

Antiepileptics

Medicines that suppress pathological neuronal firing through sodium-channel blockade, enhanced GABAergic inhibition, calcium-channel modulation or synaptic vesicle binding, grouped here by that mechanism because it predicts the interaction and toxicity profile far better than the seizure type does.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/antiepileptics>

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Quick revision

One Liner: Antiepileptics raise the threshold for pathological firing rather than curing epilepsy, and the mechanism a drug uses predicts its interactions, its adverse effects and its behaviour in pregnancy.

1. Sodium-channel blockers such as phenytoin, carbamazepine, oxcarbazepine and lamotrigine stabilise hyperexcitable membranes and inhibit repetitive neuronal firing. [5][7]
2. Carbamazepine is a potent inducer of hepatic CYP3A4 and also induces CYP1A2, 2B6 and 2C8/9/19, so it lowers the plasma concentration of many co-prescribed medicines. [2]
3. Carbamazepine also induces its own metabolism; the label states that autoinduction is completed after three to five weeks of a fixed dosing regimen. [2]
4. Phenytoin is hydroxylated by a saturable enzyme system, so small incremental doses may produce very substantial increases in serum levels. [5]
5. Lamotrigine carries a boxed warning for serious rash including Stevens-Johnson syndrome, and the label lists co-administration with valproate as a suggested risk factor. [3]
6. Valproate carries boxed warnings for hepatotoxicity, fetal risk and pancreatitis, and in the UK is contraindicated in women and girls of childbearing potential unless the Pregnancy Prevention Programme conditions are met. [4][11]
7. Levetiracetam is largely renally excreted unchanged and is neither an inhibitor of nor a high-affinity substrate for the major cytochrome P450 isoforms, which is why it carries so few interactions. [1]
8. Antiepileptic drugs as a class increase the risk of suicidal thoughts or behaviour, at an estimated incidence of 0.43% against 0.24% on placebo. [1]

Overview

1. Antiepileptic drugs suppress the abnormal, synchronised neuronal discharge that produces a seizure. They do not correct the underlying epileptogenic process, and the label for carbamazepine notes that monitoring of blood levels has increased the efficacy and safety of anticonvulsants, particularly where seizure frequency rises dramatically or adherence needs verifying. Because several of these medicines are used for years, their long-term metabolic, haematological and reproductive effects matter as much as their acute efficacy. [2]
2. The class is best learned by mechanism. Sodium-channel blockers act on the membrane itself: the phenytoin label describes the drug as tending to stabilise the threshold against hyperexcitability, and the oxcarbazepine label describes blockade of voltage-sensitive sodium channels producing stabilisation of hyperexcited neural membranes and inhibition of repetitive neuronal firing. Agents acting through GABA, through the alpha-2-delta subunit of voltage-activated calcium channels, or through the synaptic vesicle protein SV2A form the other groups. [5][7][9][1]
3. Two properties separate the older agents from the newer ones and explain most of the prescribing difficulty. The first is enzyme induction: carbamazepine and phenobarbital both induce hepatic microsomal enzymes and reduce the effect of drugs metabolised by them, including oral anticoagulants and hormonal contraceptives. The second is teratogenicity, which is why valproate has been progressively restricted in people who could become pregnant. [2][10][11]

Classification and drug examples

Intro: Grouped by the molecular target each agent acts on, because that is what predicts its interaction profile and its characteristic adverse effects. Several agents act by more than one mechanism and are placed by their dominant one.

1. Name: Voltage-gated sodium-channel blockers

1. Note: The membrane-stabilising agents. They share a tendency to cause dose-related dizziness, diplopia and ataxia, and several carry serious cutaneous risk.

