

— THE BOOK — OF SEIZURES

*A Comprehensive Guide from Ancient
Mysteries to Modern Medicine*



“The brain, in its chaos, tells the most honest stories.”

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DEDICATION

*For every patient who has ever asked, "I'm not crazy, am I?"
No. You are not. Your brain forgot the rules for a moment — and this book exists because the rules are knowable.*

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Corrections, questions and clinical feedback are welcome.

HOW TO CITE THIS BOOK

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What this book is

The Book of Seizures is one clinical argument about epilepsy, told in seventeen chapters: how a seizure is recognised, how its syndrome narrows the choice of drug, how the drug is fitted to the patient, what to do when the seizure will not stop, and what to say afterwards. It is written for the doctors who meet seizures at the bedside — in the emergency department, on the wards, in intensive care and in the clinic.

Every chapter is a step in that argument:

The seizure tells you what to treat. The syndrome tells you what will make it worse. The drug is chosen by the patient, not by the diagnosis alone — and the titration schedule is part of the drug.

Read in order, the four books are recognition, pharmacology, emergency, and conscience. Used at the bedside, Chapter 9 (the formulary) and Chapter 12 (status) are the two you will open at three in the morning. Everything else exists so that those two are used correctly.

The chapters share a grammar. Most open with a **clinical scene** — the patient as you will meet them — and the argument is built from it. **Tables** hold the numbers you will need to look up; **expert-mode** boxes hold the reasoning behind them; **red flags** mark the decisions that harm patients when they go wrong. The history in Chapter 1 is not decoration: four thousand years of getting epilepsy wrong is the best explanation of why we still do.

SCOPE, AND THE LIMITS OF IT

Dosing figures are typical adult ranges given to orient reasoning. They are not a label. They do not account for renal or hepatic adjustment, interactions, or the patient in front of you. Verify against current prescribing information and a validated interaction database before prescribing. This is a teaching reference, not a protocol.

HOW TO USE THIS BOOK

- ◆ **Read Book One before the formulary.** The syndrome decides which drugs are forbidden; Chapter 8 puts effectiveness and aggravation on one grid, and the formulary only makes sense after it.
- ◆ **At the bedside, open Chapter 9 for the agent and Chapter 12 for status epilepticus.** The protocol is time-based because the receptors are: every minute of delay weakens the drug you are about to give.
- ◆ **Chapter 16 is written the wrong way round on purpose.** Each of its twenty pitfalls is a mistake worth recognising in yourself before a patient pays for it.
- ◆ **Trial names in the text point to Appendix B.** SANAD II decides first-line choice; ESETT decides the second line in status; the references are there to be checked.
- ◆ **Test yourself with Appendix C.** 189 questions with answers and explanations, grouped by chapter — or practise them online, timed or in tutor mode, at thetract.org/seizures/qbank.

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BOOK ONE

Seeing

Recognition — history, classification, semiology, EEG, diagnosis, syndrome

The Ancient Dance

Four thousand years of watching, and one century of answering

CLINICAL SCENE

She is eight years old, standing in a Babylonian marketplace, and she falls. Her body stiffens, her eyes roll, foam gathers at the corners of her mouth. The crowd steps back. A priest is called; the diagnosis takes under a minute — the hand of the moon god Sin has seized her — and the treatment, incantation, takes longer and will not work. But something remarkable has happened. Someone wrote it down. That description, the rigidity and the fall and the eyes, will survive four thousand years and land in a modern textbook virtually unchanged. Everything that follows in this book is the story of how long it took to move from the description to the mechanism, and from the mechanism to the molecule.

WHAT YOU WILL MASTER

- Trace the arc from demonic attribution to molecular medicine — and the parallel arc from bromide to gene therapy
- Understand how etymology still shapes the words you use in clinic
- Recognise that each generation of antiseizure drug answered the *toxicity*, not the failure, of the last
- Appreciate why stigma persists, and what that demands of you

The word itself

Language is not neutral. The word *seizure* comes from the Old French *seisir* — to take possession of, to take hold. This is not metaphor; it is description. In a generalised tonic-clonic seizure the brain does exactly that: takes hold of the body with a grip so complete that nothing else can enter or leave. The Latin root *sacire* adds another layer — to seize property, to claim by force. That one word serves a legal act and a neurological event tells you how profoundly the ancients were struck by what they saw.

The Greek *epilambanein* (ἐπιλαμβάνειν) means to seize upon, to attack from above; from it, *epilepsy* — to be seized upon. The Greeks were not interested in softening the language. They named the experience from the outside in.

CLINICAL PEARL

Aura is Greek for breeze or breath — the sensation patients described before the event. Galen adopted it in the second century. We use it unchanged today because the phenomenology it captures is unchanged. When a patient describes something rising, you are hearing the same report Galen heard.

Four millennia, one table

ERA	DOMINANT UNDERSTANDING	KEY CONTRIBUTION	CLINICAL LEGACY
Sumerian ~2500 BC	Spiritual: the hand of Sin	First written seizure description — tonic-clonic, fall, frothing	Phenomenology recorded accurately despite an entirely wrong aetiology
Egyptian ~1700 BC	Physical and spiritual mixed	Edwin Smith papyrus: head wound → convulsions	First documented post-traumatic epilepsy
Babylonian ~1050 BC	Diagnostic manual	<i>Sakikku</i> lists some forty seizure types by onset, body part, time of day	The first proto-classification; includes absence-like descriptions
Greek 400 BC	Naturalistic — the brain	Hippocrates, <i>On the Sacred Disease</i>	Neurocentric model; heredity described; a Todd's-like paralysis noted
Roman 1st c. AD	Brain plus humoral theory	Galen: phlegm overflow; adopts “aura”	The word survives the theory by nineteen centuries
Islamic Golden Age 980–1037	Scientific renaissance	Ibn Sina classifies by origin; describes impaired consciousness without convulsion	Aura-based localisation nine centuries before video-EEG
Enlightenment 1770	Return to the brain	Tissot refutes lunar causation	Brain primacy enters mainstream medicine
1857	Pharmacology begins	Locock: potassium bromide	Proof that a neurological disease can be pharmacologically modified
1870	Localisation	Hughlings Jackson: focal discharges, the Jacksonian march	“Occasional, sudden, excessive, rapid and local discharges of grey matter” — still valid
1912	Sedation as therapy	Hauptmann: phenobarbital	Still on the WHO essential medicines list; still first line in much of the world on cost alone
1924	Electrophysiology	Berger invents the EEG	The seizure becomes visible
1938	Rational screening	Merritt and Putnam screen in the electroshock model, not for sedation, and find phenytoin	Seizure control separated from sedation — the conceptual birth of the field
1958–1978	The first generation completes	Ethosuximide, carbamazepine, valproate	Absence gets a specific drug; valproate gives the first true broad spectrum
1989–2000	Second generation	Vigabatrin onward; felbamate's aplastic anaemia within a year of launch	The goal shifts to tolerability and interaction burden; post-marketing surveillance is born
2004–present	Third generation and precision	Lacosamide, perampanel, cannabidiol, cenobamate, fenfluramine; ezogabine withdrawn 2017 for retinal pigmentation	Mechanism- and syndrome-specific development — and proof the pattern has not stopped
2013 →	Closed-loop and molecular	Responsive neurostimulation approved; SCN1A antisense trials open	The device that answers the seizure, and the first attempt to correct the instruction that caused it

Table 1.1 — The long arc. Dates mark first written record, first clinical use, or first approval in a major market; sources vary by a year or two depending on whether they date synthesis, trial or authorisation.

EXPERT MODE — WHY THE SUPERNATURAL PERSISTED FOR TWO THOUSAND YEARS

Hippocrates correctly identified epilepsy as a brain disease in 400 BC, and the naturalistic model still lost — for two millennia. Why? Because Hippocrates had no treatment and the priests had rituals. When medicine cannot offer hope, something else fills the gap. That is not a criticism of antiquity; it is a lesson for Tuesday. Patients who feel dismissed by biomedicine seek alternative explanations, and the answer is never condescension. It is better medicine, clearer language, and honest acknowledgement of what we still do not know.

The pattern the drug history repeats

Read the second half of Table 1.1 again and notice that no generation of antiseizure drug was displaced because it stopped working. Bromide fell to phenobarbital because of psychosis and bromoderma, not failure. Phenobarbital gave ground to phenytoin because of sedation. Phenytoin persists but is designed around, because of saturable kinetics and a cosmetic and neurological toxicity profile that a patient lives inside for forty years. The second generation exists because the first was effective and unpleasant. This is the single most useful thing to know about the formulary in Chapter 9: **the modern advance is not efficacy. Valproate and carbamazepine remain among the most effective drugs available. The advance is a wider menu of tolerability and interaction profiles, from which a specific patient can be fitted.**

The chapter Western histories forgot

Between the fall of Rome and the European Renaissance the intellectual centre of medicine moved east. Ibn Sina — Avicenna to the Latin world — wrote in *Al-Qanun fi al-Tibb* (c. 1025) that the clinical features of a seizure could indicate its origin. He described seizures arising from the brain, from the stomach, from the spleen. He described episodes of impaired consciousness without convulsion, which we would now call non-convulsive events or absence. He noted that fear, anxiety and psychoneurological change could precede seizure activity. That is an aura-based localisation framework, nine hundred years before video-EEG made it routine, and it is systematically underrepresented in Western epilepsy histories for reasons that are not purely academic.

CASE SNAPSHOT

A 32-year-old teacher has episodes where she briefly goes blank for ten to fifteen seconds, stares, then resumes conversation without realising anything happened. Colleagues report rapid blinking. She has no memory of them and has been told she is “just stressed” for three years.

Diagnosis, classic EEG, first-line treatment? Absence epilepsy (juvenile-onset given her age at presentation, though the semiology is that of childhood absence). Classic EEG: 3 Hz generalised spike-and-wave, reliably provoked by three minutes of hyperventilation. First line: ethosuximide if absence is the only seizure type; valproate if tonic-clonic seizures coexist and reproductive risk does not apply. The misdiagnosis of stress or daydreaming is tragically common — and this patient lost three years to it.

The stigma we inherited

In medieval Europe people with epilepsy were barred from marriage, inheritance and religious ceremony. The fear was literal: looking at someone having a seizure was thought to be enough to catch it. This is not primitive ignorance. It is the predictable product of a condition that is dramatic, unpredictable, public and unexplained — and those four features have generated stigma in every civilisation that ever encountered it.

Around fifty million people live with epilepsy today. In parts of sub-Saharan Africa the large majority go untreated, partly through inaccessibility of care, partly through stigma, and partly because in several languages the word for seizure is still the word for madness. The history in this chapter is not decoration. It is alive in your clinic, in the patient who waited two years to tell you about their events because they were afraid of what the diagnosis would mean.

THE SOUL OF EPILEPSY

What does it feel like to live inside a disease that has been called divine, demonic, lunar and mad — all within a single century? It feels like carrying a secret that belongs to no century at all. The seizure itself is often terrifying, alien, beyond language. But the knowledge that it will come again — at any moment, in any place — is the part that is truly disabling. Epilepsy is not primarily a disease of convulsions. It is a disease of anticipation.

IN THIRTY SECONDS

- “Seizure” = to take possession. “Epilepsy” = to be seized upon. Both etymologies are accurate clinical descriptions.
- Babylon classified seizures by 1050 BC; Hippocrates put them in the brain by 400 BC; it took two thousand more years for that to win, because he had no treatment.
- Ibn Sina described aura-based localisation and non-convulsive events in the eleventh century.
- Berger 1924, phenytoin 1938 — the modern era begins when the seizure became visible and controllable without sedation.
- Every drug generation answered the *toxicity* of the last, not its failure. That is why the formulary is a menu, not a ladder.

Making Sense of the Chaos

The ILAE 2017 framework — why classification is a prescribing act

CLINICAL SCENE

At an epilepsy conference in Vienna two neurologists argue for forty minutes about whether a patient's event is a "focal impaired awareness seizure with secondary bilateral spread" or a "focal to bilateral tonic-clonic seizure." An intensivist in the back row, who has been managing status since six in the morning, leans over and whispers: "The patient is still seizing." It is a joke and a parable. Classification must serve the patient, not the classifier. But done well it is one of the most clinically powerful acts in neurology — because in epilepsy, a classification error becomes a prescribing error within the hour.

WHAT YOU WILL MASTER

- Apply the three-level framework: seizure type → epilepsy type → epilepsy syndrome
- Separate focal from generalised onset on clinical and EEG grounds
- Use the six aetiological categories as therapeutic targets rather than labels
- Translate between the old vocabulary and the new — your patient's 1998 discharge summary uses the old one

The architecture

Before 2017 the ILAE classification had not been fundamentally restructured since 1989. Neuroscience had moved; the taxonomy had not. The revision did three things: it acknowledged mechanistic uncertainty honestly, it made aetiology a core axis rather than an afterthought, and it replaced language designed for researchers with language legible to clinicians.

FIGURE 2.1 · THE THREE LEVELS, AND WHAT EACH ONE BUYS YOU

LEVEL 1 — SEIZURE TYPE

What happens during the event. Observable, describable, needs no imaging or genetics. This is your immediate task and it tells you *what to treat*.

LEVEL 2 — EPILEPSY TYPE

Focal, generalised, combined, or unknown. This sets the broad treatment strategy and the first fork in drug choice.

LEVEL 3 — EPILEPSY SYNDROME

A recognisable cluster of seizure type, EEG, imaging, age of onset and prognosis. This is where precision treatment and honest prognostication live — and it tells you *what will make it worse*.

The whole book turns on the third level. Levels 1 and 2 choose a drug; level 3 prevents a catastrophe.

CLINICAL PEARL

The old terms are not wrong, they are imprecise. "Grand mal" is a generalised tonic-clonic seizure. "Petit mal" is a typical absence. "Complex partial" is a focal impaired awareness seizure. Know both vocabularies; the referral letter will use one and the trainee will use the other.

Onset — the foundation of everything

ONSET	HEMISPHERES	TYPICAL EEG	KEY CLINICAL FEATURE	TREATMENT IMPLICATION
Focal	One at start	Focal rhythmic theta/alpha or focal spike	May have aura; localising features	Full formulary available, including narrow-spectrum agents; surgery possible
Focal to bilateral tonic-clonic	Focal, then spreads	Focal onset evolving to generalised spike-wave	Aura precedes the bilateral convulsion	Treat the focal component; surgery possible if a focus is identified
Generalised	Both from the outset	Generalised spike-wave or polyspike-wave	No aura; immediate impairment	Broad-spectrum only. Sodium-channel blockers may worsen it.
Unknown	Undetermined	Variable or absent	Unwitnessed or unclassifiable onset	Broad-spectrum agent until classification is clarified. There is no penalty for this and a real penalty for the reverse.

Table 2.1 — Where it starts decides medication, surgical candidacy, prognosis and counselling.

EXPERT MODE — THE CONSCIOUSNESS CONUNDRUM

The 2017 revision replaced “simple partial” and “complex partial” with “focal aware” and “focal impaired awareness.” The shift matters because consciousness is not binary. A patient may appear aware and retain no memory; may appear unaware and follow commands. The 2017 language asks about awareness as a behaviour, not as a philosophical category. When in doubt, two questions settle it: could the patient respond meaningfully, and do they remember?

CASE SNAPSHOT

A 16-year-old boy is referred for “panic attacks”: sudden intense fear, a rising feeling from stomach to throat, then a blank period of one to two minutes after which he finds himself in a different position, confused. His mother says he sometimes smacks his lips. EEG shows left temporal sharp waves.

Classify it; name the syndrome; identify the rising sensation. Focal impaired awareness seizure with oroalimentary automatisms, arising from the left temporal lobe. Most likely syndrome: mesial temporal lobe epilepsy with hippocampal sclerosis. The rising epigastric sensation is an aura — itself a focal aware seizure from the mesial temporal region. This is not panic disorder. It is a surgically treatable epilepsy with a 60–70% chance of seizure freedom after anterior temporal lobectomy, and every year of “panic disorder” is a year of that outcome deferred.

The six aetiologies — because why matters

AETIOLOGY	MECHANISM	CLASSIC EXAMPLES	WHAT IT CHANGES
Structural	Visible lesion causing the epilepsy	Hippocampal sclerosis, focal cortical dysplasia, tumour, stroke, trauma	Surgical resection if drug-resistant; refer after two failed drugs
Genetic	Known or presumed variant	SCN1A (Dravet), KCNQ2, CDKL5, TSC1/2, SCN8A	Avoids catastrophic drugs; opens gene-directed therapy; changes counselling
Infectious	Direct CNS infection	Neurocysticercosis (commonest worldwide), TB, HSV, HIV	Treat the infection as the primary goal; ASMs are adjuncts
Metabolic	Derangement or inborn error	Pyridoxine dependency, PKU, mitochondrial disease, porphyria	Replace the cofactor; the drug is not the treatment. POLG disease also contraindicates valproate
Immune	CNS autoimmune inflammation	NMDAR encephalitis, LGI1, CASPR2, Rasmussen	Immunotherapy urgently; ASMs alone will fail
Unknown	Workup negative	Roughly a third of all epilepsies	Symptom control; re-evaluate periodically as genetic panels expand

Table 2.2 — Aetiology is a therapeutic target, not background information. Categories are not mutually exclusive: a patient may be structural and genetic at once.

THE DIAGNOSIS YOU CANNOT AFFORD TO MISS

Anti-NMDAR encephalitis presents as refractory focal seizures, psychiatric symptoms or altered consciousness, often in a young woman, and the serum antibody can be negative while the CSF is positive. New-onset refractory epilepsy with behavioural change and autonomic instability: send serum **and** CSF antibody panels, do not wait for the MRI to become abnormal, and start empirical immunotherapy while awaiting results where suspicion is high.

IN THIRTY SECONDS

- Three levels: seizure type → epilepsy type → syndrome. The third is the one that prevents harm.
- Focal = one hemisphere at onset. Generalised = both from the start. This single determination gates the formulary.
- The six aetiologies are treatment decisions, not labels.
- When onset is unknown, choose broad-spectrum. The cost of being wrong runs one way.
- Carbamazepine in JME or Dravet is not a pharmacology error. It is a classification error with pharmacological consequences.

The Art of Watching

Semiology — functional neuroanatomy in motion

CLINICAL SCENE

The video-EEG room is dark except for three screens. A woman in her mid-thirties is asleep. At 2:14 a.m. her right hand begins a slow, almost purposeful fumbling over the bedsheet. Her eyes open and deviate to the left. Her left arm rises into a rigid, contorted posture and holds there for twelve seconds, frozen mid-reach. The EEG erupts in rhythmic theta over the right temporal leads. She recovers slowly, confused, rubbing her nose with her right hand. The epileptologist reviewing the playback at seven does not need the report. Right temporal onset, probably mesial, non-dominant hemisphere. She is a surgical candidate — and every element of that conclusion came from the body, not the machine.

WHAT YOU WILL MASTER

- Localise onset from clinical observation alone, by lobe
- Apply the lateralising signs, with their real reliabilities
- Distinguish temporal, frontal, parietal and occipital semiology
- Understand why the first three seconds carry the diagnosis

Why semiology matters more, not less

In an era of high-resolution MRI and dense-array EEG it can seem quaint to say that watching a seizure is a primary diagnostic skill. It is not quaint. In roughly a third of patients coming to epilepsy surgery evaluation the initial MRI is reported as normal. In those patients the semiology — the story the body tells — is the most important localising information available, and a skilled observer often predicts the imaging finding before the imaging is reviewed.

CLINICAL PEARL

The first clinical change is the most localising. Everything after it is spread. This is why trained epileptologists watch seizure videos from the very beginning, frame by frame: the first three to five seconds contain the diagnostic signal, and the dramatic part contains almost none.

The four portraits

Temporal — the storyteller

Temporal lobe epilepsy is the commonest focal epilepsy in adults and accounts for around two-thirds of surgically treatable cases. The lobe houses hippocampus, amygdala and auditory cortex, which is why it produces the phenomenologically richest seizures in neurology. Mesial temporal seizures typically begin with an aura: the rising epigastric sensation most classically, described as nausea or electricity climbing from stomach to throat. Déjà vu arises from aberrant activation of parahippocampal familiarity circuits. Fear and dread reflect amygdala. Olfactory hallucinations, usually unpleasant and hard to name, reflect mesial temporal or insular activation.

The ictal phase is recognisable once seen: behavioural arrest, oroalimentary automatisms — lip-smacking, chewing, swallowing — and manual automatisms on the side *ipsilateral* to the focus, while the *contralateral* arm adopts a dystonic posture, stiff and contorted, held abnormally for the duration.

Frontal — the night owl

Frontal lobe epilepsy is the great imitator: nocturnal, brief, bizarre, and frequently misdiagnosed as parasomnia, panic disorder or a psychogenic event for years. Seizures often last under thirty seconds and are followed by almost immediate recovery with no post-ictal confusion, which confuses the picture further. Supplementary motor area seizures give the fencing posture — asymmetric tonic arm posturing, one arm extended (the figure-of-4), the other flexed, head turned toward the extended arm. Motor cortex seizures give the Jacksonian march along the homunculus. Orbitofrontal and frontopolar seizures give hypermotor activity: violent bicycling or thrashing, routinely mistaken for psychiatric agitation.

THE SOUL OF EPILEPSY

Imagine waking in the night not knowing you have just had a seizure. Your partner tells you that you screamed, sat bolt upright, and began cycling your legs violently before falling back unconscious. You remember nothing. Not the scream. Not the thrashing. Not the confusion. Just sleep, then morning, then the look on your partner's face. Frontal lobe epilepsy robs you not only of consciousness but of the memory of what your body was doing without you.

Parietal and occipital — the underdiagnosed partners

Parietal seizures are missed because they are often purely sensory: tingling, numbness, pain or electrical sensation marching along the sensory homunculus. The march is sensory, not motor, and these patients are frequently labelled functional before anyone records an EEG during symptoms. Occipital seizures produce elementary visual phenomena — colours, shapes, flashes, geometric patterns, typically in motion and confined to one hemifield. That distinguishes them from migraine aura, which tends to be monochromatic, hemianopic and slowly expanding. Complex visual hallucinations — faces, animals, scenes — suggest temporal rather than occipital involvement.

