk but only phenobarbitone and ethosuximide are a CI to breastfeeding

**Adverse effects**
Can be
  • Dose-related CNS effects explicable in terms of mode of action
  • Idiosyncratic allergic/other effects inexplicable

**Refractory epilepsy**
• 30%
• Surgery may be an option in selected cases

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**Drugs of choice in specific seizure types**

<table>
<thead>
<tr>
<th>Seizure disorder</th>
<th>Drugs of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalised</strong></td>
<td></td>
</tr>
<tr>
<td>Primary generalised tonic-clonic (grand mal)</td>
<td>valproate, carbamazepine (phenytoin)</td>
</tr>
<tr>
<td>Absence (petit mal)</td>
<td>ethosuximide, valproate</td>
</tr>
<tr>
<td>West syndrome</td>
<td>vigabatrin (oddly enough, steroids can be used, too)</td>
</tr>
<tr>
<td>Juvenile myoclonic</td>
<td>valproate, lamotrigine, topiramate</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td></td>
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</tbody>
</table>

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**Summary of mechanisms of action**

GABA-ergic
1. Facilitation of postsynaptic action  
   BZs barbiturates\(^1\)

2. Inhibition of breakdown (GABA transaminase inhibitor)  
   vigabatrin valproate

3. Inhibition of GABA reuptake  
   tiagabine

4. Direct agonist  
   gabapentin pregabalin

**Sodium channel blockers**

Bind to open sodium channels, producing use-dependent block – thus preferentially block channels in rapidly depolarising tissue

phenytoin\(^2\)  
carbamazepine lamotrigine valproate

**Other**

T-type calcium channel blocker ethosuximide

Also see below

**Future**

Development of antagonists to action of excitatory amino acids e.g. glutamate, NMDA, AMPA

**Influence on body weight**

Weight gain
- Valproate
- Gabapentin
- Pregabalin

Weight loss
- Topiramate
- Zonisamide

**Carbamazepine (Tegretol\(^1\))**

TCA derivative

**Indications**

Considered a drug of choice for
- Partial seizures
- Tonic-clonic seizures (second line)
- Neuropathic pain (e.g. trigeminal/post-herpetic neuralgia)

Also used for

\(^1\)Phenobarbitone is a much more effective anticonvulsant than might be expected from its degree of GABA potentiation  
\(^2\) Also affects calcium currents and causes intracellular protein phosphorylation
• Prophylaxis of bipolar disorder unresponsive to lithium
• Cranial DI (unlicensed)

Is a potent inducer of hepatic drug metabolising enzymes
• Own half life reduces over 2-3 weeks from 35 to 20 hours
  o Hence must start on low dose and gradually escalate
• Complex drug interactions with other anticonvulsant agents/other drugs (WOPT)

Adverse effects
• CNS: blurred vision, diplopia, N, V
  o May be dose-limiting – try altering the timing or using an MR preparation
• Heart: AV depression
• Liver: vitamin D/folate deficiency through enzyme induction, cholestatic jaundice
• Other: morbilliform rashes (may proceed to erythema multiforme), SIADH
• Rare idiosyncratic bone marrow suppression

Cost
1 years’ treatment is about £25

Phenytoin (Epanutin®)

Indications
Considered a drug of choice for
• Status epilepticus
• Tonic-clonic seizures (third line due to narrow therapeutic window)

Also used for
• Neuropathic pain
• Digoxin-induced arrhythmias
• ??Alcohol withdrawal (structurally related to barbiturates)

Contraindications
• 2nd/3rd degree heart block
• Previous bone marrow depression

Can worsen myoclonic epilepsy.

Note
• Fosphenytoin is a new, water-soluble prodrug of phenytoin
  o Better tolerated at infusion site
  o Can give IM
  o Can give more rapidly
  o Converted to phenytoin by non-specific phosphatases
  o Does not contain propylene glycol \( \rightarrow \) less CV adverse effects

Administration
• ECG monitoring
• In saline (can precipitate in dextrose)
• Avoid extravasation – very irritant

Pharmacokinetics
Phenytoin has some important pharmacokinetic considerations
• Significant plasma protein binding (90%)
• Saturation (zero order kinetics)
  o First order kinetics at low dose \( (t_{1/2} \approx 12h) \)
  o Zero order kinetics at higher therapeutic doses \( (t_{1/2} \approx 60h) \)
  o Thus, at higher dose need smaller and less frequent dose increments
• Hepatic enzyme induction
  o Potent inducer of own metabolism
    endogenous substances e.g. vitamin D and folate
    other drugs e.g. antiepileptics, warfarin, steroids etc.
• Inhibition of metabolism
  o By competition for the metabolising enzyme or direct inhibition
  o Large number of drugs

**Note**
1. Opportunity for numerous significant drug interactions
2. Always check when combining phenytoin with any other medication

**Adverse effects**
Very likely to cause SEs (thus no longer first line):
- Rashes, erythema nodosum
- Extravasation at infusion site causes purple glove syndrome, with oedema and/or necrosis of skin
- SLE, selective IgA deficiency
- Dupuytren’s
- Peripheral neuropathy
- Gum hyperplasia
- Facial coarsening
- Hirsutism (*not* hypertrichosis), alopecia
- Acne
- Impaired cognition, sedation
- Cerebellar disorders
- Fits
- Arrhythmia
- Megaloblastic anaemia (B12 malabsorption)
- Osteomalacia (vitamin D malabsorption)
- Phenytoin hypersensitivity syndrome: fever, rash, LN, hepatomegaly, abnormal LFTs, eosinophilia; can be fatal, only safe alternative = valproate

**Cost**
1 years’ treatment is about £25

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**Valproate (Epilim®)**

GABA transaminase inhibitor, but *in vitro* studies suggest that little effect at clinical dose; also induced GABA synthesis by glutamic acid decarboxylase.