1. Name: Phenytoin

Diphenylhydantoin

1. Route: Oral and intravenous

1. Note: Its label states that, possibly by promoting sodium efflux from neurons, phenytoin tends to stabilise the threshold against hyperexcitability. Saturable hepatic hydroxylation makes its serum levels disproportionate to dose. [5]

2. Name: Carbamazepine

2. Route: Oral

2. Note: Described in its label as acting by reducing polysynaptic responses and blocking post-tetanic potentiation. Absence seizures do not appear to be controlled by it. [2]

3. Name: Oxcarbazepine

3. Route: Oral

3. Note: A structural relative of carbamazepine. Its label reports clinically significant hyponatraemia below 125 mmol/L in 2.5% of treated patients in controlled epilepsy studies. [7]

4. Name: Lamotrigine

4. Route: Oral

4. Note: Carries a boxed warning for serious rash. Its label puts the incidence of serious rash at approximately 0.8% in paediatric patients and 0.3% in adults receiving it as adjunctive epilepsy therapy. [3] [5][7]

2. Name: Broad-spectrum agents with multiple mechanisms

2. Note: Agents effective across several seizure types, whose breadth of action is matched by a broader adverse-effect burden.

1. Name: Sodium valproate

Valproate

1. Route: Oral and intravenous

1. Note: Carries boxed warnings for hepatotoxicity, fetal risk and pancreatitis, and is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations. [4]

2. Name: Valproic acid

2. Route: Oral

2. Note: The free acid form. Its label reports dose-related thrombocytopenia, and hyperammonaemia that may be present despite normal liver function tests. [4]

3. Name: Topiramate

3. Route: Oral

3. Note: Inhibits carbonic anhydrase, which its label identifies as the cause of a hyperchloraemic, non-anion-gap metabolic acidosis from renal bicarbonate loss. [6] [4][6]

3. Name: Synaptic vesicle protein 2A ligands

3. Note: The group defined by binding to SV2A, notable clinically for a very clean pharmacokinetic profile alongside prominent behavioural effects.

Name: Levetiracetam

Keppra

Route: Oral and intravenous

Note: Its label states that the precise mechanism is unknown, but describes a saturable and stereoselective binding

site identified as the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. [1] [1]

4. Name: GABA-enhancing agents

4. Note: Agents that increase inhibitory GABAergic transmission. Sedation is the shared effect; the specific toxicities differ sharply between members.

1. Name: Phenobarbital

Phenobarbitone

1. Route: Oral and parenteral

1. Note: One of the few barbiturates effective as an oral anticonvulsant in subhypnotic doses, indicated for generalised and partial seizures. Tolerance and physical dependence may occur with continued use. [10]

2. Name: Vigabatrin

Sabril

2. Route: Oral

2. Note: Restricted by a boxed warning for permanent bilateral concentric visual field constriction; its label states there is no dose or exposure known to be free of the risk of vision loss. [8] [10][8]

5. Name: Alpha-2-delta calcium-channel ligands

5. Note: Agents binding the auxiliary subunit of voltage-activated calcium channels, used adjunctively in focal epilepsy and widely in neuropathic pain.

Name: Gabapentin

Neurontin

Route: Oral

Note: Binds with high affinity to the alpha-2-delta subunit of voltage-activated calcium channels, though its label states the relationship of that binding to therapeutic effect is unknown, and that it has no effect on GABA binding, uptake or degradation. [9] [9]

Mechanism of action

Summary: No single mechanism defines the class. Sodium-channel blockers stabilise hyperexcitable membranes and inhibit repetitive firing; GABA-enhancing agents raise inhibitory tone; alpha-2-delta ligands bind an auxiliary calcium-channel subunit; and levetiracetam binds the synaptic vesicle protein SV2A. Several labels state candidly that the relationship between the molecular action and the clinical anticonvulsant effect remains unproven.