CASE SNAPSHOT

A 29-year-old man has episodes of sudden fear and a sensation of electricity rising from abdomen to chest, then ninety seconds during which his wife says he stares blankly, smacks his lips and fumbles with his shirt buttons. He is confused afterwards and does not remember the event. His left arm was rigid and extended during one episode. MRI shows right hippocampal T2 signal increase.

Type, aura, lateralising sign, imaging meaning? Focal impaired awareness seizure with aura. Aura of rising epigastric sensation plus fear = mesial temporal (amygdalo-hippocampal). Lateralising sign: left arm dystonia = right hemisphere focus. MRI: right hippocampal T2 hyperintensity = hippocampal sclerosis. Right MTLE-HS, and a prime surgical candidate.

Lateralising signs — the closest thing to a physical sign

SIGN	LATERALISES TO	RELIABILITY	MECHANISM
Unilateral dystonic arm posturing	Contralateral	~90%	Ictal activation of the contralateral basal ganglia circuit
Ictal head version (forced)	Contralateral	~80%, when late in the seizure	Frontal eye field activation; the head turns away from the focus
Ictal eye deviation	Contralateral	~75%	Frontal/occipital gaze centre drives eyes contralaterally
Post-ictal Todd's paralysis	Contralateral	High when present	Post-ictal exhaustion of the motor cortex contralateral to the weakness
Unilateral manual automatisms	Ipsilateral	~70%	Automatisms arise from the preserved temporal lobe
Post-ictal nose-wiping	Ipsilateral	~80% in TLE	Mechanism unclear but reproducible
Post-ictal aphasia	Dominant	>90%	Language cortex disrupted post-ictally
Figure-of-4 (one arm extended, one flexed)	Focus is contralateral to the extended arm	~85% at the onset of secondary generalisation	SMA-type tonic posturing. Note: the older teaching that the extended arm is ipsilateral is inverted, and the inverted version has sent patients for the wrong evaluation
Ictal vomiting or spitting	Non-dominant, usually right	Moderate	Non-dominant temporal association

Table 3.1 — Reliabilities are approximate and drawn from video-EEG series; treat them as strengths of evidence, not probabilities to quote to a patient.

EXPERT MODE — THE DYSTONIA RULE

Unilateral dystonic arm posturing lateralises the focus to the contralateral hemisphere in roughly nine out of ten temporal lobe seizures. When you see a stiff, contorted, abnormally held arm during a focal seizure, the focus is almost certainly on the other side. This single sign has sent more patients to successful surgery than any other semiological feature. Memorise it, teach it, and use it before the EEG report comes back.

IN THIRTY SECONDS

- Watch the beginning, not the climax. The first clinical change is the localising one.
- Mesial TLE: rising epigastric aura + arrest + oroalimentary automatisms + contralateral dystonia.
- Frontal: nocturnal, brief, hypermotor, rapid recovery, no post-ictal confusion — and frequently misdiagnosed for years.
- Dystonic arm = contralateral focus. Post-ictal aphasia = dominant hemisphere.
- Ask the family for phone video at every visit where the diagnosis is unsettled. It is the highest-yield investigation in the assessment and it costs nothing.

Reading the Brain's Diary

EEG — from the normal baseline to the ictal–interictal continuum

CLINICAL SCENE

The report reads: “Mild to moderate diffuse encephalopathy. Occasional right temporal sharp waves. No definite seizure activity recorded.” You read it and file it. But the patient is still confused on day four. A week later, reviewing the raw traces because something feels wrong, you see it — a right temporal rhythmic theta evolving over eighty seconds into generalised spike-wave, three times in a two-hour window. The report was not wrong. The reader missed the significance. The patient had non-convulsive status for five days. This chapter is about becoming the person who sees it.

The normal EEG — know the baseline first

RHYTHM	FREQUENCY	LOCATION	STATE	CLINICAL NOTE
Alpha	8–13 Hz	Posterior	Awake, eyes closed	Blocks with eye opening. Absent alpha in the expected state = cortical dysfunction
Beta	13–30 Hz	Frontal, central	Alert, anxious	Excess beta is usually a drug effect: benzodiazepines, barbiturates, propofol
Theta	4–7 Hz	Temporal	Drowsy, N1	Excess temporal theta in a fully awake adult suggests temporal pathology — investigate
Delta	0.5–3 Hz	Diffuse	N3, infancy	Focal delta in an awake adult = structural lesion at that site. Diffuse delta = encephalopathy
Sleep spindles	11–15 Hz	Central	N2	Asymmetry suggests a hemispheric lesion; absence suggests thalamic dysfunction
Vertex waves	Broad, high amplitude	Vertex	N1–N2 transition	Can mimic epileptiform discharge — distinguished by state and location. Not pathological

Table 4.1 — You cannot call an EEG abnormal until you can say precisely what normal looks like in that state and that age.

The patterns that change what you do next

PATTERN	DESCRIPTION	ASSOCIATION	IMMEDIATE ACTION
3 Hz generalised spike-wave	Regular, bilateral synchronous; provoked by hyperventilation	Childhood and juvenile absence epilepsy	Ethosuximide or valproate; counsel on driving and water supervision
Polyspike-wave 4–6 Hz	Multiple spikes before the slow wave; generalised; photosensitive	JME and other genetic generalised epilepsies	Avoid sodium-channel blockers. Valproate or levetiracetam
Hypsarrhythmia	Chaotic, very high amplitude, asynchronous multifocal spike-wave	Infantile epileptic spasms syndrome	Urgent. Hormonal therapy ± vigabatrin within days — time to treatment predicts development
Focal rhythmic theta/alpha, evolving	Focal onset evolving in frequency, amplitude and field	An active focal seizure	This <i>is</i> a seizure. Treat now
Generalised ictal spike-wave	Rhythmic ≥3 Hz spike-wave lasting more than a few seconds	GTC or absence status	If unresponsive: status protocol
Burst-suppression	Bursts separated by suppression <10 µV	Deep anaesthesia; post-anoxic; severe metabolic	Post-anoxic with absent brainstem reflexes: very poor prognosis. Iatrogenic: appropriate target in refractory status
Triphasic waves	Frontally predominant, 1–2.5 Hz, regular	Hepatic and other metabolic encephalopathy	Treat the metabolic cause — but they mimic NCSE. Benzodiazepine trial under EEG: if the pattern <i>and</i> the clinical state improve, it was NCSE
LPDs	Focal periodic discharges 0.5–3 Hz, stereotyped	Post-stroke, herpes encephalitis, tumour, post-ictal, CJD	High seizure risk. Continuous EEG; treat if clinically encephalopathic
GPDs	Generalised periodic discharges 0.5–3 Hz	Post-anoxic, toxic-metabolic, prion, NCSE	Most ominous in the post-anoxic setting; elsewhere consider NCSE
LRDA	Focal rhythmic delta 1–3 Hz, non-evolving	Structural lesion, cortical irritability, post-ictal	At-risk pattern, not itself a seizure. Keep monitoring

Table 4.2 — The clinically critical list. The last three sit on the ictal–interictal continuum, where the EEG alone cannot decide and the clinical state must.

EXPERT MODE — SPEAK THE NEUROPHYSIOLOGIST'S LANGUAGE

ACNS standardised critical care terminology gives a systematic grid: a main term (LPDs, GPDs, LRDA, GRDA) plus modifiers (+F fast activity, +R rhythmic, +S stimulus-induced) plus prevalence, duration and amplitude. Learn it and a cEEG report stops being an opinion and becomes data you can act on. The concept it exists to serve is the **ictal–interictal continuum**: patterns that sit between clearly interictal and clearly ictal, where the decision requires clinical correlation and sometimes a treatment trial.

CLINICAL PEARL

A normal interictal EEG does not exclude epilepsy, and epileptiform discharges in someone who has never had a seizure do not establish it. The EEG modifies a clinical probability; it does not create one. Treating a discharge in a seizure-free patient adds toxicity to a person who was well.

IN THIRTY SECONDS

- Alpha blocks with eye opening; absent alpha when it should be there means cortical dysfunction.
- Focal delta in an awake adult = structural lesion. Diffuse delta = encephalopathy.
- Hypsarrhythmia is an emergency measured in days, not weeks.
- Triphasic waves: think hepatic — then do the benzodiazepine trial anyway, because it could be NCSE.
- LPDs and GPDs are not always seizures and are never safe to ignore.

The Detective Work

Diagnosis — from the history to the epilepsy-protocol MRI

CLINICAL SCENE

A 44-year-old accountant is brought in after collapsing at his desk. A colleague saw him slump forward, go rigid, then shake rhythmically for about two minutes. He bit his tongue. He was confused for twenty minutes afterwards. No prior history. BP 138/86, glucose 5.1 mmol/L. His colleague is certain it was a seizure. You are not yet certain of anything — and that productive, disciplined uncertainty is where the diagnosis begins.

The criteria — what you actually need

Before ordering anything, get the question straight: are you establishing that a *seizure* occurred, or that the patient has *epilepsy*? Different questions, different thresholds, very different consequences.

CRITERION	DETAIL	CLINICAL MEANING
Two unprovoked seizures >24 h apart	Both unprovoked — no acute precipitant	The classical definition
One unprovoked seizure + ≥60% recurrence risk	Risk conferred by a structural lesion, epileptiform EEG, or specific aetiology	Permits treatment after a first seizure in high-risk settings
An epilepsy syndrome diagnosis	Clinical plus EEG criteria for a recognised syndrome	Sufficient without multiple witnessed events

Table 5.1 — ILAE 2014 operational definition. Any one of the three is sufficient.

CLINICAL PEARL

A single witnessed generalised tonic-clonic seizure in a patient with a pre-existing cortical scar on MRI *is* epilepsy — recurrence risk exceeds 60%. You do not wait for a second event, and you can and should discuss treatment after the first.

The history is still the instrument

Four domains, asked of the patient *and* a witness:

- **The event.** What happened first? (An aura means focal onset.) How long? (Most seizures one to three minutes; functional events often longer than five.) What followed? (Post-ictal confusion is the most reliable pointer to a true seizure.) Tongue biting — lateral suggests GTCS, tip suggests a functional event.
- **The context.** What was the patient doing? Collapse while supine suggests arrhythmia or seizure; while standing suggests vasovagal syncope. Triggers: flashing lights, hyperventilation, emotion, sleep deprivation, alcohol. Time of day: morning myoclonus points to JME; nocturnal hypermotor events to frontal lobe epilepsy.
- **The background.** Head trauma, CNS infection, febrile convulsions, family history, prior unexplained events.
- **The two questions that change the drug.** Any myoclonic jerks, especially on waking? Any absence or staring episodes? Chapter 8 explains why these two decide the prescription.

EXPERT MODE — ASK THE WITNESS TO DEMONSTRATE

When a witness says “shaking,” ask them to show you with their hands. Someone miming fine tremulous movement is describing something entirely different from someone miming large-amplitude rhythmic bilateral jerking. Fine postural tremor during syncope is not the clonic phase of a GTCS. The demonstration takes ten seconds and saves months of uncertainty.

The differential — not everything is a seizure

CONDITION	KEY HISTORY	EXAMINATION	DEFINITIVE TEST
Epileptic seizure	Aura; lateral tongue bite; post-ictal confusion; stereotyped	Often normal interictally; Todd's possible	EEG + MRI; video-EEG if uncertain
Vasovagal syncope	Warmth, nausea, visual greying; triggered by standing, pain, heat	Bradycardia at the event; rapid recovery	Tilt-table; ECG; Holter
Cardiac arrhythmia	Sudden, no prodrome; exertional; family history of sudden death	Structural heart disease signs	ECG, Holter, echo, implantable loop recorder
Functional (dissociative) seizures	Gradual onset; often >5 min; emotional precipitant; eyes closed; pelvic thrusting; waxing and waning	Eyes resist opening; suggestibility; tip-of-tongue biting	Video-EEG with a captured event; ictal EEG normal
TIA	Negative symptoms — weakness, numbness; no convulsion; vascular risk factors	Focal deficit persists minutes to hours	MRI DWI; carotid Doppler; cardioembolic workup
Migraine with aura	Aura spreads over 20–30 min; headache follows; visual aura hemianopic	Usually normal; photophobia	Clinical; MRI to exclude structural cause
Hypoglycaemia	Diabetes, insulin, prolonged fasting; confusion <i>before</i> the convulsion	Diaphoresis, tachycardia	Capillary glucose during the event; insulin/C-peptide
Narcolepsy with cataplexy	Triggered by laughter or emotion; consciousness preserved; daytime sleepiness	Normal neurological examination	Polysomnography + MSLT; orexin

Table 5.2 — The conditions that are actually confused with epilepsy, and what settles each.

CASE SNAPSHOT

A 67-year-old hypertensive man with a left MCA infarct three years ago presents after a witnessed event: rhythmic right arm jerking for ninety seconds while watching television, then ten minutes of confusion. EEG shows left hemispheric slowing with occasional sharp waves. MRI shows left MCA encephalomalacia.

How many seizures, and does he have epilepsy? One witnessed seizure — and he has epilepsy by the 2014 criteria, because the structural lesion plus epileptiform EEG puts recurrence risk above 60%. Aetiology: structural, post-stroke. Treatment: levetiracetam or lamotrigine, chosen for their interaction profile alongside antiplatelets and anticoagulants. Avoid carbamazepine and phenytoin here — the induction burden in a patient on cardiovascular therapy is the whole argument.

Neuroimaging — order the right scan and know what you are looking for

MRI with an **epilepsy protocol** is the study of choice for every adult with new-onset seizures and every patient with focal epilepsy. The protocol must be requested explicitly: a standard brain MRI will miss hippocampal sclerosis, subtle focal cortical dysplasia and small cavernomas, and a normal standard scan is the commonest reason a surgical candidate is told they are not one.

SEQUENCE	WHAT IT DETECTS	KEY EPILEPSY FINDING
T1 3D volumetric	Anatomy, atrophy, lesion morphology	Hippocampal atrophy; cortical thinning in FCD
T2/FLAIR	Oedema, gliosis, signal abnormality	Hippocampal T2 hyperintensity; FCD transmantle sign
Coronal oblique T2 through hippocampi	Mesial temporal structures specifically	Gold standard for hippocampal sclerosis; asymmetry of volume and signal
Gradient echo / SWI	Blood products, calcium, iron	Cavernous malformations; post-traumatic hemosiderin; calcified lesions
DWI/ADC	Acute ischaemia, cytotoxic oedema	Transient post-ictal restricted diffusion; acute stroke-related seizure
Post-gadolinium T1	Blood–brain barrier breakdown	Tumour, encephalitis, abscess, active inflammation

CLINICAL PEARL

Hippocampal sclerosis is best seen on coronal T2 perpendicular to the hippocampal long axis. Look for three things: volume loss, T2/FLAIR signal increase, and loss of internal architecture. A normal hippocampus has a layered, jellyroll appearance; sclerosis collapses it. In bilateral disease, asymmetry remains the key finding.

IN THIRTY SECONDS

- Epilepsy = two unprovoked seizures, or one with $\geq 60\%$ recurrence risk, or a syndrome diagnosis.
- The history from patient *and* witness outperforms every machine in this chapter.
- Lateral tongue bite → seizure. Tip bite → functional. Rapid recovery without confusion → think syncope.
- Request the epilepsy protocol by name, or you will be told the MRI is normal.
- A normal EEG excludes nothing and an abnormal one confirms nothing. Context is the investigation.

When the Mind Plays Tricks

The syndromes — and the drug trap buried in each one

CLINICAL SCENE

The mother has kept a diary. Three years of mornings, in a small notebook she carries in her handbag. “Drops his spoon. Trips over nothing. Spills his orange juice.” She has been told her teenage son is clumsy, that he needs more sleep, that it is a phase. Then one morning he has a generalised tonic-clonic seizure in the kitchen and the diary suddenly reads differently. The spilling, the dropping, the tripping — those were myoclonic jerks. He has had juvenile myoclonic epilepsy for three years. The diagnosis was in the diary all along.

The clinical gallery

SYNDROME	ONSET	SEIZURE TYPES	EEG SIGNATURE	PROGNOSIS	THE DRUG TRAP
Childhood absence (CAE)	4–10 y, peak 6–7	Typical absence, 5–15 s, rapid recovery, no post-ictal state	3 Hz generalised spike-wave; provoked by 3 min hyperventilation	Excellent — most remit by adolescence	Carbamazepine worsens absence
Juvenile absence (JAE)	10–17 y	Absence, less frequent; GTCS common	3–4 Hz spike-wave; photosensitivity	Good, but often lifelong	As CAE — avoid sodium-channel blockers
Juvenile myoclonic (JME)	12–18 y	Morning myoclonic jerks; GTCS; absence in ~30%	4–6 Hz polyspike-wave; photosensitivity	Lifelong; very high relapse if treatment stops	Carbamazepine, phenytoin, gabapentin; lamotrigine may worsen myoclonus
Self-limited epilepsy with centrottemporal spikes (BECTS)	3–13 y, peak 7–10	Nocturnal focal face–arm motor; drooling; speech arrest; awareness preserved	Centrottemporal spikes, dramatically activated by sleep	Excellent — virtually all remit by 16	Treating unnecessarily. Monitoring is often the whole management
Sleep-related hypermotor epilepsy (ADNFLE)	Childhood–adolescence	Brief nocturnal hypermotor, tonic, vocalisation, in clusters	Frontal; scalp EEG often normal during events	Often good with a sodium-channel blocker	Years of psychiatric or parasomnia misdiagnosis
MTLE with hippocampal sclerosis	Any age; onset often childhood	Focal impaired awareness with aura	Temporal rhythmic theta; interictal temporal spikes	60–70% seizure-free after ATL	Delaying surgery. Refer after two drug failures, not ten years
Lennox–Gastaut	3–5 y	Tonic (especially nocturnal), atonic drop attacks, atypical absence	Slow spike-wave <2.5 Hz; paroxysmal fast activity in sleep	Poor; lifelong; intellectual disability usual	Serial drug failures. Move early to dietary and device therapy
Dravet	First year — prolonged febrile hemiclonic seizure at 6–12 months	Myoclonic, absence, focal, GTCS follow	Initially normal, then polyspike-wave with slow background	Poor; developmental slowing; SUDEP risk markedly elevated	Sodium-channel blockers are catastrophic — see below
Infantile epileptic spasms (West)	3–12 months	Spasms in clusters on waking; head drops with arm extension	Hypsarrhythmia	Depends on aetiology; around half evolve to LGS	Delay. Time to treatment is the strongest modifiable predictor of development
Rasmussen encephalitis	Mean 6 y	Progressive focal motor; epilepsia partialis continua	Progressive hemispheric slowing, atrophy on serial MRI	Progressive without hemispherotomy	Immunotherapy buys time; only surgery stops the seizures

Table 6.1 — Syndrome recognition. The last column is the reason this chapter sits before the pharmacology and not after it.

JME — the syndrome hiding in the morning

JME teaches epileptologists humility. The average time from first symptom to correct diagnosis is three to seven years, and in that time the GTCS gets treated while the myoclonic jerks — the hallmark — are dismissed as clumsiness or poor sleep. The triad: myoclonic jerks within thirty to sixty minutes of waking; generalised tonic-clonic seizures, often first in adolescence; and absence seizures in about a third. EEG shows 4–6 Hz polyspike-wave, often with marked photosensitivity.

Valproate remains the most effective agent and SANAD II confirmed it, which is precisely what makes the reproductive problem hard rather than simple. In a woman of childbearing potential, levetiracetam or lamotrigine is chosen *knowing* it is probably less effective, and that trade belongs to the patient to understand and to make.

CLINICAL PEARL

Ask every adolescent presenting with a first GTCS: have you ever dropped things in the morning, spilled your coffee, had your arms jerk? A positive answer plus a morning-timed GTCS is JME until proven otherwise. The question takes four seconds. Patients never volunteer it, because nobody considers dropping a toothbrush to be a seizure.

CASE SNAPSHOT

An 18-year-old medical student presents after her first GTCS during an examination. Her mother mentions, when asked, that she has been “flinging” her arms involuntarily for the past year, especially at breakfast. She also has brief staring episodes. A junior doctor in the ED has already prescribed carbamazepine 400 mg daily.

Diagnosis, why the drug is wrong, correct treatment? JME. Carbamazepine is a sodium-channel blocker that aggravates myoclonic and absence seizures and can increase GTCS frequency in JME. Stop it. Start levetiracetam, preferred here given valproate’s teratogenic profile in a woman of reproductive age — or valproate with full counselling and pregnancy-prevention conditions if levetiracetam fails, since it is the more effective drug. Counsel: JME is lifelong, and relapse rates on stopping medication are very high.

Dravet — the syndrome that punishes the reflex

Dravet syndrome is the archetype of precision medicine in epilepsy, and the clearest example in all of neurology of a drug that fights the biology of the disease. It is caused by loss-of-function in *SCN1A* — the gene encoding the Na_v1.1 channel — in roughly 80% of cases. Na_v1.1 is preferentially expressed in **inhibitory interneurons**. When it fails, inhibitory neurons cannot fire fast enough to maintain cortical control, and the net result is excitation.

The signature: prolonged febrile hemiclonic seizures in the first year, then multiple seizure types, then developmental slowing or regression between one and three years. The EEG is initially normal, which leads many practitioners to underestimate the presentation. By the time it becomes abnormal, developmental opportunity has been lost.

THE DRUG THAT CAN KILL IN DRAVET

Sodium-channel blockers — carbamazepine, oxcarbazepine, phenytoin, lamotrigine — further reduce the function of a channel that is already failing, and because the deficit sits in inhibitory interneurons, blocking it removes inhibition preferentially while leaving excitatory networks relatively untouched. The clinical result is increased seizure frequency, status epilepticus and accelerated cognitive decline. This is documented and preventable.

Rule: any child with a first-year febrile convulsion that is prolonged or hemiclonic — send *SCN1A* genetics before prescribing a sodium-channel blocker.

A correction carried in from the pharmacology text: vigabatrin is also avoided in Dravet, but it is *not* a sodium-channel blocker. It is an irreversible GABA-transaminase inhibitor, and it is avoided because it aggravates myoclonic seizures. Grouping it with carbamazepine teaches the wrong mechanism and produces the wrong reasoning next time.