**Indications**
Considered a drug of choice for
- Tonic-clonic seizures (first line)
- Absence seizures (second line)
- Partial seizures (third line)

Also used for
- Neuropathic pain
- Tremors

**Interactions**
- Does not induce drug metabolism but can inhibit metabolism of other anti-epileptics
- Own metabolism enhanced by other anti-epileptic agents

**Adverse effects**
Rare
- CNS: nausea, ataxia, tremor, confusion
- Others
  o Rashes
  o Hirsutism
  o Alopecia with curly regrowth after stopping
  o Weight gain (probably hypothalamic stimulation)
  o Elevated LFTs – monitor until return to normal, if ↑PT: stop (hepatotoxicity: children>adults)
  o Pancreatitis
  o Amenorrhea
  o Thrombocytopenia, pancytopenia
**Ethosuximide**

**Indications**
Considered a drug of choice for
- Simple absence seizures

Also used for
- Myoclonic seizures
- Atypical absences
- Atonic seizures
- Tonic seizures

**Adverse effects**
- SLE
- CNS: drowsiness, dizziness, ataxia
- GI upset
- Allergic reactions
- Bone marrow suppression

**Cost**
1 year’s treatment is about £150

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**Barbiturates**

E.g. [phenobarbital](https://en.wikipedia.org/wiki/Phenobarbital) (formerly phenobarbitone)
[primidone](https://en.wikipedia.org/wiki/Primidone) (largely metabolised to [phenobarbital](https://en.wikipedia.org/wiki/Phenobarbital))

**Indications**
No longer drugs of choice
Can be used as second line in all forms of epilepsy

**Adverse effects**
- Sedation
- Hyperkinesia in children
- Megaloblastic anaemia

**Cost**
1 year’s treatment is about £5 (phenobarbitone)

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**Benzodiazepines**

Most are too sedative for clinical use
Effectiveness tends to wane on long-term therapy

**Indications**
- Status epilepticus (first line – lorazepam IV or diazepam PR)³
- Clusters of seizures (clobazam)

**Adverse effects**
- Sedation
- Hypotonia
- Impaired co-ordination

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Cost
1 years’ treatment is about £150 (clonazepam)

## Other antiepileptic agents

Because effective treatments for epilepsy are available, new drugs are initially used as add-on therapy in patients who are not adequately controlled with current medication. A licence for monotherapy is usually obtained later when evidence of safety and efficacy in man has been obtained.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>Use-dependent Na⁺ channel blocker</td>
<td>Mono or combination (partial seizures, tonic-clonic seizures, Lennox–Gastaut) Less CNS effects than most older agents SEs: rashes, Stevens-Johnson syndrome, mood changes, tremor, influenza-like Sx, angioedema</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>GABA analogue; causes irreversible inhibition of GABA-transaminase</td>
<td>Withdrawn Combination only (partial seizures, West syndrome) Less CNS effects than other drugs Causes visual field defects (all GABA-ergic drugs can cause retinal toxicity, usually reversible), mood disturbance, weight gain</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>GABA analogue; developed as a GABA agonist, but little agonist activity – must have other, unknown mechanisms of action</td>
<td>Combination only (partial seizures) Other indications: neuropathic pain, augmentation of antidepressants SEs: somnolence, ataxia, dizziness, other CNS effects</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>GABA analogue</td>
<td>Combination only (partial seizures) Other indications: neuropathic pain</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Na⁺ channel blocker, Ca²⁺ channel blocker, AMPA/kainate channel inhibition, GABA channel activator (multiple effects ?due to action on channel phosphorylation, e.g. via protein kinase A)</td>
<td>Combination only (partial seizures) Avoid if Hx of renal stones</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Inhibition of GABA reuptake</td>
<td>Combination only (partial seizures)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Mechanism differs from other antiepileptics</td>
<td>Combination only (partial seizures) Well tolerated; SEs: sedation, very rare paradoxical worsening of seizures No P₄₅₀ effects</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Combined Na⁺ and T-type Ca²⁺ channel blocker Also enhanced GABA release, reduced potassium-evoked glutamate response, reduced glutamate-mediated synaptic excitation</td>
<td>Combination only (partial seizures) Only recently released in West; over a decade of use in Japan No drug interactions with most other AEDs; caution with topiramate (↑risk of kidney stones) SEs: somnolence, ataxia, rash (zonisamide is a sulphonamide), Stevens-Johnson, kidney stones, anhidrosis No major drug interactions although ↓t₁/₂ with enzyme inducers</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Na⁺ channel blocker + other</td>
<td>Combination only (Lennox-Gastaut syndrome)</td>
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<tr>
<td><strong>(Inovelon®)</strong></td>
<td>Structurally similar to lamotrigine</td>
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<tr>
<td><strong>Retigaline</strong></td>
<td>K⁺ channel activator + other</td>
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<tr>
<td><strong>Lacosamide</strong></td>
<td>Functionalised amino acid</td>
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<tr>
<td><strong>(Vimpat®)</strong></td>
<td>Exact mechanism of action unknown, but enhances slow inactivation of Na⁺ channels and binds to collapsing response mediator protein-2 (CRMP-2), which is involved in neuronal differentiation and axonal outgrowth</td>
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<tr>
<td></td>
<td>SEs: PR prolongation</td>
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</tr>
<tr>
<td></td>
<td>No drug interactions with other AEDs or OCP</td>
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</tr>
</tbody>
</table>

**AMPA antagonists**