Target: Voltage-gated sodium channels, GABAergic inhibitory transmission, the alpha-2-delta subunit of voltage-activated calcium channels, and synaptic vesicle protein SV2A

Cidal Static: Seizure-suppressing rather than disease-modifying

Kill Kinetics: Sustained suppression dependent on maintained plasma concentrations

1. Step: 1

1. Title: Membrane stabilisation through sodium-channel blockade

1. Detail: Oxcarbazepine and its metabolite produce blockade of voltage-sensitive sodium channels, resulting in stabilisation of hyperexcited neural membranes and inhibition of repetitive neuronal firing. Phenytoin is described as tending to stabilise the threshold against hyperexcitability, possibly by promoting sodium efflux from neurons. [7][5]

2. Step: 2

2. Title: Reduction of polysynaptic transmission

2. Detail: Carbamazepine has demonstrated anticonvulsant properties in animal models of electrically and chemically induced seizures, and appears to act by reducing polysynaptic responses and blocking post-tetanic potentiation. [2]

3. Step: 3

3. Title: Enhancement of inhibitory GABAergic tone

3. Detail: Barbiturates such as phenobarbital act on inhibitory transmission, and phenobarbital is among the few effective as an oral anticonvulsant at subhypnotic doses, indicated for generalised and partial seizures. [10]

4. Step: 4

4. Title: Binding of the calcium-channel alpha-2-delta subunit

4. Detail: Gabapentin binds with high affinity to the alpha-2-delta subunit of voltage-activated calcium channels. Its label is explicit that the relationship of this binding to therapeutic effect is unknown, and that despite its structural resemblance to GABA it has no effect on GABA binding, uptake or degradation. [9]

5. Step: 5

5. Title: Binding of synaptic vesicle protein SV2A

5. Detail: Levetiracetam binds a saturable, stereoselective neuronal site identified as synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. The molecular significance of that binding is not understood, but the finding suggests it may contribute to the antiepileptic mechanism. [1]

6. Step: 6

6. Title: Carbonic anhydrase inhibition as a secondary mechanism

6. Detail: Topiramate inhibits carbonic anhydrase. This is not thought to be its principal anticonvulsant action, but it accounts for two of its characteristic adverse effects: a hyperchloraemic, non-anion-gap metabolic acidosis from renal bicarbonate loss, and a raised risk of renal stones through reduced urinary citrate excretion and increased urinary pH. [6]

Major clinical uses

1. Drug: Levetiracetam

1. Organism: Not applicable

1. Indication: Adjunctive therapy for partial-onset seizures, and for myoclonic seizures in juvenile myoclonic epilepsy

1. Line: widely used

1. Note: Indicated as adjunctive therapy in partial-onset seizures in adults and children four years and older, and in myoclonic seizures in adults and adolescents twelve years and older with juvenile myoclonic epilepsy. [1]

2. Drug: Carbamazepine

2. Organism: Not applicable

2. Indication: Focal seizures and generalised tonic-clonic seizures, and trigeminal neuralgia

2. Line: established

2. Note: Not appropriate for every seizure type: its label states that absence seizures do not appear to be controlled by carbamazepine, and advises caution in mixed seizure disorders including atypical absence seizures. [2]

3. Drug: Sodium valproate

3. Organism: Not applicable

3. Indication: Generalised epilepsies, including absence and myoclonic seizures

3. Line: established, heavily restricted

3. Note: Its use is constrained by reproductive toxicity rather than by efficacy. UK regulators state it must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met. [11][4]

4. Drug: Lamotrigine

4. Organism: Not applicable

4. Indication: Adjunctive therapy for epilepsy across several seizure types

4. Line: established

4. Note: Its principal limitation is cutaneous rather than neurological; the rate of serious rash is greater in paediatric patients than in adults. [3]

5. Drug: Gabapentin

5. Organism: Not applicable

5. Indication: Adjunctive therapy for partial-onset seizures, and postherpetic neuralgia

5. Line: adjunctive

5. Note: Indicated as adjunctive therapy in partial-onset seizures with and without secondary generalisation in adults

and children three years and older, and separately for postherpetic neuralgia in adults. [9]

6. Drug: Vigabatrin

6. Organism: Not applicable

6. Indication: Reserved use in refractory epilepsy, constrained by ophthalmic toxicity

6. Line: restricted

6. Note: Its label states that risk of new and worsening vision loss continues as long as the drug is used, and that even with frequent monitoring some patients will develop severe vision loss. [8]