IN THIRTY SECONDS

- JME hides in morning clumsiness. Ask about spilling and dropping in every adolescent with a first GTCS.
- Dravet: *SCN1A* loss of function; sodium-channel blockers are catastrophic; get genetics before prescribing.
- CAE: 3 Hz spike-wave, provoked by hyperventilation, treated with ethosuximide, usually outgrown.
- MTLE-HS: the commonest surgical epilepsy in adults, 60–70% seizure-free after ATL. Refer early.
- Infantile spasms and Rasmussen are both timed diseases. Delay is the intervention that harms.

BOOK TWO

Choosing

Mechanism, spectrum, the formulary, the combinations, and the patient who modifies all of them

One Synapse, Every Target

Six mechanisms, three generations, and why rational polytherapy combines across rows

Seizures arise when excitation outruns inhibition, amplified by abnormal channel kinetics. Every approved antiseizure medication acts at one of six points on a single synapse. Learn the six and the formulary stops being a list of names.

FIGURE 7.1 · EVERY ASM TARGET ON ONE SYNAPSE

AXON — NA⁺ CHANNEL BLOCKADE

Stabilises the inactivated state, limiting sustained high-frequency firing. *Fast inactivation*: phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, rufinamide. *Slow inactivation*: lacosamide, cenobamate.

PRESYNAPTIC TERMINAL — CA²⁺ CHANNEL MODULATION

T-type: ethosuximide, valproate, zonisamide. *α2δ subunit*: gabapentin, pregabalin.

VESICLE — SV2A BINDING

Levetiracetam, brivaracetam. Modulates exocytosis and release probability.

POSTSYNAPTIC — GABA-A POTENTIATION

Channel open duration: phenobarbital, primidone. *Frequency*: benzodiazepines. Also topiramate, stiripentol, cenobamate at non-benzodiazepine sites.

CLEFT — GABA AVAILABILITY

GAT-1 reuptake block: tiagabine. Irreversible GABA-transaminase inhibition: vigabatrin.

POSTSYNAPTIC — GLUTAMATE ANTAGONISM

AMPA: perampanel; topiramate at AMPA/kainate. NMDA glycine site: felbamate.

Rational polytherapy combines across rows. Two sodium-channel blockers together add diplopia and ataxia without adding efficacy — the brainstem and cerebellum receive the full additive dose while the epileptic network receives little the first drug did not already deliver. The one pairing with evidence of genuine synergy is lamotrigine with valproate, at the cost of a halved lamotrigine titration.

Three ways to classify, none sufficient alone

Generation, mechanism and spectrum are overlapping axes. Many modern agents act at several targets at once, which is precisely what makes them broad-spectrum — valproate and topiramate are broad because they are mechanistically promiscuous, not despite it.

GENERATION	ERA	AGENTS
First	1912–1970s	Phenobarbital, primidone, phenytoin, ethosuximide, carbamazepine, valproate, the early benzodiazepines
Second	1989–2000s	Vigabatrin, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide
Third	2004–present	Pregabalin, lacosamide, rufinamide, perampanel, eslicarbazepine, brivaracetam, cannabidiol, cenobamate, fenfluramine

Spectrum, and the Drugs That Make Seizures Worse

The single most consequential distinction in the book

Narrow-spectrum agents are effective in focal epilepsy and can aggravate generalised seizure types. Give carbamazepine to a teenager whose morning myoclonus was never asked about, and you can convert juvenile myoclonic epilepsy into status epilepticus.

AGENT	FOCAL	GTC	ABSENCE	MYOCLONIC	ATONIC / TONIC
Valproate	✓	✓	✓	✓	✓
Lamotrigine	✓	✓	~	✗	✓
Levetiracetam	✓	✓	~	✓	~
Topiramate	✓	✓	~	~	✓
Zonisamide	✓	✓	~	~	~
Perampanel	✓	✓	~	✓	~
Clobazam	✓	✓	✓	✓	✓
Ethosuximide	—	—	✓	~	—
Carbamazepine	✓	✓	✗	✗	✗
Oxcarbazepine	✓	✓	✗	✗	✗
Phenytoin	✓	✓	✗	✗	~
Gabapentin / pregabalin	~	~	✗	✗	—
Vigabatrin	✓	~	✗	✗	—
Tiagabine	✓	~	✗	✗	—

Table 8.1 — Effectiveness and aggravation on one grid. ✓ effective · ~ weak or unproven · ✗ can worsen it · — not applicable.

RED FLAG — THE THREE QUESTIONS BEFORE ANY SODIUM-CHANNEL BLOCKER

1. **Any myoclonic jerks, especially on waking?** Undiagnosed JME is the commonest reason a narrow-spectrum agent makes a patient worse.
2. **Any absence or staring episodes?** Carbamazepine, oxcarbazepine, phenytoin, gabapentin, pregabalin, tiagabine and vigabatrin can all aggravate absence.
3. **Is this Dravet, or could it be?** In *SCN1A*-related Dravet the channel is already failing; blocking it further is contraindicated, and lamotrigine has a particularly clear aggravation signal.

If the syndrome is not yet clear, start broad-spectrum. There is no penalty for choosing levetiracetam or valproate before the EEG. There is a real penalty for the reverse.

Choosing by syndrome — the table the rest of the book exists to support

SYNDROME	FIRST CHOICES	AVOID
Focal epilepsy, adult	Lamotrigine or levetiracetam. SANAD II favoured lamotrigine on time to treatment failure. Carbamazepine, oxcarbazepine, lacosamide and zonisamide are all reasonable	Nothing absolute — but avoid narrow-spectrum agents until generalised epilepsy is excluded
Generalised tonic-clonic and JME	Valproate is the most effective and remains first line where reproductive risk does not apply. Otherwise levetiracetam or lamotrigine, accepting lower efficacy	Carbamazepine, oxcarbazepine, phenytoin, gabapentin, pregabalin, tiagabine, vigabatrin
Childhood absence	Ethosuximide when absence is the only seizure type; valproate if tonic-clonic seizures also occur	Lamotrigine is inferior to both. Narrow-spectrum agents worsen absence
Lennox–Gastaut	Valproate as backbone, adding lamotrigine, rufinamide, clobazam, topiramate, cannabidiol or fenfluramine. Rufinamide is particularly useful for drop attacks	Carbamazepine and vigabatrin may worsen tonic and atonic seizures
Dravet	Valproate and clobazam as the base, then stiripentol, fenfluramine or cannabidiol	Sodium-channel blockers are contraindicated: carbamazepine, oxcarbazepine, phenytoin, lamotrigine. Vigabatrin also avoided, for myoclonic aggravation
Infantile epileptic spasms	Hormonal therapy — ACTH or high-dose prednisolone — with vigabatrin. ICISS showed combination superior to hormonal therapy alone. Vigabatrin is first line and often sufficient alone in tuberous sclerosis	Delay. Time to treatment is the strongest modifiable predictor of developmental outcome
Neonatal seizures	Phenobarbital remains first line; NEOLEV2 found levetiracetam significantly less effective. Treat the cause in parallel	—
Status epilepticus	See Chapter 12	Under-dosing the benzodiazepine

Table 8.2 — Selection by syndrome. Local guidelines and availability modify the first column. The second column does not change.

EXPERT MODE — WHAT SANAD II ACTUALLY SHOWED

For **focal** epilepsy, lamotrigine was superior to levetiracetam and zonisamide on time to treatment failure, and remains the reference first-line choice.

For **generalised and unclassified** epilepsy, levetiracetam did not meet non-inferiority against valproate, and valproate was superior on time to twelve-month remission.

The practical reading: in a man, or a woman past childbearing potential, with generalised epilepsy, valproate is still the best drug. In a woman of childbearing potential the alternative is chosen knowing it is probably less effective — and that trade-off is hers to understand and to make. Both the reflex prescription of valproate and the reflex refusal of it are failures of the same conversation.

The Formulary

Twenty-seven agents, arranged by target — because the target is what you combine across

This is the reference half of the book. Doses are typical adult ranges; they orient reasoning and do not replace the label. Each monograph ends with the one thing that most often goes wrong with that drug in practice.

Sodium-channel agents

These stabilise the inactivated conformation of the voltage-gated sodium channel, limiting sustained high-frequency firing while leaving normal low-frequency signalling largely intact. The class runs from phenytoin (1938) to cenobamate (2019). Lacosamide and cenobamate act on *slow* rather than fast inactivation, which is a genuine pharmacological distinction and probably a clinical one.

Phenytoin

1938 · HYDANTOIN · FAST INACTIVATION

MECHANISM

Use-dependent block of the inactivated Na⁺ channel, prolonging recovery and suppressing sustained repetitive firing without blocking single action potentials.

INDICATIONS

Focal-onset and generalised tonic-clonic seizures; status epilepticus, usually as fosphenytoin. Ineffective and potentially aggravating in absence and myoclonic seizures.

DOSING

Load 20 mg/kg IV in status. **Rate matters:** phenytoin no faster than 50 mg/min (25 mg/min in the elderly or in cardiac disease); fosphenytoin up to 150 mg PE/min. Maintenance 300–400 mg/day. Target 10–20 mg/L total, 1–2 mg/L free.

KINETICS

~90% protein bound. Saturable Michaelis–Menten metabolism via CYP2C9 and 2C19 — within the therapeutic range the dose–concentration curve turns near-vertical. Potent inducer of CYP3A4, 2C9, 2C19 and UGT.

COMMON

Nystagmus, ataxia, diplopia, sedation, gingival hyperplasia, hirsutism, coarsened facial features, peripheral neuropathy, cerebellar atrophy with chronic use.

SERIOUS

SJS/TEN (HLA-B*15:02, and CYP2C9 poor-metaboliser status); DRESS; hepatotoxicity; purple glove syndrome; osteomalacia; megaloblastic anaemia; fetal hydantoin syndrome. IV: hypotension and arrhythmia if infused too fast.

INTERACTIONS

Induction lowers contraceptives, warfarin, DOACs, corticosteroids and most co-administered ASMs. Raised by fluconazole, isoniazid, amiodarone; lowered by carbamazepine. Valproate displaces it from albumin — the total looks normal while free drug rises.

PEARL

| A 50 mg increase near the top of the range can double the level. In hypoalbuminaemia, renal failure or pregnancy, measure the free level or the total will mislead you.

Carbamazepine

1963 EU · 1974 US · IMINOSTILBENE · AUTOINDUCER

MECHANISM

Block of the inactivated Na⁺ channel, analogous to phenytoin. Developed as a tricyclic analogue, then found effective in trigeminal neuralgia and seizures.

INDICATIONS

Focal-onset and generalised tonic-clonic seizures; trigeminal neuralgia; bipolar disorder. Aggravates absence, myoclonic and atonic seizures.

DOSING

Start 100–200 mg once or twice daily; increase by 200 mg/day weekly to 800–1200 mg/day in 2–3 doses. Target 4–12 mg/L. Expect to need an increase in the first month because of autoinduction.

KINETICS

Autoinduces its own CYP3A4 metabolism over 2–4 weeks. The 10,11-epoxide metabolite is active and contributes to both efficacy and neurotoxicity.

COMMON

Diplopia, ataxia, dizziness, sedation, hyponatraemia, benign leukopenia, weight gain.

SERIOUS

SJS/TEN with a strong HLA-B*15:02 association; DRESS and hypersensitivity linked to HLA-A*31:01; aplastic anaemia and agranulocytosis; hepatotoxicity; symptomatic hyponatraemia.

INTERACTIONS

Potent CYP3A4 inducer — lowers contraceptives, warfarin, DOACs, antipsychotics, antiretrovirals and most ASMs. Raised by macrolides, azoles and grapefruit.

PEARL

Screen for HLA-B*15:02 before starting in patients of Han Chinese, Thai, Malay, Filipino or South Asian ancestry. Check sodium and blood count at baseline, early, and whenever the dose rises.

Oxcarbazepine

1990 EU · 2000 US · PRODRUG TO MHD

MECHANISM

10-keto analogue of carbamazepine, rapidly reduced to the active monohydroxy derivative. Avoids the epoxide responsible for part of carbamazepine's toxicity.

INDICATIONS

Focal-onset seizures, monotherapy or adjunctive. Not effective in absence or myoclonic seizures and may aggravate them.

DOSING

Start 300 mg twice daily; increase by 300–600 mg/day weekly to 900–2400 mg/day. Conversion from carbamazepine roughly 1 : 1.5.

KINETICS

MHD is renally cleared — reduce in renal impairment. Weaker induction than carbamazepine, but not absent.

SERIOUS

SJS/TEN with partial HLA-B*15:02 cross-reactivity; clinically significant hyponatraemia, particularly in the elderly and with thiazides or SSRIs; cross-hypersensitivity in roughly a quarter to a third of patients allergic to carbamazepine.

PEARL

Often chosen to escape carbamazepine's induction burden or epoxide toxicity — but it is the worse drug for hyponatraemia, and switching for that reason is a common error.

Eslicarbazepine acetate

2009 EU · 2013 US · ONCE DAILY

MECHANISM

Prodrug converted almost entirely to S-licarbazepine, the active enantiomer that also constitutes part of oxcarbazepine's MHD. Enhances slow inactivation.

INDICATIONS

Focal-onset seizures, monotherapy or adjunctive, from four years.

DOSING

Start 400 mg once daily (200 mg in the elderly); increase weekly to 800–1200 mg once daily. Reduce below 50 mL/min creatinine clearance.

SERIOUS

Hyponatraemia; hypersensitivity cross-reacting with carbamazepine and oxcarbazepine; rare SJS/TEN; PR prolongation.

PEARL

Do not combine with oxcarbazepine. They share the active moiety, so the combination is a dose increase disguised as polytherapy — with two prescriptions and two copayments.

Lamotrigine

1990 UK · 1994 US · NA⁺ BLOCK + GLUTAMATE RELEASE INHIBITION

MECHANISM

Use-dependent block of *fast* inactivation, with additional presynaptic inhibition of glutamate and aspartate release — the likely reason its spectrum is broader than the rest of the class.

INDICATIONS

Focal-onset and generalised tonic-clonic seizures, Lennox–Gastaut, bipolar maintenance. One of the two preferred agents in pregnancy. Can aggravate myoclonic seizures; contraindicated in Dravet.

DOSING

Monotherapy: 25 mg daily × 2 weeks, 50 mg daily × 2 weeks, then +50 mg every 1–2 weeks to 225–375 mg/day. **With valproate, halve everything** — 25 mg alternate days × 2 weeks, then 25 mg daily. With inducers and no valproate, double the rate and the target.

KINETICS

Glucuronidated by UGT1A4. Inducers roughly halve the level; valproate roughly doubles it; oestrogen-containing contraceptives halve it, with rebound in the pill-free week.

SERIOUS

SJS/TEN — risk driven by titration speed and valproate co-therapy; DRESS; aseptic meningitis; haemophagocytic lymphohistiocytosis, rare and potentially fatal, presenting as persistent fever with cytopenias and high ferritin; arrhythmia in structural or ischaemic heart disease.

PEARL

The titration schedule is the safety intervention. If more than five half-lives are missed, restart from the beginning of the schedule rather than resuming the previous dose.

Lacosamide

2008 · SLOW INACTIVATION · IV AVAILABLE

MECHANISM

Selectively enhances *slow* inactivation rather than acting on fast inactivation — in theory a more selective effect on pathologically hyperexcitable tissue.

INDICATIONS

Focal-onset seizures, monotherapy and adjunctive, from four years. Increasingly used second-line in status epilepticus, though it was not one of the ESETT arms.

DOSING

Start 50 mg twice daily; increase by 100 mg/day weekly to 200–400 mg/day. IV load 200–400 mg over 15–60 minutes.

KINETICS

Oral bioavailability near 100%, minimal protein binding, partly CYP2C19-metabolised with substantial renal excretion of unchanged drug.

SERIOUS

PR prolongation with AV block or bradyarrhythmia, particularly in conduction disease or alongside other PR-prolonging drugs; atrial arrhythmias in cardiac patients; rare multi-organ hypersensitivity.

PEARL

Baseline ECG before starting in anyone with cardiac history, on rate-controlling drugs, or receiving an IV load.

Rufinamide

2008 · TRIAZOLE · LENNOX–GASTAUT NICHE

MECHANISM

Triazole derivative, structurally unrelated to the rest of the class, prolonging the inactivated state of the Na⁺ channel.

INDICATIONS

Adjunctive treatment in Lennox–Gastaut, particularly tonic-atonic drop attacks, from one year.

DOSING

Start 400–800 mg/day; increase every two days to 1800–3200 mg/day. Halve the start and target if valproate is present. Take with food.

SERIOUS

QT *shortening* — contraindicated in familial short QT syndrome; multi-organ hypersensitivity; status epilepticus on abrupt withdrawal.

PEARL

Baseline ECG to exclude a short QT interval — the opposite of the concern with almost every other drug you prescribe.

Cenobamate (CNB)

2019 US · 2020 EU · SLOW INACTIVATION + GABA-A

MECHANISM

Dual: enhances slow inactivation of the Na⁺ channel and acts as a positive allosteric modulator at a non-benzodiazepine site on GABA-A.

INDICATIONS

Adjunctive treatment of focal-onset seizures in adults. Responder and seizure-freedom rates in its randomised trials are the strongest reported for an adjunctive agent in drug-resistant focal epilepsy — seizure freedom during maintenance of roughly a fifth to a quarter at higher doses, not the “50%” sometimes quoted, and never demonstrated head-to-head.

DOSING

The titration is the drug. 12.5 mg/day × 2 weeks, then 25, 50, 100, 150 mg/day at two-week intervals, to a target of 200 mg/day and a maximum of 400 mg/day. Reaching target takes three months and this is not negotiable.

KINETICS

Half-life 50–60 h. CYP2E1, 2B6 and UGT2B7, with mixed induction and inhibition of other enzymes.

SERIOUS

DRESS — the reason the schedule exists. Early trials using faster escalation produced unacceptable rates; no DRESS occurred in the large open-label study using the current schedule. QT shortening.

INTERACTIONS

Inhibits CYP2C19, raising phenytoin and phenobarbital — reduce those by 25–50% as cenobamate is introduced. Induces CYP3A4, lowering hormonal contraceptives. Raises clobazam’s active metabolite substantially.

PEARL

If a patient misses more than a week, restart the titration. The temptation to catch up is exactly the behaviour that produced the DRESS signal.

GABAergic agents

Three routes to one end: potentiate the receptor, block reuptake, or block breakdown. The class contains the oldest drug still in routine use and two agents reserved for syndromes where nothing else works.

Phenobarbital

1912 · BARBITURATE · CHANNEL OPEN DURATION · POTENT INDUCER

MECHANISM

Positive allosteric modulation at the barbiturate site of GABA-A, prolonging the *duration* of chloride channel opening — in contrast to benzodiazepines, which increase its frequency. At high concentration it opens the channel directly, which is why overdose is lethal in a way benzodiazepine overdose usually is not.

INDICATIONS

Focal and generalised tonic-clonic seizures; neonatal seizures; status epilepticus as a later-line agent.

DOSING

Load 15–20 mg/kg IV at no more than 50–100 mg/min. Maintenance 60–180 mg/day. Target 15–40 mg/L.

KINETICS

Half-life 53–140 h — steady state takes weeks. Potent broad inducer of CYP1A2, 2C9, 2C19 and 3A4.

SERIOUS

Physical dependence with a withdrawal syndrome that includes seizures and autonomic instability; osteomalacia and accelerated bone loss; SJS/TEN; respiratory depression; Dupuytren contracture and frozen shoulder with long-term use.

PEARL

Cognitively the worst drug in this book, and still one of the most important — it costs a few dollars a year and it works. In neonatal seizures it remains first line: NEOLEV2 found levetiracetam significantly less effective.

Primidone

1952 · METABOLISED TO PHENOBARBITAL AND PEMA

MECHANISM

Effectively a prodrug: metabolised to phenobarbital and phenylethylmalonamide, both active, while retaining independent antiseizure activity.

INDICATIONS

Focal and generalised tonic-clonic seizures; now more often prescribed for essential tremor, where it is first line alongside propranolol.

DOSING

Start 100–125 mg at night; increase every three days to 750–1500 mg/day. Much lower doses usually suffice for tremor. Monitor the derived phenobarbital level, not primidone.

COMMON

A characteristic severe first-dose reaction — dizziness, nausea and sedation out of proportion to the dose. Otherwise as phenobarbital.

PEARL

Warn the patient about the first dose specifically. Patients who are not warned stop the drug after one tablet.

Benzodiazepines

1960S DIAZEPAM · 1975 CLONAZEPAM · CHANNEL OPEN FREQUENCY

MECHANISM

Positive allosteric modulation at the α - γ subunit interface of GABA-A, increasing the *frequency* of chloride channel opening. They require GABA to be present, and that ceiling effect is why they are safer in overdose than barbiturates.

INDICATIONS

First line for acute seizure termination and status epilepticus. Clonazepam and clobazam are used chronically, particularly in myoclonic seizures, Lennox–Gastaut and Dravet.

DOSING

Status: IV lorazepam 0.1 mg/kg (max 4 mg per dose, may repeat once); IV diazepam 0.15–0.2 mg/kg (max 10 mg); IM midazolam 10 mg with no IV access, or buccal/intranasal in the community. Chronic: clonazepam 0.5–2 mg twice daily.

KINETICS

Diazepam is highly lipophilic — fastest on, fastest to redistribute, so a brief clinical effect despite a long half-life. Lorazepam is less lipophilic and lasts longer in brain, which is why it is preferred in status.

SERIOUS

Tolerance to the antiseizure effect within months; dependence with a withdrawal syndrome that itself provokes seizures; paradoxical disinhibition in children and the elderly; respiratory arrest with rapid IV injection or concurrent opioids.

PEARL

In status the commonest error is not the choice of benzodiazepine but under-dosing it, and then blaming the drug when the seizure continues. Give the full weight-based dose, and give the second one.

Clobazam (CLB)

1975 · 1,5-BENZODIAZEPINE · A2 PREFERENCE

MECHANISM

A 1,5-benzodiazepine, distinct from the 1,4 structure of the others, binding preferentially at α 2-containing GABA-A receptors — thought to explain less sedation and slower tolerance.

