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
  development in children

Disadvantages

- 20% relapse in 1y, another 20% in 5y, then rare
    - More likely if severe, slow to control, multidrug 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

Drugs of choice in specific seizure types

Seizure disorder	Drugs of choice
Generalised	
Primary generalised tonic-clonic (grand mal)	valproate carbamazepine (phenytoin)
Absence (petit mal)	ethosuximide valproate
West syndrome	vigabatrin (oddly enough, steroids can be used, too)
Juvenile myoclonic	valproate lamotrigine topiramate
Partial	carbamazepine lamotrigine valproate

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®)

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
    - 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
    - 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
- $2^{nd}/3^{rd}$ degree heart block
- Previous bone marrow depression

Can worsen myoclonic epilepsy.

Note
- **Fosphenytoin** is a new, water-soluble prodrug of phenytoin
    - Better tolerated at infusion site
    - Can give IM
    - Can give more rapidly
    - Converted to phenytoin by non-specific phosphatases
    - Does not contain propylene glycol → 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)
    - First order kinetics at low dose ($t_{1/2}$ approx. 12h)
    - Zero order kinetics at higher therapeutic doses ($t_{1/2}$ approx. 60h)
    - Thus, at higher dose need smaller and less frequent dose increments
- Hepatic enzyme induction
    - Potent inducer of own metabolism
      endogenous substances e.g. vitamin D and folate
      other drugs e.g. antiepileptics, warfarin, steroids etc.

- Inhibition of metabolism
    - By competition for the metabolising enzyme or direct inhibition
    - 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 (B_{12} 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

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
    - Rashes
    - Hirsutism
    - Alopecia with curly regrowth after stopping
    - Weight gain (probably hypothalamic stimulation)
    - Elevated LFTs – monitor until return to normal, if ↑PT: stop (hepatotoxicity: children>adults)
    - Pancreatitis
    - Amenorrhoea
    - Thrombocytopenia, pancytopenia

Cost
1 years' treatment is about £100

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 years' treatment is about £150

Barbiturates

E.g. phenobarbital (formerly phenobarbitone)
primidone (largely metabolised to 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 years' treatment is about £5 (phenobarbitone)

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

[3] WALKER, M. (2005): Status epilepticus – an evidence-based guide. *BMJ* **331**:673-7.

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.

Agent	Mechanism	Comments
Lamotrigine (Lamictal®)	Use-dependent Na^+ channel blocker	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
Vigabatrin (Sabril®)	GABA analogue; causes irreversible inhibition of GABA-transaminase	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
Gabapentin (Neurontin®)	GABA analogue; developed as a GABA agonist, but little agonist activity – must have other, unknown mechanisms of action	Combination only (partial seizures) Other indications: neuropathic pain, augmentation of antidepressants SEs: somnolence, ataxia, dizziness, other CNS effects
Pregabalin (Lyrica®)	GABA analogue	Combination only (partial seizures) Other indications: neuropathic pain
Topiramate (Topamax®)	Na^+ channel blocker, Ca^{2+} channel blocker, AMPA/kainate channel inhibition, GABA channel activator (multiple effects ?due to action on channel phosphorylation, e.g. via protein kinase A)	Combination only (partial seizures) Avoid if Hx of renal stones
Tiagabine (Gabitril®)	Inhibition of GABA reuptake	Combination only (partial seizures)
Levetiracetam (Keppra®)	Mechanism differs from other antiepileptics • Only works in true seizures, not in induced seizure models which were used to develop classical antiepileptics • May offer benefit where other drugs have failed Main mechanism: binds to SV2A (synaptic vesicle protein 2A), which might bind calcium-sensing synaptotagmin and thus modulate transmitter exocytosis Awaiting further characterisation	Combination only (partial seizures) Well tolerated; SEs: sedation, very rare paradoxical worsening of seizures No P_{450} effects
Zonisamide (Zonegran®)	Combined Na^+ and T-type Ca^{2+} channel blocker Also enhanced GABA release, reduced potassium-evoked glutamate response, reduced glutamate-mediated synaptic excitation	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 $\downarrow t_{1/2}$ with enzyme inducers
Rufinamide	Na^+ channel blocker + other	Combination only (Lennox-Gastaut syndrome)

(Inovelon®)	Structurally similar to lamotrigine	
Retigaline	K^+ channel activator + other	
Lacosamide (Vimpat®)	Functionalised amino acid 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	SEs: PR prolongation No drug interactions with other AEDs or OCP
AMPA antagonists		