7. Drug: Phenobarbital

7. Organism: Not applicable

7. Indication: Generalised and partial seizures

7. Line: older agent

7. Note: Still widely used internationally where cost and availability govern choice, but sedation, enzyme induction and dependence limit its place where alternatives exist. [10]

Pharmacokinetics

1. Drug: Phenytoin

1. Route: Oral and intravenous

1. Absorption: Oral absorption varies by formulation

1. Csf Penetration: Not applicable

1. Metabolism: Hepatic hydroxylation by a saturable enzyme system

1. Elimination: Hepatic

1. Half Life: Variable and concentration-dependent

1. Dose Adjust: Saturable metabolism means small incremental doses may produce very substantial increases in serum levels [5]

2. Drug: Carbamazepine

2. Route: Oral

2. Absorption: Oral

2. Csf Penetration: Not applicable

2. Metabolism: CYP3A4 is the major isoform forming carbamazepine-10,11-epoxide

2. Elimination: Hepatic

2. Half Life: Variable, because the drug induces its own metabolism

2. Dose Adjust: Autoinduction is completed after three to five weeks of a fixed dosing regimen [2]

3. Drug: Levetiracetam

3. Route: Oral and intravenous

3. Absorption: Oral

3. Csf Penetration: Not applicable

3. Metabolism: Not a high-affinity substrate for hepatic cytochrome P450 isoforms

3. Elimination: Renal; 66% of the dose is excreted unchanged

3. Half Life: Short

3. Dose Adjust: Reduced in impaired renal function, with supplemental doses after dialysis [1]

4. Drug: Gabapentin

4. Route: Oral

4. Absorption: Oral

4. Csf Penetration: Not applicable

4. Metabolism: Not appreciably metabolised

4. Elimination: Renal excretion as unchanged drug

4. Half Life: Short

- 4. Dose Adjust: Adjustment recommended in renal impairment and in patients undergoing haemodialysis [9]
- 5. Drug: Phenobarbital
- 5. Route: Oral and parenteral
- 5. Absorption: Oral
- 5. Csf Penetration: Not applicable
- 5. Metabolism: Hepatic microsomal enzyme system
- 5. Elimination: Approximately 25% to 50% of a dose is eliminated unchanged in the urine
- 5. Half Life: Long
- 5. Dose Adjust: Induces hepatic microsomal enzymes, altering the metabolism of other drugs [10]
- 1. This page gives no dose regimens. Selection, titration and monitoring of an antiepileptic belong to the treating clinician working from a current prescribing reference, because they depend on seizure type, age, comorbidity, pregnancy plans and concurrent medicines.
- 2. Two pharmacokinetic behaviours in this class are examined repeatedly: the saturable hydroxylation of phenytoin, and the autoinduction by carbamazepine of its own metabolism. [5][2]
- 3. The renally cleared agents, levetiracetam and gabapentin, are the ones that avoid hepatic interaction problems but require attention to renal function instead. [1][9]

Adverse effects

- 1. Effect: Central nervous system effects
 - 1. Detail: The levetiracetam label groups its central nervous system adverse events into somnolence and fatigue, coordination difficulties, and behavioural abnormalities. Sedation and unsteadiness are shared across much of the class. [1]
- 2. Effect: Cognitive and language difficulty with topiramate
 - 2. Detail: Reported as confusion, psychomotor slowing, difficulty with concentration or attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties. [6]
- 1. Effect: Suicidal thoughts or behaviour
 - 1. Detail: Antiepileptic drugs as a class increase this risk for any indication. Pooled analyses found approximately twice the risk against placebo, an estimated incidence of 0.43% against 0.24%, or roughly one additional case for every 530 patients treated.
 - 1. Action: A recognised class effect that warrants monitoring for mood change; assessment and any change of treatment rest with the treating clinician. [1]
- 2. Effect: Serious cutaneous reactions
 - 2. Detail: Carbamazepine carries a boxed warning for serious and sometimes fatal dermatologic reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, estimated at 1 to 6 per 10,000 new users in mainly Caucasian populations and about ten times higher in some Asian countries. Lamotrigine carries its own boxed warning for serious rash.
 - 2. Action: Both labels direct that treatment is reconsidered at the first sign of rash unless the rash is clearly not drug related. [2][3]
- 3. Effect: Aplastic anaemia and agranulocytosis with carbamazepine
 - 3. Detail: Its boxed warning reports a risk of these reactions 5 to 8 times greater than in the general population, against an untreated background of approximately six per million per year for agranulocytosis and two per million per year for aplastic anaemia.
 - 3. Action: Complete pretreatment haematological testing is obtained as a baseline, and discontinuation is considered if significant bone marrow depression develops. [2]
- 4. Effect: Hepatotoxicity and pancreatitis with valproate
 - 4. Detail: Hepatic failure resulting in fatalities has occurred, usually within the first six months of treatment, and children under two are at considerably increased risk. Life-threatening pancreatitis, sometimes haemorrhagic with rapid