INDICATIONS

Adjunctive in Lennox–Gastaut; widely used in Dravet, in myoclonic epilepsies, and for catamenial seizure clusters.

DOSING

Start 5–10 mg/day; increase weekly to 20–40 mg/day. **Reduce by 25–50% when stiripentol or cannabidiol is added.**

KINETICS

N-desmethyclobazam is active, has a much longer half-life than the parent, and accumulates in CYP2C19 poor metabolisers and with CYP2C19 inhibitors.

PEARL

When a child on clobazam becomes sedated after cannabidiol is started, the answer is almost always to reduce the clobazam rather than the cannabidiol.

Vigabatrin

1989 EU · 2009 US · IRREVERSIBLE GABA-TRANSAMINASE INHIBITION

MECHANISM

Covalent, irreversible inhibition of GABA-transaminase. The effect lasts until new enzyme is synthesised, so duration of action is uncoupled from plasma half-life. **Not a sodium-channel blocker.**

INDICATIONS

Infantile spasms — first line in tuberous sclerosis complex; refractory focal seizures as add-on. Restricted by a mandatory risk-management programme in most jurisdictions. Aggravates absence and myoclonic seizures.

DOSING

Infantile spasms 50 mg/kg/day increasing over days to 100–150 mg/kg/day. Adults 500 mg twice daily to 1–3 g/day.

SERIOUS

Permanent bilateral concentric visual field constriction in a substantial proportion of long-term users, usually asymptomatic until advanced — baseline and periodic perimetry required. Reversible MRI signal change in basal ganglia and brainstem of treated infants.

PEARL

The visual toxicity is irreversible and silent. This is a drug reserved for situations where its unique efficacy — in tuberous sclerosis above all — outweighs a permanent sensory loss the patient cannot feel arriving.

Tiagabine

1997 · GAT-1 REUPTAKE INHIBITION

MECHANISM

Selective inhibition of the GAT-1 transporter, prolonging the presence of released GABA in the cleft.

INDICATIONS

Adjunctive therapy in focal-onset seizures. Rarely used now, for the reason below.

SERIOUS

Non-convulsive status epilepticus and new-onset seizures in patients *without* epilepsy prescribed it off-label for pain or psychiatric indications — the basis of a boxed warning.

PEARL

A rational, selective mechanism that produced a paradoxical and unpredictable seizure risk. It belongs in this book mainly as a lesson about mechanism-led optimism.

Stiripentol

2007 EU · 2018 US · GABA-A POTENTIATION + DELIBERATE CYP INHIBITION

MECHANISM

Direct GABA-A potentiation at a site distinct from the benzodiazepine site, plus potent inhibition of CYP3A4, 2C19 and 1A2. **The enzyme inhibition is not a side effect — it is part of the strategy.**

INDICATIONS

Seizures in Dravet syndrome, specifically in combination with clobazam and valproate.

DOSING

50 mg/kg/day, added to existing clobazam and valproate whose doses are typically reduced by 25–50% at the same time.

SERIOUS

Neutropenia and thrombocytopenia; toxicity from the elevated concentrations of the drugs it is combined with.

PEARL

The only drug here designed around a pharmacokinetic interaction rather than in spite of one. Monitor the blood count, and reduce the partner drugs before the patient becomes toxic rather than after.

Broad-spectrum and multi-mechanism agents

Valproate

1967 FR · 1978 US · THE BROADEST SPECTRUM AVAILABLE

MECHANISM

Multiple and incompletely defined: weak Na⁺ block, T-type Ca²⁺ modulation, increased GABA synthesis and reduced degradation, histone deacetylase inhibition. The breadth of mechanism matches the breadth of spectrum.

INDICATIONS

Focal, generalised tonic-clonic, absence, myoclonic and atonic seizures; JME; Lennox–Gastaut; Dravet; bipolar disorder; migraine prophylaxis.

DOSING

Start 10–15 mg/kg/day; increase by 5–10 mg/kg weekly to 15–60 mg/kg/day, commonly 1000–2000 mg/day. Target 50–100 mg/L. IV load in status 40 mg/kg.

KINETICS

Protein binding saturates at higher concentrations, so free drug rises faster than the total suggests. Inhibits UGT and CYP2C9.

SERIOUS

Fatal hepatotoxicity, highest under two years on polytherapy; pancreatitis; hyperammonaemic encephalopathy, which occurs at normal drug levels and responds to L-carnitine; teratogenicity and neurodevelopmental harm; polycystic ovary-like changes.

INTERACTIONS

Doubles lamotrigine. Raises phenobarbital and rufinamide. Displaces phenytoin from albumin. **Carbapenems drop valproate levels by 60–90% within a day, unpredictably and unrecoverably.**

PEARL

Regulatory restriction has replaced advice. Valproate must not be used in women or girls of childbearing potential except within a pregnancy prevention programme, and several jurisdictions extended restrictions in 2024 to men under 55 planning conception.

RED FLAG — VALPROATE AND POLG

Pathogenic *POLG* variants — Alpers–Huttenlocher and related mitochondrial disorders — carry a very high risk of fatal valproate hepatotoxicity, and valproate is contraindicated where they are known or suspected.

The presentation that should stop you: a child or young adult with unexplained epilepsy plus developmental regression, liver dysfunction, ataxia, migraine with occipital features, ophthalmoplegia or neuropathy. Refractory status epilepticus of unclear cause in a young person belongs on this list.

Where suspicion is real, test before prescribing. Where the situation is urgent and testing is impossible, choose another drug — the alternatives are adequate, and this complication is not survivable often enough to gamble.

Ethosuximide

1958 · T-TYPE CALCIUM BLOCK · ABSENCE ONLY

MECHANISM

Selective block of T-type Ca^{2+} current in thalamic relay neurons, interrupting the thalamocortical oscillation that generates 3 Hz spike-and-wave.

INDICATIONS

Childhood and juvenile absence epilepsy — and nothing else. No efficacy in tonic-clonic or focal seizures, so a patient with both needs a different or additional drug.

DOSING

Start 250 mg once or twice daily; increase by 250 mg every 4–7 days to 20–40 mg/kg/day, typically 750–1500 mg/day. Target 40–100 mg/L.

SERIOUS

Blood dyscrasias including aplastic anaemia; SJS/TEN; a lupus-like reaction; psychosis and behavioural change — all rare.

PEARL

The Glauser trial settled this: ethosuximide and valproate are equally effective in childhood absence and both beat lamotrigine, but ethosuximide causes significantly less attentional impairment. That makes it first choice when absence is the only seizure type.

Gabapentin

1993 · $\text{A}_2\Delta$ LIGAND · SATURABLE ABSORPTION

MECHANISM

Binds the $\alpha_2\delta$ subunit of presynaptic voltage-gated Ca^{2+} channels, reducing calcium entry and excitatory transmitter release. Despite the name it has no action at GABA receptors.

INDICATIONS

Adjunctive in focal seizures, where efficacy is modest; far more used for neuropathic pain. Aggravates absence and myoclonic seizures.

DOSING

300 mg day one, twice daily day two, three times daily day three; then to 900–3600 mg/day. Reduce by creatinine clearance.

KINETICS

Not metabolised; renally excreted unchanged. Absorption is saturable, so bioavailability *falls* as the dose rises — a ceiling no other ASM has.

SERIOUS

Respiratory depression with opioids or in respiratory disease; misuse and dependence, prompting scheduling in several countries.

PEARL

A weak antiseizure drug with a useful safety profile in polypharmacy. Doubling the dose does not double the level.

Pregabalin

2004 · $\text{A}_2\Delta$ LIGAND · LINEAR KINETICS

MECHANISM

The same $\alpha_2\delta$ target as gabapentin, with higher affinity and linear, non-saturable absorption.

INDICATIONS

Adjunctive in focal seizures; neuropathic pain; generalised anxiety disorder in some jurisdictions. Aggravates myoclonic seizures.

DOSING

Start 75 mg twice daily; increase within a week to 150–600 mg/day. Reduce by creatinine clearance.

SERIOUS

Misuse and physical dependence — a controlled substance in the US, UK and elsewhere; angioedema; respiratory depression with opioids.

PEARL

Take a substance-use history before prescribing either gabapentinoid, particularly alongside opioids, where the combination has a documented mortality signal.

Topiramate

1996 · FOUR MECHANISMS · CARBONIC ANHYDRASE INHIBITION

MECHANISM

The most mechanistically diverse ASM: Na⁺ block, GABA-A potentiation at a non-benzodiazepine site, AMPA/kainate antagonism, weak carbonic anhydrase inhibition.

INDICATIONS

Focal-onset and generalised tonic-clonic seizures, Lennox–Gastaut; migraine prophylaxis; weight management in combination formulations.

DOSING

Start 25 mg at night; increase by 25–50 mg weekly to 200–400 mg/day. Slower titration substantially reduces the cognitive and paraesthesia burden.

SERIOUS

Nephrolithiasis; acute angle-closure glaucoma, typically within a month of starting and requiring immediate discontinuation; oligohidrosis and hyperthermia in children; metabolic acidosis; oral clefts and small-for-gestational-age infants with prenatal exposure.

PEARL

European regulators introduced pregnancy-prevention conditions in 2023, moving topiramate closer to valproate's status. A 2024 sibling-controlled analysis found no clear association with autism or intellectual disability once maternal epilepsy was accounted for — but the malformation risk stands.

Zonisamide

1989 JP · 2000 US · SULFONAMIDE · NA⁺ + T-TYPE + CARBONIC ANHYDRASE

MECHANISM

Na⁺ channel block, T-type Ca²⁺ modulation, weak carbonic anhydrase inhibition.

INDICATIONS

Focal-onset seizures, adjunctive and in some regions monotherapy; used off-label in myoclonic epilepsies and infantile spasms.

DOSING

Start 100 mg once daily; increase by 100 mg every two weeks to 300–500 mg/day. Half-life around 60 h permits once-daily dosing.

SERIOUS

Nephrolithiasis; oligohidrosis and hyperthermia in children; metabolic acidosis; SJS/TEN and other sulfonamide-type hypersensitivity.

PEARL

Cross-reactivity between antibiotic and non-antibiotic sulfonamides is weaker than once believed, but a history of SJS to any sulfonamide is still a reason to choose something else.

Felbamate

1993 · NMDA GLYCINE-SITE ANTAGONISM · RESTRICTED USE

MECHANISM

NMDA receptor antagonism at the glycine site, GABA-A potentiation, and Na⁺ channel block.

INDICATIONS

Refractory Lennox–Gastaut and refractory focal epilepsy, when benefit is judged to outweigh risk. Genuinely effective — which is why it still exists.

DOSING

Start 1200 mg/day; increase to 2400–3600 mg/day. Reduce concomitant ASMs by 20–33% as it is introduced.

SERIOUS

Aplastic anaemia and fulminant hepatic failure, both with substantial mortality, appearing within a year of launch. Written informed consent and regular blood counts and liver tests are required.

PEARL

Felbamate is the reason modern ASM approval looks the way it does. Efficacy established in trials of a few hundred patients cannot exclude an idiosyncratic reaction occurring in one in several thousand.

SV2A, glutamate and the newest targets

Levetiracetam (LEV)

1999 EU · 2000 US · SV2A LIGAND · NO MEANINGFUL INTERACTIONS

MECHANISM

Binds synaptic vesicle glycoprotein 2A, modulating vesicle exocytosis and release probability. Binding affinity across structural analogues correlates with antiseizure potency — unusually good evidence that the target is the mechanism.

INDICATIONS

Broad spectrum: focal-onset, generalised tonic-clonic and myoclonic seizures. Standard for rapid IV loading in status and perioperatively.

DOSING

Start 500 mg twice daily; increase by 500–1000 mg/day every two weeks to 1000–3000 mg/day. IV load in status 60 mg/kg, max 4500 mg, over 15 minutes. Reduce by creatinine clearance.

KINETICS

Bioavailability near 100%, negligible protein binding, no CYP metabolism, renal elimination. Clearance rises substantially in pregnancy.

SERIOUS

Psychosis and severe behavioural disturbance, more likely with pre-existing psychiatric illness or intellectual disability; suicidality under the class-wide warning; rare severe cutaneous reactions.

INTERACTIONS

Essentially none of pharmacokinetic significance — which is why it is the default in oncology, transplantation, hepatic disease and complex polypharmacy.

PEARL

Ask specifically about mood and irritability at every review, and ask the family rather than only the patient. Pyridoxine is widely used for the behavioural effect but the evidence is thin; switching to brivaracetam has better support.

Brivaracetam (BRV)

2016 · SV2A · HIGHER-AFFINITY SUCCESSOR

MECHANISM

Binds SV2A with roughly 15–30 times the affinity of levetiracetam and greater selectivity; a rationally optimised successor with faster brain penetration.

INDICATIONS

Focal-onset seizures, adjunctive and monotherapy in many regions, from one month of age. IV formulation available.

DOSING

Start 50 mg twice daily; range 100–200 mg/day. IV and oral interchangeable milligram for milligram. Conversion from levetiracetam roughly 10 : 1 to 15 : 1, done overnight without cross-titration.

SERIOUS

Psychiatric and behavioural symptoms of the same kind as levetiracetam, generally less frequent and less severe — but not absent.

PEARL

The main use is rescuing a patient who responds to SV2A blockade but cannot tolerate levetiracetam's behavioural effect. Roughly half improve after the switch. Do not run the two together — see Chapter 10.

Perampanel

2012 · AMPA ANTAGONIST · HALF-LIFE 105 H

MECHANISM

Selective non-competitive antagonism of the postsynaptic AMPA glutamate receptor — the first ASM built around this target.

INDICATIONS

Focal-onset seizures, monotherapy and adjunctive, and primary generalised tonic-clonic seizures. Also effective in myoclonus, including progressive myoclonic epilepsies.

DOSING

Start 2 mg at night; increase by 2 mg every two weeks (weekly if on enzyme inducers) to 4–12 mg once daily. Dose at bedtime — this substantially reduces dizziness.

KINETICS

Half-life around 105 h, so steady state takes three weeks and any dose change declares itself late. Extensively CYP3A4-metabolised; inducers roughly halve the level.

SERIOUS

Serious psychiatric and behavioural reactions — aggression, hostility, homicidal ideation — carrying a dedicated boxed warning separate from the class suicidality warning. Dose-related, commoner in adolescents and with rapid titration. Falls in the elderly.

PEARL

Discuss the behavioural risk explicitly with the patient and someone who lives with them before the first dose. The very long half-life means a problem takes weeks to appear and weeks to clear.

Cannabidiol

2018 · NON-CB1 CANNABINOID · DRAVET, LGS, TSC

MECHANISM

Not through CB1 or CB2, and not intoxicating. Proposed actions include GPR55 antagonism, TRPV1 modulation and inhibition of adenosine reuptake. The mechanism responsible for the antiseizure effect remains undetermined.

INDICATIONS

Seizures in Dravet, Lennox–Gastaut and tuberous sclerosis complex.

DOSING

Start 2.5 mg/kg twice daily; after a week 5 mg/kg twice daily; maximum 10 mg/kg twice daily (12.5 in TSC). Give with a consistent fat intake — a high-fat meal raises exposure several-fold.

SERIOUS

Dose-dependent transaminase elevation, markedly more frequent with concomitant valproate — check liver function at baseline, one, three and six months and after any increase. Thrombocytopenia, again mostly with valproate.

INTERACTIONS

Potent CYP2C19 inhibitor; raises N-desmethyclobazam several-fold.

PEARL

The contrast with unregulated artisanal CBD products is the point worth making to families: this is a standardised pharmaceutical with randomised evidence, defined dosing and known interactions. Those products are none of those things.

Fenfluramine

2020 · SEROTONERGIC · A REPURPOSED ANORECTIC

MECHANISM

Promotes presynaptic serotonin release and agonises 5-HT receptors, particularly 5-HT_{2C}, with additional sigma-1 activity. Unlike any other approved ASM.

INDICATIONS

Seizures in Dravet and Lennox–Gastaut. The reduction in convulsive seizure frequency in the Dravet trials was among the largest reported for that population.

DOSING

Start 0.1 mg/kg twice daily; increase over two weeks to a maximum of 0.35 mg/kg twice daily (capped at 26 mg/day). With stiripentol, maximum 0.2 mg/kg twice daily, capped at 17 mg/day.

SERIOUS

Valvular heart disease and pulmonary arterial hypertension — the toxicities that withdrew fenfluramine as an anorectic in 1997. Echocardiography before starting, six-monthly during treatment, and once three to six months after stopping, under a mandatory monitoring programme. No trial patient developed valvulopathy at these doses; the requirement stands regardless.

INTERACTIONS

Contraindicated within two weeks of a monoamine oxidase inhibitor. Theoretical serotonin syndrome risk with other serotonergic drugs.

PEARL

A withdrawn anorectic re-approved decades later at a fraction of the dose for a population with a very different risk–benefit calculus. Few drugs illustrate as clearly that toxicity is a property of dose and context, not of the molecule alone.

Combinations That Do Harm

Four kinds of failure — name the kind and you can predict the combination

Polytherapy is unavoidable in refractory epilepsy, but a large share of the combinations in common use add toxicity without adding control. The failures fall into four recognisable kinds. Learn the kinds and you will not need to memorise a list.

FIGURE 10.1 · THE FOUR KINDS

KIND 1 — PHARMACODYNAMIC REDUNDANCY

Same target, double the toxicity, roughly single the efficacy.

KIND 2 — PHARMACOKINETIC COLLISION

One drug silently rewrites the concentration of the other.

KIND 3 — ADDITIVE ORGAN TOXICITY

Two drugs, one organ, one shared failure mode.

KIND 4 — MECHANISTIC OPPOSITION

The drug fights the biology of the disease. The rarest and the most damaging.

None of these is an absolute prohibition. A red combination can still be right in a patient who has failed everything else — it means you should be able to say why, in one sentence, in the notes.

Kind 1 — Pharmacodynamic redundancy

Two drugs at the same target give you the side effects twice and the efficacy roughly once. The brainstem and cerebellum receive the full additive dose; the epileptic network receives little that the first drug did not already deliver.

COMBINATION	WHAT HAPPENS	INSTEAD
Carbamazepine + lamotrigine	Two sodium-channel blockers. Diplopia, ataxia and dizziness rise sharply and are often misattributed to disease progression. Carbamazepine also halves lamotrigine by induction, so the patient gets the toxicity of one and the level of neither	Pair a sodium-channel blocker with an SV2A or GABAergic agent
Carbamazepine + phenytoin	Same target, and each induces the other's metabolism. Levels drift for weeks and neither reaches a stable therapeutic concentration	Choose one. No clinical situation requires both
Carbamazepine or phenytoin + lacosamide	Sodium-channel redundancy plus a conduction problem: lacosamide prolongs PR and the older agents have their own cardiac effects. Neurotoxicity is the common outcome; bradyarrhythmia is the dangerous one	Withdraw the older agent as lacosamide is introduced. Baseline ECG either way
Oxcarbazepine + eslicarbazepine	They share the active moiety. This is not polytherapy; it is a dose increase with two prescriptions	One or the other, at an adequate dose
Levetiracetam + brivaracetam	Identical target. Brivaracetam cannot usefully displace levetiracetam at the same site, and the behavioural burden persists	Switch outright — roughly 10 : 1 to 15 : 1, no cross-taper needed
Topiramate + zonisamide	Both inhibit carbonic anhydrase and both cause cognitive slowing. Stones, acidosis, oligohidrosis and word-finding difficulty all compound. Adding the ketogenic diet does the same	Pick one; if the diet is in use, prefer neither

Kind 2 — Pharmacokinetic collision

Here the combination is not irrational, but one drug rewrites the other's concentration. These are manageable when anticipated and dangerous when discovered.

COMBINATION	MECHANISM	WHAT TO DO
Valproate + lamotrigine	Valproate inhibits glucuronidation and roughly doubles lamotrigine. Rapid titration in this setting is the commonest antecedent of lamotrigine-associated Stevens–Johnson syndrome	Not a combination to avoid — it is the one pairing with real synergy. Halve every step of the schedule and target roughly half the usual dose
Valproate + carbapenem	Meropenem, imipenem and ertapenem drop valproate by 60–90% within a day, by a mechanism dose increases cannot overcome	Avoid outright. Change the antibiotic, or cover with a different ASM for the duration
Valproate + phenytoin	Valproate displaces phenytoin from albumin and inhibits its metabolism. The total looks normal or low while free, active phenytoin rises	Measure free phenytoin. Increasing the dose on a total level here makes a toxic patient more toxic
Cannabidiol or stiripentol + clobazam	Both potently inhibit CYP2C19 and raise N-desmethyloclobazam several-fold. The resulting sedation is routinely blamed on the newly added drug	Reduce clobazam by 25–50% when either is introduced — before the patient becomes drowsy, not after
Cenobamate + phenytoin or phenobarbital	Cenobamate inhibits CYP2C19 and raises both substantially, during a titration that already takes three months	Reduce phenytoin and phenobarbital by 25–50% as cenobamate is introduced, and monitor levels through the titration
Any enzyme inducer + a narrow-index co-medication	Phenytoin, carbamazepine, phenobarbital and primidone lower warfarin, DOACs, hormonal contraceptives, corticosteroids, statins, antiretrovirals, chemotherapy and immunosuppressants	In oncology, transplantation or HIV care, start from the interaction-quiet agents: levetiracetam, brivaracetam, lacosamide, gabapentinoids

Kind 3 — Two drugs, one organ

COMBINATION	THE SHARED TARGET
Valproate + cannabidiol	Liver. Transaminase elevation is substantially more frequent with the pair than either alone. LFTs at baseline, one, three and six months, and after every increase
Valproate + topiramate	Ammonia. Both raise it; together they produce hyperammonaemic encephalopathy at entirely normal drug levels. Confusion in a patient on this pair is an ammonia measurement, not a dose increase
Gabapentinoid + opioid	Respiratory drive. A documented mortality signal, worst in the elderly and in respiratory disease
Phenobarbital or benzodiazepine + any sedative	Respiratory drive and cognition. In older adults this pairing is also a falls-and-fracture prescription
Levetiracetam + perampanel	Behaviour. Both carry aggression and irritability signals, perampanel with its own boxed warning. Together, in an adolescent, expect it and warn the family before the first dose

Kind 4 — Fighting the underlying biology

THREE YOU MUST NOT GET WRONG

- Sodium-channel blockers in Dravet.** *SCN1A* loss of function principally affects inhibitory interneurons; blocking the channel further removes inhibition preferentially.
- Narrow-spectrum agents in undiagnosed generalised epilepsy.** Carbamazepine, oxcarbazepine, phenytoin, gabapentin, pregabalin, tiagabine and vigabatrin can aggravate absence and myoclonic seizures, and in JME can precipitate status.
- Valproate where POLG disease is possible.** Not an interaction, but the same category of error: the drug meets a mitochondrial defect it cannot survive, and the hepatotoxicity that follows is frequently fatal.