progression to death, has been reported in both children and adults.

4. Action: Serum liver tests are performed before therapy and at frequent intervals thereafter, especially during the first six months; abdominal pain, nausea, vomiting or anorexia require prompt medical evaluation. [4]

5. Effect: Permanent visual field loss with vigabatrin

5. Detail: Permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability, and in some cases decreased visual acuity. Risk rises with dose and cumulative exposure, and continues for as long as the drug is used and possibly after it is stopped.

5. Action: The label states that even with frequent monitoring some patients will develop severe vision loss, which is why the agent is reserved. [8]

6. Effect: Respiratory depression with gabapentin and opioids

6. Detail: Respiratory depression and sedation, sometimes resulting in death, have been reported following coadministration of gabapentin with opioids, and in the setting of underlying respiratory impairment.

6. Action: Relevant wherever a patient on gabapentin is also receiving an opioid or another central nervous system depressant. [9]

1. Drug: Oxcarbazepine

1. Effect: Hyponatraemia. Sodium below 125 mmol/L occurred in 2.5% of treated patients across fourteen controlled epilepsy studies, generally in the first three months, and SIADH has been reported after marketing. [7]

2. Drug: Carbamazepine

2. Effect: Hyponatraemia, in many cases caused by the syndrome of inappropriate antidiuretic hormone secretion, with a risk that appears to be dose-related. [2]

3. Drug: Phenytoin

3. Effect: Gingival hyperplasia, coarsening of the facial features, enlargement of the lips and hypertrichosis. [5]

4. Drug: Topiramate

4. Effect: Hyperchloraemic non-anion-gap metabolic acidosis, renal stones, oligohidrosis with reduced sweating, and a syndrome of acute myopia with secondary angle-closure glaucoma. [6]

5. Drug: Valproate

5. Effect: Dose-related thrombocytopenia, and hyperammonaemia that may be present despite normal liver function tests. [4]

6. Drug: Phenobarbital

6. Effect: Tolerance and psychological and physical dependence with continued use; abrupt cessation after prolonged use in a dependent person may cause withdrawal including delirium, convulsions and possibly death. [10]

Contraindications, precautions and interactions

1. Valproate is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations, and in children under two years of age clinically suspected of having a mitochondrial disorder. [4]

2. In the UK, valproate medicines must not be used in women and girls of childbearing potential unless the conditions of the Pregnancy Prevention Programme are met. [11]

1. Patients with ancestry in genetically at-risk populations should be screened for HLA-B*1502 before carbamazepine is started, and those testing positive should not be treated with it unless the benefit clearly outweighs the risk. [2]

2. Roughly a quarter to a third of patients who have had hypersensitivity reactions to carbamazepine will experience hypersensitivity reactions with oxcarbazepine, so a documented carbamazepine reaction is directly relevant to the choice of successor. [7]

3. Valproate exposure in pregnancy causes physical birth defects in around 10 in every 100 babies against a background rate of 2 to 3 in 100, and neurodevelopmental disorders in approximately 30 to 40 in every 100 children exposed. [11]