The unifying lesson, one more time: the seizure type tells you what to treat; the syndrome tells you what will make it worse. Only the second question prevents these three.

EXPERT MODE — THE POLYTHERAPY PARADOX

Across the pivotal trials, one appropriately chosen drug achieves seizure freedom in roughly 47% of patients. A second adds about 13%. A third adds about 4%. Everything beyond that adds one to two percent while meaningfully increasing side effect burden and interaction risk.

The implication is not that polytherapy is wrong. It is that after two well-chosen, adequately dosed trials have failed, the correct next step is to **reconsider the diagnosis and evaluate for surgery or neuromodulation** — not to write a third prescription. Polytherapy in a drug-resistant patient who is a surgical candidate is a delay, not a treatment.

The Patient Modifies the Drug

Pregnancy, age, organ failure, levels, and stopping

Pregnancy and reproductive planning

Most comparative human data comes from prospective registries — the North American AED Pregnancy Registry, the UK and Ireland register, and EURAP. The framing that matters: uncontrolled convulsive seizures are themselves dangerous to mother and fetus, so the question is never whether to treat but with what.

RISK TIER	AGENTS	DETAIL
Highest	Valproate	Major malformation risk around 10%, dose-dependent — neural tube, cardiac and orofacial defects, hypospadias. Uniquely among ASMs, a consistent signal for reduced IQ and increased autism risk after in-utero exposure. Pregnancy prevention programme conditions apply
Intermediate	Topiramate, phenobarbital, phenytoin, carbamazepine	Topiramate: oral clefts and small-for-gestational-age infants; EU pregnancy-prevention conditions since 2023. Carbamazepine carries a modest, dose-dependent risk. Phenobarbital and phenytoin have well-described teratogenic syndromes
Most reassuring	Lamotrigine, levetiracetam	The largest reassuring registry datasets, and MONEAD found no adverse effect on cognitive outcomes at three and six years. Preferred when treatment must continue through pregnancy — though no ASM is proven free of risk

- **Plan before conception, not after.** The neural tube closes before most pregnancies are recognised, so switching agents at the first positive test achieves little. Every consultation with a woman of childbearing potential is a pre-conception consultation.
- **Folic acid** before conception and through the first trimester; dose varies by guideline and is higher with valproate or an enzyme-inducing agent.
- **Lamotrigine clearance rises steeply in pregnancy**, driven by oestrogen-induced glucuronidation, and levels can fall by more than half by the third trimester. Monitor and increase — then reduce within days of delivery, or the patient becomes toxic in the puerperium. Levetiracetam and oxcarbazepine clearance also rise.
- **Do not stop an effective drug abruptly because a patient is pregnant.** Seizure control protects the pregnancy.
- **Breastfeeding** is generally supported with lamotrigine and levetiracetam; monitor the infant for sedation, particularly with phenobarbital.

TWO COUNSELLING POINTS THAT GET MISSED

Contraception is bidirectional. Enzyme-inducing ASMs reduce hormonal contraceptive efficacy, and oestrogen-containing contraceptives halve lamotrigine levels. Starting or stopping the pill changes the epilepsy treatment; starting or stopping the ASM changes the contraceptive plan. An intrauterine device or depot progestogen sidesteps most of it.

Cross-reactivity among the aromatic ASMs is high. Phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and lamotrigine share an aromatic structure, and a serious rash with one predicts substantial risk with the others. After SJS or DRESS on any of them, move to a structurally unrelated agent — levetiracetam, valproate, topiramate, gabapentin or a benzodiazepine.

Catamenial patterns

Perimenstrual progesterone withdrawal lowers the seizure threshold in a recognisable subset. Options include acetazolamide across days −3 to +3, perimenstrual clobazam, and hormonal stabilisation discussed with gynaecology. Establish the pattern with a seizure diary against cycle days before treating it — the diagnosis is made on paper, not on impression.

Children and older adults

WHAT DIFFERS	
Children	Clear hepatically metabolised drugs faster per kilogram and often need higher mg/kg doses. Valproate hepatotoxicity risk concentrates under two years, on polytherapy, and in mitochondrial disease. Oligohidrosis with topiramate and zonisamide matters most in hot climates and febrile illness. Levetiracetam behavioural effects are more prominent. Enzyme induction affects growth and bone accrual over years of exposure
Older adults	Lower albumin and reduced clearance raise the free fraction of phenytoin and valproate, so total levels mislead. Levetiracetam and lamotrigine are usually preferred first line for new-onset epilepsy, largely on interaction burden. Sedating agents drive falls and fractures. Inducers interact with the cardiovascular drugs these patients already take and accelerate bone loss. Start at half the standard dose, titrate more slowly, target lower, monitor more often. Renal dosing is the rule, not the exception

Therapeutic drug monitoring

Levels help for drugs with narrow indices, non-linear kinetics, or established concentration–effect relationships. For everything else they answer three questions: is the patient taking it, has an interaction changed things, and is the dose right in organ impairment.

AGENT	RANGE	WHEN IT HELPS
Phenytoin	10–20 mg/L total; 1–2 mg/L free	Always. Non-linear kinetics make it unusable without levels. Measure free drug in hypoalbuminaemia, renal failure, pregnancy, or alongside valproate
Valproate	50–100 mg/L	Suspected toxicity, hepatic dysfunction, pregnancy, polytherapy. Correlation with effect is weak — do not chase the number in a seizure-free patient
Carbamazepine	4–12 mg/L	During autoinduction, suspected toxicity, or when an interacting drug is started
Phenobarbital	15–40 mg/L	The long half-life makes titration blind without levels
Ethosuximide	40–100 mg/L	Titration and adherence
Lamotrigine	No fixed range	Pregnancy and the postpartum period above all; also when contraception or an interacting drug changes
LEV, BRV, gabapentin, pregabalin, lacosamide, topiramate, zonisamide	No fixed range	Adherence, renal dosing, pregnancy

Which organ clears it — and whether a metabolite changes the answer

FIGURE 11.1 · ELIMINATION, IN FOUR QUADRANTS

RENAL, NO ACTIVE METABOLITE

Gabapentin, pregabalin, levetiracetam, vigabatrin, topiramate in part. Reduce by creatinine clearance; forgiving in liver disease.

RENAL CLEARANCE OF AN ACTIVE METABOLITE

Oxcarbazepine (MHD), eslicarbazepine. Renal impairment prolongs the active moiety, not the parent.

HEPATIC, INACTIVE METABOLITE

Phenytoin, lamotrigine, tiagabine, perampanel, brivaracetam, valproate, cenobamate. Caution mainly in hepatic impairment.

HEPATIC PARENT, ACTIVE RENALLY CLEARED METABOLITE

Midazolam (1-OH-midazolam glucuronide), fenfluramine (norfenfluramine), carbamazepine (10,11-epoxide). **Either organ failing prolongs the effect.**

The last quadrant is the ICU trap. Midazolam is the standard example: hepatic metabolism produces an active metabolite that is renally excreted, which is why a patient on a midazolam infusion who develops acute kidney injury takes days rather than hours to wake.

Stopping and tapering

- **Never stop abruptly.** Withdrawal seizures are distinct from the underlying epilepsy and can be more severe than anything the patient had before treatment.
- **Benzodiazepines and barbiturates** carry a true physiological withdrawal syndrome — tremor, autonomic instability, seizures, occasionally delirium — and need tapers over weeks to months.
- **Rufinamide** labelling specifically warns of status epilepticus on abrupt discontinuation; **tiagabine** should be tapered even when prescribed for something other than epilepsy.
- **Cross-taper when switching for lack of efficacy:** establish the new agent before withdrawing the old one.
- **Withdrawing therapy after remission is a decision about relapse risk, not about the drug.** Seizure-free duration, syndrome, EEG and MRI

findings, and what a relapse would cost the patient — licence, occupation, pregnancy — all belong in the conversation. Relapse risk is meaningfully higher than with continued treatment, and much of it falls in the first year.

BOOK THREE

Acting

The emergency, the critically ill brain, the operation, and the conversation

Status Epilepticus

The clock is the treatment

CLINICAL SCENE

The arrest bleep goes at 02:47. You run. The patient in bay four is a 58-year-old man with herpes simplex encephalitis, admitted three days ago, seizing continuously for six minutes. Saturations 88%. Jaw clenched. The bed is shaking. The nurse has already drawn up lorazepam. You call the time: 02:48. You know that in six minutes his GABA-A receptors will begin internalising and the drug in that syringe will start to lose its target. You know that at thirty minutes some of the damage becomes irreversible. You know the protocol from memory, because you learned it before you needed it — which is the only time it is useful to learn it.

Why five minutes

The definition changed from thirty minutes to five not because someone redrew a line, but because of neurobiology. Physiological seizures self-terminate within one to three minutes in most cases. A seizure continuing past five minutes is almost certainly not going to stop on its own — the inhibitory mechanisms that normally abort it have already failed. Waiting thirty minutes was waiting for a fire to go out while the building burned.



At around twelve minutes, GABA-A receptors begin trafficking away from the synaptic membrane, reducing the number of targets available to a benzodiazepine. This is why early treatment is not merely guideline-recommended; it is mechanistically time-critical. Every minute of delay reduces the efficacy of the drug you are about to give.

The time-based protocol

WINDOW	PHASE	AGENT	DOSE	IF NO RESPONSE
0–5 min	Stabilisation	No drug yet	Airway, breathing, circulation. Glucose. Thiamine if at risk. Two IV lines. ECG. Time the seizure.	Draw up the benzodiazepine; activate the team
5–20 min	First line	Benzodiazepine	IV lorazepam 0.1 mg/kg, max 4 mg, repeat once. No IV access: IM midazolam 10 mg, or buccal/intranasal	Escalate at 20 minutes — but only after the <i>full</i> dose and the second dose
20–40 min	Second line	Levetiracetam, valproate or fosphenytoin — equivalent per ESETT	LEV 60 mg/kg (max 4500 mg); VPA 40 mg/kg; fosphenytoin 20 mg PE/kg	Refractory SE → ICU and anaesthesia
40–60 min	Refractory	IV anaesthetic + intubation	Propofol 1–2 mg/kg then 2–12 mg/kg/h; or midazolam 0.2 mg/kg then 0.1–2 mg/kg/h	Continuous EEG mandatory; target seizure cessation or burst-suppression
>24 h	Super-refractory	Ketamine + a second anaesthetic; specialist ICU	Ketamine 1.5 mg/kg then 1.2–5 mg/kg/h; pentobarbital coma; ketogenic diet	Consider immunotherapy if autoimmune; pyridoxine trial in children

Table 12.1 — Refractory = failure of two lines. Super-refractory = 24 hours of anaesthesia or recurrence on weaning.

EXPERT MODE — ESETT, AND WHAT IT ACTUALLY SETTLED

ESETT randomised 384 patients with established status — still seizing after benzodiazepines — to levetiracetam 60 mg/kg, fosphenytoin 20 mg PE/kg, or valproate 40 mg/kg. Seizure cessation at sixty minutes without intubation: 47%, 45% and 46%. No significant difference.

The question “which second-line drug?” therefore now has one correct answer: **whichever is safest for this specific patient**. Avoid valproate in hepatic disease and in pregnancy. Avoid fosphenytoin in cardiac conduction disease and in the elderly on rate-control drugs. Reach for levetiracetam when neither is clear, in oncology and transplantation, and whenever the interaction burden is unknown.

Note also what ESETT did *not* test: lacosamide, now widely used second-line on reasonable observational grounds, was not an arm.

Non-convulsive status — the invisible emergency

NCSE is status without visible convulsive activity: altered consciousness, confusion, behavioural change or coma. Without EEG the diagnosis cannot be made. It has been found in 8–48% of comatose ICU patients when continuous EEG is applied. That is not a rare finding; it is a common finding in a population that is almost never monitored.

The clinical clue is **unexplained encephalopathy that does not fit the proposed medical cause**. A patient with hepatic encephalopathy far more obtunded than the ammonia justifies. A post-anoxic patient with rhythmic delta. A septic patient not improving as expected. In all of these, NCSE belongs on the differential and cEEG is the only way to exclude it.

TREAT THE EEG, NOT THE BEDSIDE IMPRESSION

A patient in NCSE may look simply confused or deeply sedated. They may open their eyes, make sounds, move purposelessly — all of which may be seizure activity misread as preserved consciousness. Order continuous EEG for any unexplained altered consciousness lasting more than ten minutes in a critically ill patient. A therapeutic trial of IV benzodiazepine under EEG can be both diagnostic and therapeutic — **but the trial is only positive if the clinical state improves alongside the EEG**. A pattern that resolves while the patient remains unchanged has told you nothing except that you have sedated them.

IN THIRTY SECONDS

- Five minutes is a biological threshold, not an administrative one.
- Under-dosing the benzodiazepine is the commonest error in the whole of epileptology. Full weight-based dose, then the second one.
- ESETT: levetiracetam, valproate and fosphenytoin are equivalent. Choose on comorbidity.
- NCSE occurs in 8–48% of comatose ICU patients and is invisible without EEG.
- Refractory status means ICU, anaesthesia and continuous EEG — and a hard look for an autoimmune or mitochondrial cause in a young person.

Seizures in the ICU

Electrographic storms in critically ill brains

CLINICAL SCENE

A routine post-op neuro-ICU morning. Your patient — 67, day three after right-sided clipping of an MCA aneurysm — is drowsy but rousable, GCS 12. You attribute it to the procedure, the anaesthesia, the opioids. Then the nurse mentions a witnessed generalised shake overnight, ninety seconds, documented as “possible tremor.” You attach continuous EEG. Focal temporal rhythmic theta evolving into generalised polyspike activity, three times in six hours. He has been in and out of seizures all night, and his drowsiness is post-ictal. This is not an unusual story. This is Tuesday.

8–20%

SEIZURES AFTER ANEURYSMAL SAH

15–25%

EARLY SEIZURES AFTER TBI

14–20%

SEIZURES IN ICH ON CEEG

8–48%

NCSE IN COMATOSE PATIENTS ON CEEG

CONDITION	PROPHYLAXIS?	AGENT	DURATION
Aneurysmal SAH	Controversial; most guidelines short-term only	Levetiracetam	3–7 days; avoid long-term unless a seizure occurs
Traumatic brain injury	Yes — early post-traumatic seizure prophylaxis	Levetiracetam or phenytoin; levetiracetam preferred on tolerability	7 days. Late-epilepsy prophylaxis is not evidence-based and does not prevent epilepsy
Ischaemic stroke	Not routinely	If a seizure occurs: levetiracetam or lamotrigine long-term	Stratify post-stroke epilepsy risk (SeLECT, CAVE)
Intracerebral haemorrhage	Not recommended	Levetiracetam if treatment is needed; avoid phenytoin	Treat only if seizures occur, and stop inherited prophylaxis
Bacterial meningitis	Treat aggressively during the acute phase	Levetiracetam	Duration of acute illness; reassess at 6–12 months
Herpes simplex encephalitis	Treat aggressively; high seizure burden and NCSE common	Levetiracetam; consider valproate; full SE protocol if needed	Often long-term — HSE has a high post-encephalitic epilepsy rate. Start aciclovir immediately regardless of seizure control
Post-cardiac arrest	Treat seizures detected on cEEG	Levetiracetam ± phenobarbital for post-anoxic myoclonus	Myoclonic status does not by itself establish a hopeless prognosis — treat, and prognosticate separately and later

Table 13.1 — Prophylaxis by condition. The recurring theme: prophylaxis is evidence-based in far fewer situations than it is practised in.

CLINICAL PEARL

Phenytoin in intracerebral haemorrhage is associated with worse neurological outcomes across multiple observational studies. The mechanism is not settled — cognitive impairment, vasospasm, cardiac effects at high levels — but the association is consistent enough to change practice. In ICH, and increasingly wherever an IV agent is needed in the ICU, levetiracetam is the default.

EXPERT MODE — CONTINUOUS EEG IS A STANDARD, NOT A LUXURY

Continuous monitoring (24–48 hours; 48–72 if suspicion is high) is indicated for comatose patients after cardiac arrest, unexplained altered consciousness, TBI or SAH with clinical or subclinical seizures, suspected NCSE, and any patient whose encephalopathy is disproportionate to the proposed cause. Without cEEG, a majority of seizures in critically ill patients are simply invisible. That is not a technology problem. It is a standard-of-care problem, and if your unit does not have it, that is something to advocate for rather than work around.

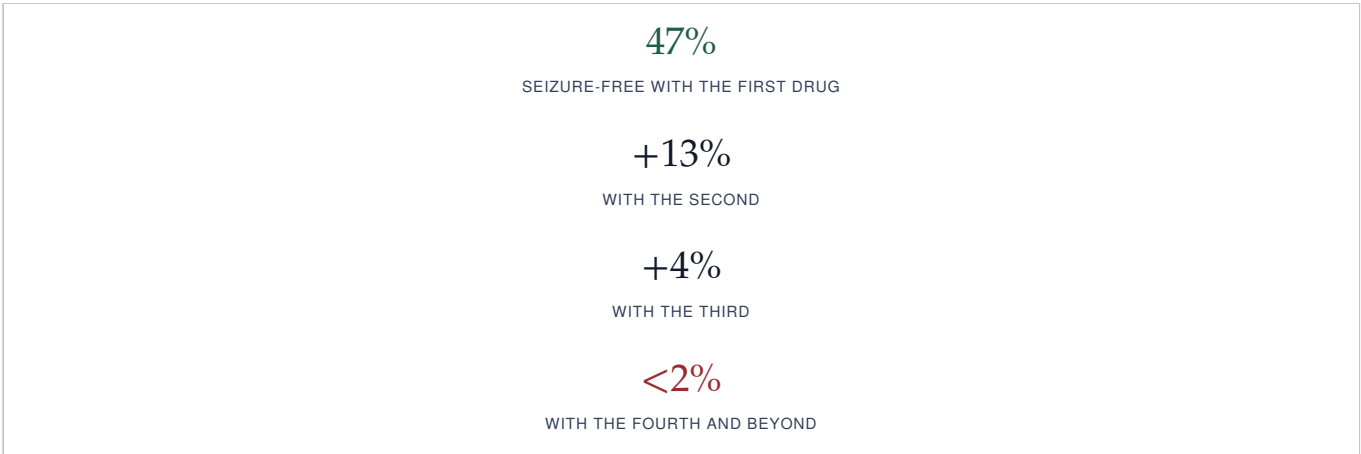
Cutting Edge

Surgery and neuromodulation — when medicine is not enough

CLINICAL SCENE

She has had epilepsy since she was fourteen. She is thirty-one. Seven medications, in seven combinations. Three jobs lost to unpredictable events. She cannot drive. She cannot be alone with her infant daughter because of the fall risk. She sits across from you holding a folder of EEG reports and a printout of everything she has tried, and asks: “Is there anything left?” You look at the MRI. Clear right hippocampal atrophy on coronal T2. Clear right temporal onset on video-EEG. Non-dominant hemisphere. You say: “Yes. There is an operation that gives you around a two-in-three chance of never having another seizure.” She starts to cry.

The threshold — know when to stop prescribing



These numbers from Kwan and Brodie have been replicated repeatedly. The pharmacological plateau is real, and it has a direct clinical implication: after two appropriate, adequately dosed, tolerated trials have failed, do not add a third drug when you should be arranging a surgical evaluation.

CLINICAL PEARL

Drug-resistant epilepsy is defined by the ILAE as failure of two adequate, well-tolerated, appropriately chosen trials — not by years elapsed. A patient who fails levetiracetam at three months and carbamazepine at six months is drug-resistant at six months of diagnosis, not at ten years. That distinction is worth a decade of someone's life.

PROCEDURE	BEST INDICATION	SEIZURE-FREE RATE	MAIN RISKS
Anterior temporal lobectomy	Unilateral MTLE with hippocampal sclerosis	60–70% at five years (dominant); 70–80% non-dominant	Superior quadrantanopia; verbal memory decline in dominant resections; naming deficit
Lesionectomy	Discrete lesion — ganglioglioma, DNET, cavernoma, FCD	70–85% if resection is complete	Location-dependent; motor or language risk near eloquent cortex
Hemispherotomy	Rasmussen, hemimegalencephaly, large perinatal stroke	80–90%	Hemiparesis (often pre-existing); homonymous hemianopia; language if dominant and older child
Corpus callosotomy	Atonic drop attacks; LGS; bilateral focal with falls	50–80% reduction in drop attacks; complete freedom rare	Disconnection syndrome, usually transient with anterior two-thirds
Laser interstitial thermal therapy	Mesial temporal targets; hypothalamic hamartoma; small FCD	~58–65% for MTLE; >90% for hypothalamic hamartoma	Incomplete ablation; highly operator-dependent; retreatment possible

Table 14.1 — Resective surgery. Seizure-free rates are typical published figures; local series vary.

EXPERT MODE — WHY THE WIEBE TRIAL CHANGED EVERYTHING

Before the 2001 randomised trial, epilepsy surgery was treated as a last resort — something attempted after every drug had failed. Wiebe and colleagues randomised eighty patients with temporal lobe epilepsy to surgery or continued medical therapy: 58% of the surgical group were free of seizures impairing awareness at one year, against 8% of the medical group. The trial did not discover that surgery works. It produced the level of evidence that *obligates* us to offer it. Failure to arrange surgical evaluation after two drug failures is, by the standards of evidence-based medicine, a failure of care.

DEVICE	MECHANISM	BEST PATIENT	MEDIAN EFFICACY	DISTINCTIVE FEATURE
VNS (1997)	Ascending vagal afferents → brainstem NTS → widespread cortical modulation	Drug-resistant focal epilepsy, not a resection candidate, any age	~50% of patients achieve ≥50% reduction; seizure freedom uncommon	Magnet-triggered and heart-rate-triggered stimulation; mood improvement independent of seizure reduction
RNS (2013)	Closed loop: intracranial EEG detects, then stimulates focally within milliseconds	One or two identified foci; bilateral mesial temporal is a specific strength	~75% median reduction at nine years; improves over time	Records intracranial EEG continuously — the only device that also gives you data
DBS-ANT (2018)	Open-loop stimulation of the anterior thalamic nucleus → limbic circuit modulation	Bilateral or multifocal drug-resistant epilepsy, frontal or temporal	56% median reduction at two years (SANTE); responder rate improves with time	Continued improvement over five-plus years; watch mood and memory

Table 14.2 — Neuromodulation, when resection is not possible.

CASE SNAPSHOT

A 38-year-old man with bilateral mesial temporal lobe epilepsy — independent right and left temporal onsets on video-EEG — has failed five medications. MRI shows bilateral hippocampal atrophy. He is not a bilateral resection candidate because of memory risk. Seizures 15–20 per month.

Which device, and why? RNS. Electrodes can be placed in both hippocampi, detect activity from either focus independently, and deliver responsive stimulation to whichever is active. This is precisely the indication it was designed for and where its outcome data are strongest. VNS is a reasonable adjunct; bilateral ANT-DBS is also evidence-based. Whichever is chosen, it is added to optimal medical therapy, not instead of it.

SUDEP, and the Conversations You Must Have

The shadow we must name — and the four things every patient should be told

CLINICAL SCENE

The family asks to speak to you privately. They sit in the relatives’ room with the door closed. The father speaks first. “He was fine. He went to bed at ten. He had been well controlled for two months. In the morning he was face-down in his pillow. He was twenty-three years old.” You have heard this before. You will hear it again. And the first thing that family will ask is: did anyone ever tell us this could happen?

SUDEP is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic, non-drowning death in a person with epilepsy, with or without evidence of a preceding seizure, excluding documented status epilepticus, in whom post-mortem examination reveals no toxicological or anatomical cause of death.

The mechanism is incompletely understood. The leading account is post-ictal depression of respiratory and cardiac control mediated by brainstem suppression following a generalised tonic-clonic seizure. Ictal hypoxia, apnoea and peri-ictal arrhythmia all contribute. Prone position during and after a convulsion impairs respiratory mechanics and is independently modifiable.

RISK FACTOR	EFFECT	EVIDENCE	MODIFIABLE?
GTCS frequency ≥3/year	Roughly an order-of-magnitude increase	High — multiple cohorts	Yes — optimise seizure control. This is the dominant lever
Drug-resistant epilepsy	Several-fold increase over well-controlled epilepsy (annual risk of the order of 1 in 150, against roughly 1 in 1000 in unselected epilepsy)	High	Yes — surgery, neuromodulation
Nocturnal seizures	Three- to five-fold	Moderate	Partially — supervision, detection
Prone sleeping position	Independently increased	Moderate (MORTEMUS)	Yes — counsel side or supine
Living alone / unsupervised at night	Increased; supervision is protective	Moderate	Yes — discuss with family or partner
Dravet syndrome	Around ten-fold versus epilepsy overall	High	Partially — maximise control; stiripentol, fenfluramine, cannabidiol
Non-adherence	Increased, largely through GTCS frequency	High	Yes — and the conversation itself improves it
Complete seizure freedom	Risk approaches that of the general population	High	The most powerful modifiable factor there is

Table 15.1 — Risk factors. Incidence figures vary substantially between cohorts; the ordering is more robust than the absolute numbers, and the numbers should be given to patients as ranges rather than certainties.

Both the AAN and the AES recommend discussing SUDEP at diagnosis and periodically thereafter. Studies consistently show that most patients and families want to know when asked, and that avoidance is experienced as a failure of care rather than a kindness. Frame it around prevention: here is the risk, here is what drives it, here is everything we are going to do to reduce it.

THE FOUR THINGS EVERY PATIENT SHOULD BE TOLD

1. **SUDEP** — because the dominant modifiable factors are seizure control and adherence, and patients who understand the risk adhere better. Withholding it protects you, not them.
2. **The class-wide suicidality warning.** A pooled analysis across eleven ASMs found approximately double the rate of suicidal ideation or behaviour, an absolute increase of about one per 500 treated. It applies to the class, not to individual drugs, and it warrants asking about mood at review rather than withholding treatment.
3. **Driving, swimming, bathing, heights.** Most patients will not ask, and the consequences of not knowing fall on them and on other people. Document what you said.
4. **Reproductive planning,** for every patient of childbearing potential, at every visit — not at the visit where a pregnancy is announced.

THE SOUL OF EPILEPSY

What does it mean to live knowing you might die in your sleep from a disease you did not choose? It means checking the mattress alarm every night before bed. It means not being alone. It means your partner sleeps lightly. It means the most frightening thing you can do is fall asleep in a room by yourself. And it means that when your neurologist says “I need to talk to you about something important,” you already know the conversation matters — because you have asked yourself the question in the dark, many times, long before anyone offered to answer it.

BOOK FOUR

Becoming

The failure modes, and what is coming next

How to Confirm You Are a Bad Epileptologist

Twenty pitfalls, written the wrong way round

The fastest way to learn a specialty's failure modes is to state them as instructions. Everything below happens in real clinics, written as advice you should not take. If more than three feel familiar, that is the point of the chapter rather than a reason to stop reading — most of these are errors of habit, not of knowledge.

In the clinic

1. **Diagnose epilepsy from the seizure type and never ask about the syndrome.** Seizure type tells you what to treat; syndrome tells you what will make it worse. A patient labelled "generalised tonic-clonic" who actually has JME will be given carbamazepine and will get worse in a way you will attribute to the disease.
2. **Never ask a teenager about morning jerks.** The single question that identifies JME takes four seconds, and patients never volunteer it because they do not consider dropping a toothbrush to be a seizure.
3. **Treat the EEG rather than the patient.** A normal interictal EEG does not exclude epilepsy, and discharges in someone who has never had a seizure do not establish it. Chasing discharges in a seizure-free patient adds toxicity to a person who was well.
4. **Accept "blackout" at face value and never speak to a witness.** Diagnosing from the patient's own account of a period of unconsciousness is diagnosing from the one person who was not there.
5. **Never watch a video the family has taken.** Phone video is the highest-yield investigation in the whole assessment and it costs nothing. Ask for it at every visit where the diagnosis is unsettled.
6. **Assume drug-resistant epilepsy means you have not yet found the right drug.** After two appropriate, adequately dosed, tolerated agents have failed, the chance a third produces freedom is small. That is the moment to reconsider the diagnosis and refer for surgical evaluation — not to start a fourth.

When prescribing

7. **Titrate lamotrigine at whatever speed the seizures seem to demand.** The schedule exists because of Stevens–Johnson syndrome. If the patient needs control faster than lamotrigine can safely provide it, the answer is a different drug, not a faster titration.
8. **Add a second sodium-channel blocker when the first half-works.** You will double the diplopia and ataxia and add very little control. Combine across mechanisms.
9. **Prescribe valproate to a woman of childbearing potential without a conversation.** Roughly one in ten exposed pregnancies carries a major malformation, the neurodevelopmental signal is real and dose-dependent, and a pregnancy prevention programme is now a regulatory requirement rather than a matter of discretion.
10. **Alternatively, refuse valproate to every woman on principle and never explain the trade.** The opposite error, and it also harms. SANAD II found valproate superior for generalised epilepsy, so choosing an alternative is a decision to accept less effective treatment. She is entitled to understand that she is making that trade, and to make it herself.
11. **Start an enzyme-inducing drug and say nothing about contraception.** The interaction runs both ways. Unplanned pregnancy on valproate is a foreseeable consequence of a conversation not had.
12. **Increase the phenytoin dose because the total level is low.** In hypoalbuminaemia, renal failure, pregnancy or alongside valproate the total underestimates free drug — and near the therapeutic range the kinetics are saturable, so a small increase produces a large one. Measure the free level.
13. **Treat the drug level rather than the patient in front of you.** A seizure-free patient with a level below range needs no change. A patient with nystagmus and ataxia at a level inside the range is toxic. Ranges are population guidance, not targets.
14. **Give a benzodiazepine in status, watch it fail, and conclude the benzodiazepine failed.** Give the full weight-based dose, give the second dose, and only then move on.
15. **Stop an antiseizure drug abruptly because the patient developed a side effect.** Withdrawal seizures can be worse than anything the patient started with. Cross-taper — unless the reaction is a serious rash or an organ injury, in which case stop, and know you have made that choice.

On follow-up

16. **Never ask about mood.** Levetiracetam and perampanel carry substantial behavioural burdens and the whole class carries a suicidality

signal. Patients rarely connect irritability to a tablet, and families notice before patients do. Ask both.

17. **Never mention SUDEP because the conversation is uncomfortable.** The main modifiable factors are seizure control and adherence, and patients who understand the risk adhere better.
18. **Manage epilepsy without ever mentioning driving, swimming, bathing or working at height.** Most patients will not ask, and the consequences fall on them and on other people. Document what you said.
19. **Assume a patient whose seizures worsened is non-adherent.** Sometimes true. But also consider a new interacting drug, a switched generic, pregnancy, sleep deprivation, alcohol, intercurrent illness — or that the drug you chose is aggravating the syndrome you did not identify.
20. **Keep every drug the patient has ever been started on.** Refractory epilepsy accumulates prescriptions. Ask of each whether it was ever demonstrably effective, and withdraw the ones that were not — slowly, one at a time. Removing a drug is a clinical intervention, and patients often improve.

THE INVERSE, STATED PLAINLY

- Take a syndromic diagnosis before a drug decision, and ask the two questions — morning jerks, absences — that change it.
- Choose broad-spectrum while the syndrome is uncertain, and give each agent an adequate dose and an adequate trial before calling it a failure.
- Treat the patient's seizures and the patient's tolerability — not the serum level and not the EEG.
- After two well-chosen drugs have failed, stop adding and start reconsidering: the diagnosis first, then surgical candidacy.
- Say the uncomfortable things out loud — teratogenicity, driving, mood, SUDEP. They are the parts of the consultation that change outcomes.

What Is Coming

Genes, molecules, machines — and the discipline to tell the real from the announced

CLINICAL SCENE

The year is not fixed, but the patient is real: a four-year-old with SCN1A-confirmed Dravet syndrome, forty seizures in the past month despite four medications. Her parents have read everything. They ask: “Is there anything coming?” You think about the antisense trial that opened enrolment three months ago. About the automated MRI post-processing that found a Type II focal cortical dysplasia in a child whose scan had been read as normal twice. About the closed-loop device that is learning another child’s seizure signature more precisely every week. And you answer honestly: “Yes. More than at any point in the history of this disease.”

Molecular therapy — the right target for the right disease

The genetic revolution in epilepsy had two phases. The first, largely complete, was diagnostic: identifying which variants cause which syndromes. The second, underway now, is therapeutic: correcting the molecular defect rather than suppressing its consequences.

APPROACH	MECHANISM	TARGETS	STAGE	REALISTIC HORIZON
Antisense oligonucleotides	Single-stranded RNA/DNA modulating splicing or expression	SCN1A upregulation; KCNT1 knockdown	Early-phase human trials	The nearest of these to clinic
AAV gene delivery	Viral vector delivers a functional copy or a regulatory cassette to CNS neurons	SCN1A, KCNQ2, CLN3	Phase I/II for some targets	Five to ten years to first approvals if data support
RNA interference	Targeted mRNA degradation	Gain-of-function SCN8A; tau	Preclinical, animal efficacy shown	Beyond ten years
CRISPR editing	Targeted correction of a pathogenic variant	Point mutations in monogenic epilepsies	Preclinical; CNS delivery remains the obstacle	Ten to fifteen years
Optogenetics	Light-activated control of specific neuron populations	Interneuron activation to abort seizures	Research tool only	A tool, not yet a therapy

SCN1A is the most advanced target and the clearest in all of epileptology: loss of function in a single gene, expressed in a defined cell population, producing a predictable syndrome. That is exactly the shape of problem molecular medicine solves first.

Pipeline pharmacology

- **Soticlestat** — a cholesterol 24-hydroxylase inhibitor reducing NMDA overactivation, studied in Dravet and Lennox–Gastaut. Phase 3 results have been mixed, and the programme illustrates how often a clean mechanism fails to translate.
- **Neurosteroids.** Ganaxolone is approved for CDKL5 deficiency disorder and acts at the extrasynaptic GABA-A neurosteroid site, which does not develop the tolerance that limits benzodiazepines. Trials continue in status epilepticus.
- **Subtype-selective sodium-channel agents** designed to treat gain-of-function channelopathies such as SCN8A without worsening loss-of-function disorders such as Dravet — the mechanistic answer to Chapter 10’s fourth kind of harm.
- **Precision therapy already in practice:** everolimus for tuberous sclerosis, the ketogenic diet for GLUT1 deficiency, pyridoxine for pyridoxine-dependent epilepsy, and sodium-channel blockers for gain-of-function SCN2A and SCN8A. In all of these the genotype, not the seizure type, chooses the drug.

Machines — what is actually real

APPLICATION	STATUS	EVIDENCE	CLINICAL IMPACT
Automated spike detection on EEG	Several commercial systems, some cleared for clinical use	High sensitivity, lower specificity than an expert reader	Reduces review time on long recordings; assists non-expert readers in the ICU
MRI lesion detection (MELD and similar)	Multicentre validation complete	Good — detects FCD in a substantial share of scans reported as normal	Changes surgical candidacy in patients previously called non-lesional. The strongest real example in the field
Wearable seizure detection	Cleared devices for convulsive seizures; mattress and watch-based systems in use	Good for GTCS; poor for subtle focal events	Caregiver alerting for SUDEP prevention; a far better seizure diary than memory
Surgical outcome prediction	Research phase, academic centres	Emerging; needs multicentre validation	Not yet a clinical standard
Pharmacogenomics	HLA typing already standard practice	Established for HLA-B*15:02 and carbamazepine	The field's first routine precision success, and it predates the current wave entirely

EXPERT MODE — CALIBRATED OPTIMISM

Automated MRI surface analysis finding lesions in scans reported as normal is not hype: it is peer-reviewed, multicentre, externally validated, and it changes what happens to a patient. But it is one application. For every validated tool there are a hundred seizure-prediction apps with no published validation at all. Hold new technology to the standard you would hold any diagnostic test: peer-reviewed evidence, independent validation, and demonstrable clinical utility. Be enthusiastic and demand evidence. Those are not in tension.

THE SOUL OF EPILEPSY

The history of epilepsy is the history of humanity learning, very slowly and with great resistance, that the brain is explainable — that what looks divine or demonic or mad has a mechanism. We are now at the extraordinary moment when the mechanism can be targeted at its source, when we can imagine not merely suppressing seizures but correcting the instruction that created them. This is not the end of the story. It is the last chapter of the preamble. The real history of epilepsy — the one where it is cured, where stigma is a footnote, where every affected child has access to precision treatment — is still being written. We are writing it now: in clinic, in the ICU, in the lab, and in the willingness to have difficult conversations with frightened families at two in the morning.

THE SUMMARY, IF THERE IS ONE

- Match mechanism to *syndrome*, not to seizure type alone. The syndrome is what tells you which drugs will make things worse.
- Broad-spectrum first when the syndrome is unclear. The cost of being wrong runs one way.
- Interaction burden, reproductive potential, comorbidity and age narrow the list faster than efficacy data does — most first-line agents are of comparable efficacy and differ mainly in what they cost the patient.
- The titration schedule is part of the drug for lamotrigine and cenobamate, not a suggestion about convenience.
- After two adequate drug trials, the next intervention is a referral, not a prescription.
- The modern formulary's advance over the twentieth century's is not efficacy. It is a wider menu of tolerability, from which a specific patient can be fitted.



“The brain, in its chaos, tells the most honest stories.” — NAJM

Abbreviations

ACNS	American Clinical Neurophysiology Society	LGS	Lennox–Gastaut syndrome
ACTH	Adrenocorticotrophic hormone	LPD	Lateralised periodic discharges
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	LRDA	Lateralised rhythmic delta activity
ASM	Antiseizure medication (formerly AED)	MHD	Monohydroxy derivative of oxcarbazepine
ATL	Anterior temporal lobectomy	MONEAD	Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs
BRV	Brivaracetam	MTLE-HS	Mesial temporal lobe epilepsy with hippocampal sclerosis
CBZ	Carbamazepine	NCSE	Non-convulsive status epilepticus
CLB	Clobazam	NEOLEV2	Levetiracetam versus phenobarbital in neonatal seizures
CNB	Cenobamate	PE	Phenytoin equivalents
DOAC	Direct oral anticoagulant	POLG	Polymerase gamma
DRESS	Drug reaction with eosinophilia and systemic symptoms	RNS	Responsive neurostimulation
ESETT	Established Status Epilepticus Treatment Trial	SANAD	Standard and New Antiepileptic Drugs trial
FCD	Focal cortical dysplasia	SJS / TEN	Stevens–Johnson syndrome / toxic epidermal necrolysis
GAT-1	GABA transporter 1	SUDEP	Sudden unexpected death in epilepsy
GPD	Generalised periodic discharges	SV2A	Synaptic vesicle glycoprotein 2A
ICISS	International Collaborative Infantile Spasms Study	TDM	Therapeutic drug monitoring
ILAE	International League Against Epilepsy	TSC	Tuberous sclerosis complex
JME	Juvenile myoclonic epilepsy	UGT	Uridine diphosphate glucuronosyltransferase
LEV	Levetiracetam	UKISS	United Kingdom Infantile Spasms Study
LTG	Lamotrigine	VNS	Vagus nerve stimulation

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Question bank

One hundred and eighty-nine single-best-answer questions written from the chapters of this book. They are built to test reasoning rather than recall: most stems are clinical, the distractors are the mistakes clinicians actually make, and each explanation closes with the point worth keeping.

HOW TO USE IT

- **After each chapter**, answer its questions before turning to the answers — the retrieval is the learning.
- **Difficulty** is marked ●○○ (core), ●●○ (applied) and ●●● (specialist).
- **Answers and explanations** follow the questions, grouped by chapter. The italic line under each explanation is the take-home point.
- **The same questions can be practised online**, timed or in tutor mode, with the answers shuffled each time: *thetract.org/seizures/qbank*.

1 The Ancient Dance

4 QUESTIONS

1 DRUG HISTORY ●○○

A trainee argues that phenytoin, carbamazepine and valproate were displaced by newer agents because they stopped working in a growing share of patients. Which statement best describes why each generation of antiseizure drug gave ground to the next?

- A Older agents became unaffordable after their patents expired
- B Each generation answered the toxicity of the last, not its failure
- C Newer agents won head-to-head efficacy trials against older ones
- D Regulators withdrew older agents once safer drugs were licensed
- E Pharmacological resistance accumulated in the population over decades

2 DRUG HISTORY ●●○

In 1938 Merritt and Putnam identified phenytoin. Why is this regarded as the conceptual birth of modern epilepsy pharmacology?

- A It was the first agent with efficacy in absence seizures
- B It was the first drug designed against a known molecular target
- C They selected for seizure suppression, not sedation, in the electroshock model
- D It was the first antiseizure drug proven effective in a randomised controlled trial
- E It was the first drug shown to modify a neurological disease

3 HISTORY OF SEMIOLOGY ●●○

Which historical figure described seizures with impaired consciousness and no convulsion, and proposed that the features of a seizure indicate its origin — an aura-based localisation framework nine centuries before video-EEG?

- A Hughlings Jackson, who described the focal march
- B Galen, who adopted the term 'aura'
- C Ibn Sina (Avicenna), in *Al-Qanun fi al-Tibb*
- D The author of the Edwin Smith papyrus
- E Tissot, who refuted lunar causation

4 DRUG HISTORY ●●○

Which antiseizure medication was discontinued in 2017 after retinal pigmentation limited its use?

- A Tiagabine
- B Fenfluramine
- C Felbamate
- D Ezogabine
- E Vigabatrin

5 OLD AND NEW TERMS

•••

A 1998 discharge summary describes “complex partial seizures with secondary generalisation”. Which ILAE 2017 description is equivalent?

- A Focal aware seizure, evolving to bilateral tonic-clonic
- B Unknown-onset tonic-clonic seizure with impaired awareness
- C Generalised tonic-clonic seizure with focal features at onset
- D Focal non-motor seizure with secondary generalisation
- E Focal impaired awareness, evolving to focal to bilateral tonic-clonic

6 UNKNOWN ONSET

•••

A 19-year-old woman is found by her flatmate after an unwitnessed nocturnal convulsion. She is now alert. There is no further history yet, and EEG and MRI are booked for next week. Her doctor wants to start treatment today. Which agent is most appropriate?

- A Carbamazepine
- B Gabapentin
- C Oxcarbazepine
- D Phenytoin
- E Levetiracetam

7 THREE LEVELS

•••

In the ILAE three-level framework, which level most directly tells you which drugs will make the patient worse?

- A Epilepsy type
- B Seizure type
- C Epilepsy syndrome
- D Aetiology
- E Seizure frequency

8 IMMUNE AETIOLOGY

•••

A 24-year-old woman has a two-week illness of agitation, insomnia and paranoia, followed by frequent focal seizures that continue despite two ASMs. She now has orofacial dyskinesias and labile blood pressure. MRI brain is normal and serum NMDA-receptor antibody is negative. What is the most appropriate next step?

- A Send CSF antibodies and start empirical immunotherapy while awaiting results
- B Repeat MRI in two weeks before considering an autoimmune cause
- C Wait for the CSF result before giving any immunotherapy
- D Add a third antiseizure medication and reassess in a week
- E Diagnose a primary psychiatric illness, since the serum antibody is negative

9 INFECTIOUS AETIOLOGY

•••

Which is the commonest infectious cause of epilepsy worldwide?

- A Cerebral malaria
- B HIV-associated opportunistic infection
- C Tuberculoma
- D Neurocysticercosis
- E Herpes simplex encephalitis

10 METABOLIC AETIOLOGY

•••

A neonate has seizures from day two that continue despite phenobarbital and levetiracetam. An IV pyridoxine trial under EEG abolishes both the seizures and the discharges within minutes. Which principle should guide long-term management?