4. Carbamazepine should be used cautiously in mixed seizure disorders that include atypical absence seizures, where it has been associated with increased generalised convulsions. [2]

1. With: Drugs metabolised by hepatic cytochrome enzymes
1. Effect: Carbamazepine is a potent inducer of CYP3A4 and also induces CYP1A2, 2B6 and 2C8/9/19, and may therefore reduce the plasma concentrations of co-prescribed medicines. [2]
2. With: Hormonal contraceptives
2. Effect: Concomitant carbamazepine may render them less effective because plasma hormone concentrations may fall; breakthrough bleeding and unintended pregnancies have been reported. [2]
3. With: Oral anticoagulants
3. Effect: Barbiturates induce hepatic microsomal enzymes, increasing metabolism and decreasing the anticoagulant response of oral anticoagulants. [10]
4. With: Valproate co-administered with lamotrigine
4. Effect: Listed in the lamotrigine label among the suggested, though unproven, factors that may increase the risk of rash, alongside exceeding the recommended initial dose or the recommended rate of dose escalation. [3]
5. With: Opioids and other central nervous system depressants
5. Effect: Respiratory depression and sedation, sometimes fatal, have been reported when gabapentin is given with opioids. [9]

Comparison tables

Title: What separates the members in practice

Caption: Mechanism predicts the interaction profile and the characteristic toxicity. Choice of agent belongs to the treating clinician working from a current prescribing reference.

1. Key: drug
1. Label: Drug
1. Is Row Header: true
2. Key: mechanism
2. Label: Dominant mechanism
3. Key: clearance
3. Label: Main clearance route
4. Key: signature
4. Label: Signature problem
1. Drug: Phenytoin
1. Mechanism: Sodium-channel stabilisation
1. Clearance: Saturable hepatic hydroxylation
1. Signature: Disproportionate rise in serum level with small dose increments; gingival hyperplasia [5]
2. Drug: Carbamazepine
2. Mechanism: Reduced polysynaptic response and post-tetanic potentiation
2. Clearance: Hepatic, via CYP3A4, with autoinduction
2. Signature: Broad enzyme induction; HLA-B*1502-linked SJS/TEN; aplastic anaemia [2]
3. Drug: Oxcarbazepine
3. Mechanism: Voltage-sensitive sodium-channel blockade
3. Clearance: Hepatic
3. Signature: Hyponatraemia, and cross-hypersensitivity in carbamazepine-reactive patients [7]
4. Drug: Lamotrigine
4. Mechanism: Sodium-channel blockade
4. Clearance: Hepatic
4. Signature: Serious rash, with valproate co-administration among the suggested risk factors [3]
5. Drug: Valproate
5. Mechanism: Multiple

5. Clearance: Hepatic
5. Signature: Hepatotoxicity, pancreatitis, and reproductive toxicity that now governs its use [4][11]
6. Drug: Topiramate
6. Mechanism: Multiple, including carbonic anhydrase inhibition
6. Clearance: Renal and hepatic
6. Signature: Metabolic acidosis, renal stones, oligohydrosis, word-finding difficulty [6]
7. Drug: Levetiracetam
7. Mechanism: SV2A binding
7. Clearance: Renal, largely unchanged
7. Signature: Behavioural abnormalities, against an unusually clean interaction profile [1]
8. Drug: Gabapentin
8. Mechanism: Alpha-2-delta subunit binding
8. Clearance: Renal, as unchanged drug
8. Signature: Respiratory depression when combined with opioids [9]
9. Drug: Vigabatrin
9. Mechanism: GABAergic
9. Clearance: Renal
9. Signature: Permanent visual field constriction, with no risk-free exposure [8]
10. Drug: Phenobarbital
10. Mechanism: GABAergic
10. Clearance: Hepatic, with 25-50% excreted unchanged
10. Signature: Sedation, enzyme induction, tolerance and dependence [10]

High-yield exam pearls

1. Pearl: Carbamazepine induces its own metabolism, and autoinduction is completed after three to five weeks of a fixed dosing regimen.
1. Why: It explains why a level checked early in treatment does not predict the steady-state level, which is a favourite examination point. [2]
2. Pearl: Phenytoin's hepatic hydroxylation is saturable, so small incremental doses may increase the half-life and produce very substantial increases in serum levels.
2. Why: This is the classic example of non-linear kinetics in a therapeutic drug, and the reason phenytoin toxicity appears abruptly. [5]
3. Pearl: HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia, and screening is directed before carbamazepine is started in at-risk populations.
3. Why: It is the standard example of pharmacogenomic screening entering a drug label as a pre-treatment requirement. [2]
4. Pearl: Levetiracetam is neither an inhibitor of nor a high-affinity substrate for the major cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes.
4. Why: It is the reason levetiracetam is so often chosen where polypharmacy or hepatic disease makes an enzyme-inducing agent unattractive. [1]
5. Pearl: Topiramate's metabolic acidosis is hyperchloraemic and non-anion-gap, caused by renal bicarbonate loss through carbonic anhydrase inhibition.
5. Why: The acid-base pattern is specific enough to be asked directly, and it links the drug's mechanism to its adverse effect. [6]
6. Pearl: Both carbamazepine and oxcarbazepine cause hyponatraemia, and roughly 25% to 30% of patients hypersensitive to carbamazepine will react to oxcarbazepine.
6. Why: Switching between the two is a common clinical scenario, and the shared liabilities are the point being tested.

[2][7]

Common exam traps

1. Trap: Assuming a broad-spectrum antiepileptic is safe in every seizure type.
1. Correction: Carbamazepine does not appear to control absence seizures, and has been associated with increased generalised convulsions in mixed seizure disorders including atypical absence. [2]
2. Trap: Treating the antiepileptic suicidality warning as specific to one agent.
2. Correction: It is a class warning: antiepileptic drugs increase the risk of suicidal thoughts or behaviour in patients taking them for any indication, not only for epilepsy. [1]
3. Trap: Describing gabapentin as a GABA agonist because of its name and structure.
3. Correction: Gabapentin is structurally related to GABA but has no effect on GABA binding, uptake or degradation; it binds the alpha-2-delta subunit of voltage-activated calcium channels. [9]
4. Trap: Believing that careful monitoring makes vigabatrin's visual toxicity avoidable.
4. Correction: Its label states that no dose or exposure is known to be free of the risk, and that even with frequent monitoring some patients will develop severe vision loss. [8]
5. Trap: Assuming valproate's restriction in pregnancy is a general caution like other antiepileptics.
5. Correction: It is a contraindication with a formal programme attached: UK regulators state it must not be used in women and girls of childbearing potential unless Pregnancy Prevention Programme conditions are met. [11]

Self-test questions

1. Question: A patient stabilised on carbamazepine has a serum level checked one week after starting and again after six weeks, with no dose change. The later level is markedly lower. What best explains this?
1. Autoinduction of carbamazepine's own metabolism
2. Development of tolerance at the sodium channel
3. Reduced gastrointestinal absorption over time
4. Displacement from plasma protein binding
1. Explanation: Carbamazepine induces its own metabolism, and the label states that autoinduction is completed after three to five weeks of a fixed dosing regimen, so levels fall over that period without any dose change. [2]
2. Question: Which antiepileptic is described in its label as neither an inhibitor of nor a high-affinity substrate for human liver cytochrome P450 isoforms?
1. Levetiracetam
2. Carbamazepine
3. Phenobarbital
4. Phenytoin
2. Explanation: The levetiracetam label states that the drug and its major metabolite are neither inhibitors of nor high-affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. [1]
3. Question: A patient of Han Chinese ancestry is being considered for carbamazepine. Which pre-treatment step does the label direct?
1. Screening for the HLA-B*1502 allele
2. Measuring serum bicarbonate
3. Formal visual field perimetry
4. Testing for POLG gene mutations
3. Explanation: The boxed warning directs that patients with ancestry in genetically at-risk populations are screened for HLA-B*1502 before carbamazepine is started, and that those testing positive should not be treated unless the benefit clearly outweighs the risk. [2]
4. Question: Which adverse effect of topiramate follows directly from its inhibition of carbonic anhydrase?