- A Add valproate to cover residual generalised seizures
- B Continue both ASMs and stop pyridoxine once the EEG normalises
- C Switch to vigabatrin, as the response implies a GABA disorder
- D Lifelong pyridoxine; the cofactor, not the ASM, is the treatment
- E Wean pyridoxine after three months, as dependency is self-limiting

11 AETIOLOGY OVERLAP

•••

A child with a pathogenic TSC2 variant has focal seizures arising from a cortical tuber visible on MRI. How should the aetiology be classified under ILAE 2017?

- A Metabolic, because TSC disturbs mTOR signalling
- B Genetic only, because the variant is the root cause
- C Unknown, until surgery confirms the tuber is epileptogenic
- D Structural only, because a visible lesion always takes precedence over a variant
- E Both structural and genetic — the categories are not mutually exclusive

12 AWARENESS

•••

During a focal seizure a patient keeps her eyes open, looks around the room and appears to follow events. Afterwards she has no memory of the episode. How should awareness be classified?

- A Retained, because her eyes stayed open throughout
- B Generalised, because memory loss implies bilateral involvement
- C Impaired — awareness requires both meaningful responsiveness and recall
- D Unclassifiable without ictal EEG
- E Retained, because she appeared to look around

13 LATERALISING SIGNS

•••

Video-EEG captures a seizure in a 33-year-old man: a rising epigastric sensation, behavioural arrest, lip-smacking, fumbling movements of the right hand, and a stiff, contorted left arm held for 20 seconds. Afterwards he wipes his nose with his right hand. Where is the seizure most likely to begin?

- A Right mesial temporal lobe
- B Right supplementary motor area
- C Left mesial temporal lobe
- D Left frontal operculum
- E It cannot be lateralised on semiology alone

14 LATERALISING SIGNS

•••

Which of the following lateralises to the hemisphere IPSILATERAL to the seizure focus?

- A Post-ictal Todd's paralysis
- B Ictal eye deviation
- C Forced ictal head version
- D Unilateral dystonic arm posturing
- E Post-ictal nose-wiping

15 FIGURE-OF-4

•••

Just before a nocturnal seizure generalises, the patient adopts an asymmetric posture: right arm extended at the elbow, left arm flexed, head turned toward the extended arm. Which hemisphere is the focus most likely to be in?

- A Right — the head turns toward the focus
- B It is a generalised posture that does not lateralise
- C Left — ipsilateral to the flexed arm
- D Left — contralateral to the extended arm
- E Right — ipsilateral to the extended arm

16 LATERALISING SIGNS

•••

A right-handed woman is unable to name objects or produce fluent speech for six minutes after each of her focal seizures, though she follows simple commands. Which hemisphere is most likely involved?

- A Right frontal lobe, given preserved comprehension
- B Bilateral temporal lobes
- C Either — post-ictal aphasia does not lateralise
- D Left (dominant) hemisphere
- E Right (non-dominant) hemisphere

17 LATERALISING SIGNS

•••

A patient with temporal lobe epilepsy vomits during several of his recorded seizures. What does this sign suggest?

- A A dominant, usually left, temporal focus
- B A non-dominant, usually right, temporal focus
- C A functional rather than epileptic event
- D An occipital focus
- E Generalised onset

18 FRONTAL LOBE EPILEPSY

•••

A 22-year-old man has several events a night, each under 30 seconds: he sits bolt upright, shouts and cycles his legs violently, then is fully oriented immediately. The events are identical each time. Scalp EEG during one event is obscured by artefact. His GP diagnosed night terrors. What is the most likely diagnosis?

- A Sleep-related hypermotor epilepsy
- B Functional (dissociative) seizures
- C Nocturnal panic attacks with hyperventilation
- D REM sleep behaviour disorder
- E NREM arousal parasomnia (sleep terrors)

19 OCCIPITAL VS MIGRAINE

•••

A 26-year-old woman has stereotyped episodes of brightly coloured circles moving in her left visual field, lasting about 90 seconds, sometimes followed by headache. Which feature most favours an occipital seizure over migraine aura?

- A Complex visual hallucinations of faces, animals and whole scenes lasting minutes
- B Onset in a young woman with a family history of migraine
- C Black-and-white zigzags expanding slowly over 20 minutes
- D Being followed by a throbbing headache
- E Coloured, moving shapes in one hemifield lasting under two minutes

20 PARIETAL LOBE EPILEPSY

•••

A 34-year-old woman has stereotyped episodes of tingling that start in her left hand and spread up the arm to the face over 30 seconds, lasting two minutes. She has no motor signs and has been labelled functional. Where is the likely focus?

- A Left ventral posterior thalamus
- B Right primary somatosensory cortex
- C Left primary somatosensory cortex
- D Right primary motor cortex
- E Right mesial temporal lobe

21 SEMIOLOGY PRINCIPLE

•••

When reviewing a seizure video to localise onset, which part of the recording carries the most localising information?

- A The point of maximum motor activity
- B The first three to five seconds of clinical change
- C The bilateral convulsive phase
- D The last ten seconds before the convulsion stops
- E The post-ictal phase

22 HEAD VERSION

•••

After 40 seconds of staring and automatisms, a patient's head turns forcefully and sustainedly to the right, and the seizure then becomes bilateral tonic-clonic. Which hemisphere is the focus most likely in?

- A Bilateral
- B Right
- C Neither — late version does not lateralise
- D Left
- E Cannot be stated without the eye movements

23 TEMPORAL AURAS

•••

A patient describes an unpleasant, hard-to-name burning smell seconds before each seizure. Which region is most likely generating the aura?

- A Supplementary motor area
- B Dorsolateral prefrontal cortex
- C Mesial temporal or insular cortex
- D Primary motor cortex
- E Occipital cortex

4 Reading the Brain's Diary

12 QUESTIONS

24 NORMAL EEG

•••

An awake adult is recorded with eyes closed. There is no posterior dominant rhythm; the background is diffuse theta. What does this indicate?

- A An excess of medication-related fast activity
- B Cortical dysfunction, since alpha is expected in this state
- C A normal drowsy pattern in an alert adult
- D A normal variant of no clinical significance
- E A focal structural lesion of the occipital lobe causing loss of the rhythm

25 NORMAL EEG

•••

An ICU patient's EEG shows prominent diffuse 18–25 Hz activity over frontal and central regions. What is the most likely explanation?

- A Non-convulsive status epilepticus
- B Hepatic encephalopathy with frontally predominant triphasic waves
- C Sedative drug effect (e.g. benzodiazepine, propofol)
- D Bifrontal structural lesions such as tumour
- E Diffuse hypoxic–ischaemic brain injury

26 FOCAL SLOWING

•••

An awake, alert 58-year-old with one focal seizure has continuous polymorphic delta activity over the left frontal region. What does this most likely indicate?

- A A structural lesion at that site — image it
- B A diffuse encephalopathy
- C A benign variant seen in drowsy adults, which needs no further action
- D Normal deep sleep (N3)
- E An interictal epileptiform discharge

27 TRIPHASIC WAVES VS NCSE

•••

A 61-year-old with cirrhosis is unresponsive (GCS 8). EEG shows frontally predominant 1.5 Hz triphasic-morphology discharges. Under EEG, IV lorazepam abolishes the discharges, but over the next 30 minutes his responsiveness does not change at all. What does this trial show?

- A It confirms hepatic encephalopathy and excludes NCSE
- B Nothing diagnostic: the EEG improved but the patient did not
- C It confirms NCSE requiring an anaesthetic infusion
- D It confirms non-convulsive status epilepticus
- E It proves the pattern is metabolic, so monitoring can stop

28 HYPSSARRHYTHMIA

•••

A 6-month-old has clusters of brief flexor spasms on waking. EEG shows chaotic, very high-amplitude, asynchronous multifocal spike-wave. What is the most appropriate next step?

- A Repeat the EEG in four weeks to confirm
- B Start carbamazepine and review in clinic
- C Start levetiracetam and review in three months
- D Await the genetic results before deciding whether any treatment is needed
- E Start hormonal therapy, with or without vigabatrin, within days

29 PERIODIC PATTERNS

•••

Three days after a large right MCA infarct, a patient is more drowsy than expected. EEG shows stereotyped right hemispheric periodic discharges at 1 Hz. How should this be interpreted?

- A Definite electrographic status requiring an anaesthetic infusion
- B High seizure risk: continue cEEG and treat if encephalopathic
- C A benign post-stroke pattern needing no further monitoring
- D Distorted sleep spindles over the infarcted hemisphere
- E Triphasic waves of metabolic origin needing no EEG follow-up

30 RHYTHMIC DELTA

•••

After resection of a left frontal tumour, a patient's cEEG shows non-evolving left frontal rhythmic delta at 1.5 Hz, with no change in clinical state. What is the appropriate response?

- A Treat it as an at-risk pattern and keep monitoring
- B Report it as normal N3 sleep
- C Treat as status epilepticus and start an anaesthetic infusion
- D Stop monitoring, since it is not epileptiform
- E Give phenytoin loading immediately

31 BURST-SUPPRESSION

•••

Burst-suppression appears in two ICU patients: one on a midazolam infusion for refractory status, the other comatose after cardiac arrest with absent brainstem reflexes and no sedation. Which statement is correct?

- A An appropriate treatment target in both
- B A very poor prognostic sign in both
- C A treatment target in the first; ominous in the second
- D A seizure pattern in both that needs escalation
- E Uninterpretable in both and best ignored

32 GENERALISED PATTERNS

•••

A 15-year-old's EEG shows generalised 4–6 Hz polyspike-and-wave with a photoparoxysmal response. Which drug class should be avoided?

- A Benzodiazepines such as clobazam
- B Broad-spectrum agents such as valproate
- C SV2A ligands such as levetiracetam
- D Sodium-channel blockers such as carbamazepine
- E AMPA antagonists such as perampanel

33 INTERPRETING DISCHARGES

•••

A 30-year-old pilot has an EEG for headaches. It shows occasional generalised spike-and-wave. He has never had a seizure or any suspicious event, and his examination and MRI are normal. What is the correct approach?

- A Diagnose JME and counsel on lifelong treatment
- B Repeat EEGs until the discharges clear, then decide
- C Start valproate because the discharges are generalised
- D Start levetiracetam to prevent a first seizure
- E No ASM: discharges without seizures do not make epilepsy

34 NORMAL VARIANTS

•••

During drowsiness and light sleep a broad, high-amplitude sharply contoured wave appears maximally at the vertex. What is the most likely interpretation?

- A Vertex waves — a normal sleep transient
- B Generalised epileptiform discharges
- C Frontal intermittent rhythmic delta
- D Lateralised periodic discharges
- E Triphasic waves

35 ACNS TERMINOLOGY

•••

A cEEG report reads "LPDs+F, right temporal, frequent". What does the "+F" modifier mean?

- A Frontally predominant
- B Followed by suppression
- C Superimposed fast activity
- D Fluctuating frequency
- E Focal evolution confirming a seizure

36 DEFINING EPILEPSY

•••

A 67-year-old man on apixaban for atrial fibrillation, with a left MCA infarct three years ago, has 90 seconds of rhythmic right arm jerking followed by ten minutes of confusion. EEG shows left hemispheric slowing with sharp waves; MRI shows left MCA encephalomalacia. Which statement is correct?

- A He has epilepsy, and phenytoin is preferred for its long track record and low cost
- B He has epilepsy after this single seizure; levetiracetam is an appropriate choice
- C He has epilepsy, and carbamazepine is the preferred agent
- D This was a provoked seizure and no treatment is indicated
- E He needs a second unprovoked seizure before epilepsy can be diagnosed

37 TONGUE BITING

•••

Which pattern of tongue injury most suggests a functional (dissociative) seizure rather than a generalised tonic-clonic seizure?

- A Biting at the tip of the tongue
- B No tongue biting at all
- C Biting with blood-stained froth
- D Biting on the lateral border
- E Bilateral lateral border bites

38 THE WITNESS

•••

A woman says her husband was “shaking” during a collapse at a restaurant. What is the single most useful next step in taking her history?

- A Ask whether he has a family history of epilepsy
- B Ask whether he was incontinent
- C Ask how long he was unconscious
- D Ask her to demonstrate the movements with her hands
- E Order an EEG before taking further history

39 SYNCOPE

•••

A 19-year-old standing in a hot, crowded hall feels warm and nauseated, notices her vision greying, then collapses. Friends see a few irregular jerks for under 15 seconds. She is fully oriented within a minute. What is the most likely diagnosis?

- A Generalised tonic-clonic seizure
- B Cardiac arrhythmia
- C Functional seizure
- D Hypoglycaemia
- E Vasovagal syncope

40 FUNCTIONAL SEIZURES

•••

A 25-year-old woman has 20-minute episodes of waxing and waning thrashing with pelvic thrusting. During an event her eyes are closed and she resists eye opening. Which investigation establishes the diagnosis?

- A Tilt-table testing
- B Video-EEG capturing a typical event
- C A routine 20-minute interictal EEG
- D Serum prolactin 6 hours after an event
- E Epilepsy-protocol MRI

41 CARDIAC SYNCOPE

•••

A 17-year-old collapses without warning during a football match and is briefly stiff with a few jerks. His uncle died suddenly at 30. Which investigation pathway is most important?

- A Tilt-table testing alone
- B ECG, Holter and echocardiography
- C Serum prolactin and creatine kinase
- D Epilepsy-protocol MRI brain
- E EEG after sleep deprivation

42 IMAGING

•••

A 31-year-old with focal impaired awareness seizures has failed two ASMs. A standard brain MRI was reported as normal. What is the most appropriate imaging step?

- A FDG-PET instead of MRI
- B MRI requested explicitly with an epilepsy protocol
- C Repeat the standard MRI with contrast
- D No further imaging — proceed straight to VNS
- E CT brain with contrast

43 HIPPOCAMPAL SCLEROSIS

•••

Which MRI sequence is the gold standard for hippocampal sclerosis?

- A Axial diffusion-weighted imaging with ADC map
- B Axial susceptibility-weighted imaging
- C Post-gadolinium volumetric T1
- D Sagittal 3D FLAIR through the whole brain
- E Coronal oblique T2 through the hippocampi

44 IMAGING

•••

A young man with focal seizures has a small T2 lesion with a mixed-signal core. Which sequence best demonstrates blood products to confirm a cavernous malformation?

- A SWI or gradient echo
- B Coronal oblique T2
- C 3D volumetric T1
- D Diffusion-weighted imaging
- E Post-gadolinium T1

45 DIFFERENTIAL DIAGNOSIS

•••

A 20-year-old has episodes in which his knees buckle and his head drops when he laughs, with consciousness fully preserved. He also falls asleep in lectures. Which test is most likely to confirm the diagnosis?

- A Prolonged video-EEG
- B Tilt-table testing
- C Epilepsy-protocol MRI
- D Polysomnography with MSLT
- E 24-hour Holter monitoring

6 When the Mind Plays Tricks

13 QUESTIONS

46 JME

•••

An 18-year-old female medical student has her first GTCS during an exam after a sleepless week. Her mother reports a year of involuntary arm “flinging” at breakfast and brief staring spells. The ED doctor started carbamazepine 400 mg daily. What is the best management?

- A Stop carbamazepine and start levetiracetam
- B Continue carbamazepine and add levetiracetam
- C Increase carbamazepine to 800 mg daily
- D Switch to oxcarbazepine for better tolerability
- E Start valproate today with no further discussion

47 JME

•••

A 24-year-old man has JME with morning myoclonus and two GTCS. He has no plans to father children in the near future and no liver disease. Which drug is most likely to give the best seizure control?

- A Levetiracetam
- B Carbamazepine
- C Valproate
- D Ethosuximide
- E Lamotrigine

48 JME

•••

A 27-year-old woman with JME has been seizure-free for five years on levetiracetam and asks to stop. Which counselling statement is most accurate?

- A Five years seizure-free means remission is permanent
- B JME remits in most patients by their mid-twenties
- C Relapse risk is the same as in self-limited childhood epilepsies
- D JME is usually lifelong and relapse after stopping is very high
- E She can stop abruptly because levetiracetam has no withdrawal risk

49 CHILDHOOD ABSENCE

•••

A 7-year-old girl has dozens of 10-second staring spells a day. Three minutes of hyperventilation provokes 3 Hz generalised spike-and-wave with a typical absence. She has had no other seizure type. What is the first-line treatment?

- A Valproate
- B Ethosuximide
- C Lamotrigine
- D Levetiracetam
- E Carbamazepine

50 ABSENCE WITH GTCS

•••

A 9-year-old boy with typical absences and 3 Hz spike-wave has now also had two generalised tonic-clonic seizures. Which single agent is most appropriate?

- A Valproate
- B Ethosuximide
- C Oxcarbazepine
- D Gabapentin
- E Carbamazepine

51 SELF-LIMITED EPILEPSY WITH CENTROTEMPORAL SPIKES

•••

An 8-year-old boy has had two nocturnal events in a year: drooling, twitching of one side of the face and speech arrest, with preserved awareness. EEG shows centrottemporal spikes markedly activated by sleep. Development and MRI are normal. What is the most appropriate management?

- A Start carbamazepine at bedtime
- B Explain the prognosis; monitoring alone is often enough
- C Refer for epilepsy surgery evaluation
- D Start valproate and continue it until he reaches 18 years of age
- E Start levetiracetam with EEG every three months

52 DRAVET

•••

An 8-month-old had a 40-minute febrile hemiclonic seizure; at 10 months she has another prolonged febrile seizure. EEG and development are normal. A colleague suggests carbamazepine because the seizures look focal. What is the most appropriate step?

- A Start carbamazepine, since the hemiclonic semiology indicates focal-onset epilepsy
- B Send SCN1A genetic testing and avoid sodium-channel blockers
- C No further work-up, as the EEG is normal
- D Reassure — febrile seizures are benign
- E Start lamotrigine as a well-tolerated alternative

53 DRAVET MECHANISM

•••

Why do sodium-channel blockers worsen seizures in SCN1A-related Dravet syndrome?

- A They cause hyponatraemia that lowers the seizure threshold
- B They block T-type calcium channels in thalamic relay neurons
- C They induce the metabolism of co-prescribed antiseizure drugs
- D The variant is gain-of-function and the drugs paradoxically amplify it
- E Nav1.1 loss is in inhibitory interneurons; blocking it removes inhibition

54 INFANTILE SPASMS

•••

A 4-month-old with tuberous sclerosis complex develops clusters of spasms on waking, and EEG shows hypsarrhythmia. What is the first-line treatment?

- A Topiramate
- B Vigabatrin
- C Phenobarbital
- D Carbamazepine
- E Levetiracetam

55 INFANTILE SPASMS

•••

A 5-month-old without tuberous sclerosis has new infantile spasms with hypsarrhythmia and a normal MRI. According to ICISS, which initial treatment gives the best response?

- A Levetiracetam, then hormones if it fails
- B Hormonal therapy alone
- C Ketogenic diet
- D Hormonal therapy plus vigabatrin
- E Vigabatrin alone

56 LENNOX-GASTAUT

•••

A 6-year-old has nocturnal tonic seizures, atypical absences and frequent atonic drop attacks with injuries. EEG shows slow spike-wave under 2.5 Hz and paroxysmal fast activity in sleep. He takes valproate. Which add-on is particularly useful for his drop attacks?

- A Gabapentin
- B Rufinamide
- C Vigabatrin
- D Ethosuximide
- E Carbamazepine

57 RASMUSSEN ENCEPHALITIS

•••

A 6-year-old has worsening right-sided focal motor seizures, now continuous (epilepsia partialis continua), with progressive left hemispheric atrophy on serial MRI and a new right hemiparesis. What is the only treatment that stops the seizures?

- A Long-term immunotherapy
- B Corpus callosotomy
- C High-dose levetiracetam with clobazam
- D Vagus nerve stimulation
- E Hemispherectomy

58 SLEEP-RELATED HYPERMOTOR EPILEPSY

•••

A 15-year-old has clusters of brief nocturnal hypermotor events with vocalisation; his father had similar events as a teenager. Scalp video-EEG during two events shows no clear ictal change. Which statement is correct?

- A The family history makes Dravet syndrome the likeliest diagnosis
- B A normal ictal EEG confirms functional seizures and excludes epilepsy
- C Valproate is the only drug likely to control these events
- D A normal ictal scalp EEG proves these events are NREM parasomnias
- E A normal scalp EEG does not exclude it; Na-channel blockers often work

59 LAMOTRIGINE MECHANISM

Which description of lamotrigine's mechanism is correct?

- A Fast-inactivation block plus inhibition of glutamate release
- B Irreversible inhibition of GABA-transaminase
- C T-type calcium block in thalamic relay neurons
- D Enhancement of slow sodium-channel inactivation
- E Binding to synaptic vesicle protein SV2A, modulating neurotransmitter release

60 SODIUM-CHANNEL AGENTS

Which two agents act primarily by enhancing SLOW inactivation of the sodium channel?

- A Oxcarbazepine and topiramate
- B Phenytoin and carbamazepine
- C Lacosamide and cenobamate
- D Lamotrigine and rufinamide
- E Zonisamide and valproate

61 GABA-A

Why is barbiturate overdose often lethal, while benzodiazepine overdose alone usually is not?

- A Benzodiazepines are cleared far faster than barbiturates in overdose
- B Barbiturates irreversibly inhibit GABA-transaminase in overdose
- C Barbiturates can open the channel without GABA; benzodiazepines cannot
- D Benzodiazepines act only at extrasynaptic GABA-A receptors
- E Barbiturates additionally block sodium channels at toxic concentrations

62 CALCIUM CHANNELS

Through which mechanism is ethosuximide effective in absence seizures?

- A Blocking T-type calcium current in thalamic relay neurons
- B Binding the $\alpha 2\delta$ subunit of presynaptic calcium channels
- C Antagonising postsynaptic AMPA receptors
- D Blocking fast sodium-channel inactivation in cortex
- E Potentiating GABA-A at the benzodiazepine site

63 GABAPENTIN MECHANISM

What is the mechanism of gabapentin?