1. Hyperchloraemic non-anion-gap metabolic acidosis

2. Gingival hyperplasia

3. Aplastic anaemia

4. Permanent visual field constriction

4. Explanation: The topiramate label attributes a hyperchloraemic, non-anion-gap metabolic acidosis to renal bicarbonate loss caused by the drug's inhibitory effect on carbonic anhydrase. [6]

5. Question: Which statement about gabapentin's mechanism is correct?

1. It binds the alpha-2-delta subunit of voltage-activated calcium channels and has no effect on GABA binding

2. It is a direct agonist at the GABA-A receptor

3. It blocks voltage-gated sodium channels in the same way as phenytoin

4. It inhibits GABA transaminase irreversibly

5. Explanation: The gabapentin label states that it binds with high affinity to the alpha-2-delta subunit of voltage-activated calcium channels, and that despite being structurally related to GABA it has no effect on GABA binding, uptake or degradation. [9]

6. Question: A patient develops a serum sodium of 122 mmol/L three weeks after starting a new antiepileptic. Which agent is most characteristically associated with this?

1. Oxcarbazepine

2. Gabapentin

3. Vigabatrin

4. Lamotrigine

6. Explanation: The oxcarbazepine label reports that 2.5% of treated patients in fourteen controlled epilepsy studies had a sodium below 125 mmol/L, generally within the first three months of treatment. [7]

7. Question: Which of these is listed in the lamotrigine label as a suggested factor that may increase the risk of serious rash?

1. Co-administration with valproate

2. Concurrent renal impairment

3. Co-administration with levetiracetam

4. A history of febrile convulsions

7. Explanation: The label lists coadministration with valproate, exceeding the recommended initial dose, and exceeding the recommended dose escalation as suggestions, yet to be proven, that the risk of rash may be increased. [3]

Frequently asked questions

1. Question: Why are antiepileptics grouped by mechanism rather than by seizure type?

1. Answer: Because mechanism predicts what a drug will do outside the brain. Two agents used for the same seizure type can differ completely in whether they induce hepatic enzymes, how they are cleared, and what their characteristic toxicity is. Carbamazepine's enzyme induction and levetiracetam's near-absence of cytochrome interaction come from their mechanisms and pharmacokinetics, not from the seizures they treat. [2][1]

2. Question: Do antiepileptic drugs cure epilepsy?

2. Answer: No. They suppress seizure activity while they are being taken. That is why the class carries long-term concerns such as enzyme induction, bone marrow and hepatic toxicity, and reproductive risk, and why abrupt withdrawal of an agent such as phenobarbital in a dependent patient can precipitate convulsions. [10]

3. Question: Why is valproate restricted so much more tightly than other antiepileptics?

3. Answer: Because of the size of the reproductive risk. UK regulators report physical birth defects in around 10 in every 100 exposed babies against a background of 2 to 3 in 100, and neurodevelopmental disorders in approximately 30 to 40 in every 100 exposed children, which is why a formal Pregnancy Prevention Programme governs its use rather than a general caution. [11]

4. Question: Which antiepileptics interact least with other medicines?

4. Answer: The renally cleared agents. Levetiracetam is largely excreted unchanged and does not act as an inhibitor of or a high-affinity substrate for the major cytochrome P450 isoforms, and gabapentin is eliminated by renal excretion as unchanged drug. Both instead require attention to renal function, and gabapentin has an important interaction with opioids. [1][9]

5. Question: What makes phenytoin's dosing unusually difficult?

5. Answer: Its hepatic hydroxylation is saturable, so once the enzyme system approaches saturation a small increase in dose can produce a very substantial increase in serum level. The relationship between dose and concentration is therefore non-linear, unlike most drugs. [5]

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