- A Direct agonism at GABA-A receptors
- B Inhibition of GABA reuptake via GAT-1
- C Inhibition of GABA-transaminase
- D Binding the $\alpha 2\delta$ calcium-channel subunit
- E Positive modulation of GABA-B receptors

64 VIGABATRIN MECHANISM

A patient stops vigabatrin. Why does its pharmacological effect persist well beyond five plasma half-lives?

- A It irreversibly inhibits GABA-transaminase
- B It binds irreversibly to sodium channels
- C It is sequestered in adipose tissue
- D It induces its own metabolism
- E It has a long-lived active metabolite

65 SV2A

What makes the evidence that SV2A binding is levetiracetam's antiseizure mechanism unusually strong?

- A It was designed from the SV2A crystal structure
- B It has no other known molecular target
- C Affinity across analogues tracks antiseizure potency
- D SV2A knockout mice are resistant to seizures
- E Its levels correlate tightly with seizure control

66 RATIONAL POLYTHERAPY

A patient with focal epilepsy has a partial response to an adequate dose of carbamazepine. Which add-on is most rational on mechanistic grounds?

- A Lacosamide
- B Phenytoin
- C Oxcarbazepine
- D Levetiracetam
- E Lamotrigine

67 GLUTAMATE ANTAGONISTS

Which ASM is a selective, non-competitive antagonist of the postsynaptic AMPA receptor?

- A Lacosamide
- B Brivaracetam
- C Perampanel
- D Topiramate
- E Felbamate

68 SYNERGY

Which ASM pairing has evidence of genuine synergy?

- A Levetiracetam with brivaracetam
- B Oxcarbazepine with eslicarbazepine
- C Topiramate with zonisamide
- D Carbamazepine with lamotrigine
- E Lamotrigine with valproate

69 AGGRAVATION

••○

A 17-year-old with JME was started on lamotrigine. As the dose rises through 200 mg/day, his GTCS stop but his morning jerks become more frequent. What is the most likely explanation?

- A Lamotrigine is causing a hypersensitivity reaction
- B This is the natural progression of JME regardless of treatment
- C Lamotrigine can aggravate myoclonic seizures
- D Lamotrigine levels are subtherapeutic
- E He is non-adherent to the evening dose

70 SANAD II

••○

A 45-year-old man with no comorbidities has newly diagnosed focal epilepsy. According to SANAD II, which agent is the reference first-line choice?

- A Lamotrigine
- B Gabapentin
- C Levetiracetam
- D Zonisamide
- E Valproate

71 SANAD II

••○

What did SANAD II show for newly diagnosed generalised and unclassified epilepsy?

- A Levetiracetam failed non-inferiority; valproate was better
- B Levetiracetam was non-inferior to valproate
- C Lamotrigine was superior to valproate
- D Levetiracetam was superior on time to treatment failure
- E Valproate and levetiracetam were equivalent on all outcomes

72 AGGRAVATION

••○

A 10-year-old boy with frequent absences and one GTCS was started on oxcarbazepine for the convulsion. Within weeks his absences have doubled. What is the best change?

- A Add ethosuximide and continue oxcarbazepine
- B Switch to gabapentin
- C Replace oxcarbazepine with valproate
- D Switch to carbamazepine
- E Increase oxcarbazepine

73 AGGRAVATION

••○

Which of the following can aggravate absence and myoclonic seizures?

- A Clobazam
- B Valproate
- C Ethosuximide
- D Vigabatrin
- E Levetiracetam

74 NEONATAL SEIZURES

••○

A term neonate with hypoxic–ischaemic encephalopathy has electroclinical seizures. The cause is being treated. Which ASM is first line?

- A Phenytoin
- B Phenobarbital
- C Levetiracetam
- D Valproate
- E Topiramate

75 DRAVET TREATMENT

••○

A 3-year-old with SCN1A-confirmed Dravet syndrome still has frequent convulsive seizures on valproate and clobazam. Which add-on is most appropriate?

- A Lamotrigine
- B Stiripentol
- C Oxcarbazepine
- D Phenytoin
- E Vigabatrin

76 VALPROATE CHOICE

••○

A 54-year-old post-menopausal woman has newly diagnosed generalised epilepsy with GTCS and myoclonus. Liver function is normal. Which agent is most likely to control her seizures?

- A Valproate
- B Carbamazepine
- C Lamotrigine
- D Levetiracetam
- E Phenytoin

77 VALPROATE COUNSELLING

••○

A 22-year-old woman has generalised epilepsy with GTCS. Which approach best reflects the evidence and regulation?

- A Defer all treatment until she has completed her family
- B Refuse valproate on principle without explaining the trade-off
- C Offer LEV or LTG, explaining lower likely efficacy; valproate only under a PPP
- D Prescribe valproate as the most effective drug, without discussing alternatives
- E Prescribe carbamazepine to avoid valproate's teratogenicity

78 CHILDHOOD ABSENCE

••○

Parents of a 6-year-old with childhood absence epilepsy ask for lamotrigine because they read it is well tolerated. Which statement best reflects the evidence?

- A Lamotrigine is preferred because ethosuximide impairs attention more
- B Lamotrigine worsens absence and is contraindicated
- C Lamotrigine and ethosuximide are equivalent on efficacy, and lamotrigine spares attention
- D Lamotrigine is the most effective drug for childhood absence
- E Lamotrigine is less effective than both ethosuximide and valproate in childhood absence

79 AGGRAVATION

...

A 21-year-old with well-controlled JME on levetiracetam is prescribed a drug for generalised anxiety. Over the following month his morning jerks return. Which drug is the most likely culprit?

- A Pregabalin
- B Propranolol
- C Cognitive behavioural therapy
- D Sertraline
- E Buspirone

80 BEFORE A SODIUM-CHANNEL BLOCKER

...

An ED doctor plans carbamazepine for a 16-year-old after a first GTCS. Which questions must be asked before prescribing any sodium-channel blocker?

- A Morning jerks, absences, and whether this could be Dravet
- B Drug allergies, renal and hepatic function
- C Exam stress, caffeine intake and screen time
- D Family history, alcohol use and recent sleep pattern
- E Headache, visual aura and vomiting

9 The Formulary

40 QUESTIONS

81 PHENYTOIN

...

A patient's phenytoin level is 9 mg/L on 300 mg/day. The dose is increased to 400 mg/day. Ten days later he has nystagmus and ataxia, with a level of 28 mg/L. What explains this?

- A Autoinduction failing after the dose increase
- B Interaction with a newly started enzyme inducer
- C Reduced protein binding caused by the higher dose
- D Laboratory error, since a one-third dose increase cannot triple a steady-state level
- E Saturable metabolism: near the range, small dose rises cause large level rises

82 PHENYTOIN

...

A 70-year-old ICU patient with sepsis, AKI and albumin 18 g/L is on phenytoin. He is seizure-free but drowsy with nystagmus. Total phenytoin is 7 mg/L. The team proposes increasing the dose. What should be done?

- A Measure the free phenytoin level before changing the dose
- B Add valproate to raise the phenytoin level
- C Increase the dose to bring the total into the 10–20 mg/L range
- D Switch to carbamazepine
- E Give a reload of 10 mg/kg

83 PHENYTOIN IV

...

An 81-year-old with ischaemic heart disease needs IV phenytoin. What is the maximum infusion rate?

- A 100 mg/min
- B 50 mg/min
- C 25 mg/min
- D No limit if on a cardiac monitor
- E 150 mg/min

84 PHENYTOIN

...

Hours after peripheral IV phenytoin, a patient's hand becomes swollen, painful and purple-blue distal to the cannula. What is this?

- A DRESS
- B Compartment syndrome from fluid overload
- C Stevens–Johnson syndrome
- D Raynaud phenomenon
- E Purple glove syndrome

85 CARBAMAZEPINE PHARMACOGENOMICS

...

A 30-year-old Filipino man with focal epilepsy and trigeminal neuralgia is to start carbamazepine. What should be done first?

- A Test for HLA-A*31:01 only
- B No genetic testing is needed
- C Test for HLA-B*15:02
- D Check CYP2C9 genotype
- E Measure thiopurine methyltransferase

86 CARBAMAZEPINE PHARMACOGENOMICS

...

Which HLA allele is associated with carbamazepine-induced DRESS and hypersensitivity reactions, including in European and Japanese populations?

- A HLA-A*31:01
- B HLA-B*15:02
- C HLA-DQB1*06:02
- D HLA-B*58:01
- E HLA-B*57:01

87 CARBAMAZEPINE

•••

A patient started carbamazepine 600 mg/day with a level of 9 mg/L at day 7. At week 4 seizures recur and the level is 5 mg/L, with good adherence and no new drugs. What is the explanation?

- A Saturable absorption at higher doses
- B Accumulation of an inactive metabolite
- C Displacement of carbamazepine from albumin by its own epoxide metabolite
- D Autoinduction of CYP3A4 over the first 2–4 weeks
- E Non-adherence despite his account

88 OXCARBAZEPINE

•••

A 74-year-old on carbamazepine and a thiazide has symptomatic sodium of 126 mmol/L. The team proposes switching to oxcarbazepine. What is the best response?

- A Switch to levetiracetam or lamotrigine instead
- B Continue carbamazepine and restrict fluids to one litre a day
- C Switch to oxcarbazepine and replace the thiazide with an SSRI
- D Switch to oxcarbazepine at a 1:1.5 conversion and recheck sodium
- E Switch to eslicarbazepine once daily to reduce sodium loss

89 ESLICARBAZEPINE

•••

A patient on oxcarbazepine 1200 mg/day has partial control, and eslicarbazepine is added. What is the problem with this combination?

- A The combination causes clinically significant QT shortening and arrhythmia
- B Eslicarbazepine blocks oxcarbazepine conversion to MHD
- C Eslicarbazepine induces oxcarbazepine metabolism
- D There is no problem; it is rational polytherapy
- E They share the active moiety: a dose increase posing as polytherapy

90 LAMOTRIGINE TITRATION

•••

A patient on valproate 1000 mg/day needs lamotrigine added. What is the correct starting schedule?

- A 50 mg daily for 2 weeks, then 100 mg daily
- B 25 mg on alternate days for 2 weeks, then 25 mg daily for 2 weeks
- C 12.5 mg daily for 2 weeks, then 25 mg daily
- D 50 mg twice daily from the start
- E 25 mg daily for 2 weeks, then 50 mg daily for 2 weeks, then +50 mg every 2 weeks

91 LAMOTRIGINE RESTART

•••

A patient on lamotrigine 300 mg/day stopped it for ten days while travelling. She wants to restart at her usual dose today. What is the correct advice?

- A Switch to a different drug, as lamotrigine cannot be restarted
- B Restart at 300 mg/day with an antihistamine
- C Restart at 150 mg/day for a week, then 300 mg
- D Restart from the beginning of the titration schedule
- E Restart at 300 mg/day

92 LAMOTRIGINE

•••

Five weeks after starting lamotrigine, a 30-year-old has persistent high fever, splenomegaly, pancytopenia and ferritin of 9,000 µg/L. Which serious reaction is most likely?

- A Aseptic meningitis
- B Stevens–Johnson syndrome
- C Neuroleptic malignant syndrome
- D Aplastic anaemia
- E Haemophagocytic lymphohistiocytosis

93 LACOSAMIDE

•••

A 68-year-old on verapamil with first-degree AV block needs IV lacosamide loading. What is the main safety concern?

- A QT shortening with risk of ventricular arrhythmia
- B Respiratory depression
- C PR prolongation and AV block
- D Hepatotoxicity
- E Hyponatraemia

94 RUFINAMIDE

•••

Before starting rufinamide for Lennox–Gastaut, a baseline ECG is recommended. What is it looking for?

- A A short QT interval
- B PR prolongation
- C A long QT interval
- D Left ventricular hypertrophy
- E Brugada pattern

95 CENOBAMATE

•••

A patient is at 100 mg/day of cenobamate, eight weeks into titration, and misses ten days of doses. What should be done?

- A Restart the titration from the beginning
- B Resume at 100 mg/day
- C Resume at 150 mg/day to catch up
- D Stop cenobamate permanently
- E Resume at 50 mg/day for one week, then 100 mg

96 CENOBAMATE INTERACTIONS

•••

A woman on phenytoin and a combined oral contraceptive starts cenobamate. Two months later she is ataxic. Which pair of interactions applies?

- A Cenobamate inhibits CYP2C19, raising phenytoin, and induces CYP3A4, lowering contraceptive efficacy
- B Cenobamate induces CYP2C19, lowering phenytoin, and inhibits CYP3A4, raising contraceptive levels
- C Cenobamate has no meaningful interactions
- D Phenytoin raises cenobamate; no contraceptive interaction
- E Cenobamate displaces phenytoin from albumin and has no contraceptive interaction

97 CENOBAMATE EFFICACY

•••

Which statement about cenobamate's efficacy is most accurate?

- A About half of patients became seizure-free during the maintenance phase of the pivotal trial
- B It was superior to lacosamide in a head-to-head trial
- C Its efficacy matches placebo once dropouts are accounted for
- D It is licensed as first-line monotherapy for generalised epilepsy
- E About a fifth seizure-free at the highest dose; no head-to-head data

98 PHENOBARBITAL

•••

A 60-year-old on phenobarbital for 25 years has a painful, stiff shoulder and nodular thickening of both palms. Which is the most likely explanation?

- A Vitamin D deficiency myopathy
- B Phenytoin-induced neuropathy
- C Steroid-induced avascular necrosis
- D Long-term phenobarbital
- E Early rheumatoid arthritis

99 PRIMIDONE

•••

A patient with essential tremor takes one tablet of primidone and has severe dizziness, nausea and sedation. What should she have been told?

- A This means she is a CYP2C19 poor metaboliser and needs testing
- B This indicates a hypersensitivity reaction and primidone must stop
- C It is an early sign of idiosyncratic hepatotoxicity
- D A first-dose reaction is typical; warning prevents patients stopping
- E This shows the dose is far too high for essential tremor

100 BENZODIAZEPINE KINETICS

•••

Why is lorazepam preferred to diazepam for status epilepticus despite diazepam's longer elimination half-life?

- A Diazepam cannot be given by the intravenous route
- B Diazepam redistributes out of brain quickly; lorazepam stays longer
- C Lorazepam does not cause respiratory depression
- D Diazepam has no active metabolites to prolong its effect
- E Lorazepam is more lipophilic, so it crosses into brain faster than diazepam does

101 CLOBAZAM INTERACTIONS

•••

A child with Lennox–Gastaut on clobazam becomes very sleepy two weeks after cannabidiol is started. What is the best adjustment?

- A Stop the cannabidiol
- B Reduce the clobazam
- C Add a stimulant
- D Reduce both by half
- E Switch clobazam to clonazepam

102 VIGABATRIN

•••

What monitoring is essential for a patient on long-term vigabatrin?

- A Monthly liver function tests
- B Baseline and periodic perimetry
- C Six-monthly echocardiography
- D Serum sodium every three months
- E HLA-B*15:02 testing

103 TIAGABINE

•••

A 45-year-old without epilepsy is prescribed tiagabine off-label for chronic pain. A week later she has fluctuating confusion and reduced responsiveness. What is the most important diagnosis to exclude?

- A Hyponatraemia
- B Non-convulsive status epilepticus
- C Serotonin syndrome
- D Hepatic encephalopathy
- E Neuroleptic malignant syndrome

104 STIRIPENTOL

•••

Stiripentol is added for a child with Dravet on clobazam and valproate. Which management is correct?

- A Cut clobazam and valproate by 25–50% and monitor the blood count
- B Increase clobazam, as stiripentol induces its metabolism
- C Monitor the ECG for QT shortening during titration
- D Stop valproate, as the combination is contraindicated
- E Keep other drugs unchanged and check levels after a month

105 VALPROATE TOXICITY

•••

A 35-year-old on valproate and topiramate becomes confused and drowsy over a week. Valproate level is 72 mg/L and liver function tests are normal. What is the most useful next test, and the specific treatment if it is positive?

- A EEG; IV lorazepam
- B Plasma ammonia; L-carnitine
- C Valproate free level; reduce the dose
- D CT brain; observe
- E Serum lipase; stop valproate

106 VALPROATE AND POLG

•••

A 17-year-old with new refractory focal status epilepticus has a history of ataxia, sensory neuropathy, episodic occipital headaches with visual phenomena, and mildly raised transaminases. Which second-line agent should be avoided?

- A Lacosamide
- B Valproate
- C Levetiracetam
- D Fosphenytoin
- E Phenobarbital

107 VALPROATE TOXICITY

•••

In which group is the risk of fatal valproate hepatotoxicity highest?

- A Adolescents on monotherapy
- B Children under two years on polytherapy
- C Adults on valproate for bipolar disorder
- D Women during pregnancy
- E Adults over 65 on monotherapy

108 VALPROATE REGULATION

•••

Which statement about valproate regulation is accurate?

- A Restrictions were lifted across Europe in 2024 after reassuring data
- B A PPP for women of childbearing potential; 2024 measures added precautions for men
- C Restrictions apply only once a woman is already known to be pregnant
- D Restrictions apply only when valproate is prescribed for bipolar disorder
- E It is contraindicated in every woman under 50, with no exception for need

109 GABAPENTIN

•••

A patient's gabapentin is increased from 1800 to 3600 mg/day, but the plasma level barely changes. Why?

- A Renal clearance of gabapentin rises with dose
- B Gabapentin absorption is saturable, so bioavailability falls as the dose rises
- C Gabapentin is highly protein bound
- D Gabapentin has an active metabolite that competes with the parent drug for absorption
- E Gabapentin autoinduces its hepatic metabolism

110 TOPIRAMATE

•••

Three weeks after starting topiramate, a 38-year-old has sudden bilateral eye pain, blurred vision and headache. Intraocular pressure is markedly raised. What should be done?

- A Continue topiramate and start timolol drops
- B Add acetazolamide and continue topiramate
- C Halve the topiramate dose and review in clinic in one week with pressure checks
- D Stop topiramate now and get urgent ophthalmology review
- E Switch from topiramate to zonisamide

111 TOPIRAMATE AND ZONISAMIDE

•••

A 9-year-old on zonisamide is admitted in summer with a temperature of 40.2 °C after outdoor play, with hot dry skin and no infection found. What is the most likely mechanism?

- A Serotonin syndrome
- B Neuroleptic malignant syndrome
- C Viral illness missed on screening
- D DRESS syndrome
- E Drug-induced oligohidrosis

112 ZONISAMIDE

•••

A patient with focal epilepsy had Stevens–Johnson syndrome from co-trimoxazole. Zonisamide is being considered. What is the best course?

- A Prescribe zonisamide with antihistamine cover
- B Prescribe zonisamide; cross-reactivity is negligible
- C Choose a different agent
- D Desensitise to sulfonamides first
- E Prescribe zonisamide at half the usual dose

113 FELBAMATE

•••

Felbamate is considered for refractory Lennox–Gastaut. Which requirements apply?

- A Serum sodium and ECG before each dose increase
- B Echocardiography before starting and every six months
- C HLA-B*15:02 screening and a baseline ECG
- D Written consent with regular blood counts and liver tests
- E Baseline perimetry and repeat visual fields every six months

114 LEVETIRACETAM TO BRIVARACETAM

•••

A 19-year-old on levetiracetam 2000 mg/day is seizure-free but has become irritable and aggressive. The family wants to keep the benefit. What is the best evidence-supported option?

- A Add brivaracetam to levetiracetam
- B Add pyridoxine, which reliably reverses levetiracetam's behavioural effects in most patients
- C Switch to perampanel
- D Halve the levetiracetam and accept more seizures
- E Switch overnight to brivaracetam at roughly 10:1–15:1, without cross-titration

115 LEVETIRACETAM

•••

A renal transplant recipient on tacrolimus and mycophenolate develops focal seizures. Which ASM is the usual default?

- A Phenytoin
- B Valproate
- C Carbamazepine
- D Levetiracetam
- E Phenobarbital

116 PERAMPANEL

•••

A 16-year-old is starting perampanel. Which counselling is most important?

- A Avoid all dairy products while taking it
- B Stop immediately if he feels dizzy on day one
- C Check liver function every month
- D Have visual fields tested at baseline and every six months during treatment
- E Warn him and his family about aggression; dose at bedtime

117 PERAMPANEL

•••

A patient with progressive myoclonic epilepsy has disabling action myoclonus despite valproate and levetiracetam. Which agent has recognised efficacy in this setting?

- A Lamotrigine
- B Vigabatrin
- C Gabapentin
- D Perampanel
- E Carbamazepine

118 CANNABIDIOL

•••

A child with Dravet syndrome on valproate starts pharmaceutical cannabidiol. Which monitoring is most important?

- A Echocardiography before starting and six-monthly
- B ECG for PR prolongation after each increase
- C Serum sodium at baseline and then monthly
- D Baseline and six-monthly visual field testing
- E Liver tests at baseline, 1, 3 and 6 months

119 FENFLURAMINE

•••

Fenfluramine is started for Dravet syndrome. Which monitoring schedule is required?

- A ECG and blood pressure at baseline and then yearly
- B Baseline perimetry and repeat visual fields yearly
- C Echo before, six-monthly during, and 3–6 months after stopping
- D Liver function tests monthly for the first six months
- E Echocardiography only if cardiac symptoms develop

120 FENFLURAMINE

•••

A 20 kg child with Dravet syndrome takes stiripentol. What is the maximum fenfluramine dose?

- A 0.35 mg/kg twice daily, capped at 26 mg/day
- B 0.1 mg/kg twice daily, capped at 10 mg/day
- C Fenfluramine is contraindicated with stiripentol
- D 0.5 mg/kg twice daily, no cap
- E 0.2 mg/kg twice daily, capped at 17 mg/day

10 Combinations That Do Harm

12 QUESTIONS

121 REDUNDANCY

•••

A patient on carbamazepine has lamotrigine added. Six weeks later she has diplopia and ataxia, yet her lamotrigine level is low. What explains both findings?

- A Lamotrigine displaces carbamazepine from albumin, raising free drug
- B Lamotrigine inhibits carbamazepine metabolism, raising its level
- C Redundant Na-channel toxicity, and CBZ induction halves lamotrigine
- D Lamotrigine absorption saturates at higher doses
- E She is a CYP2C9 poor metaboliser of both drugs

122 REDUNDANCY

•••

What happens when carbamazepine and phenytoin are combined?

- A Carbamazepine displaces phenytoin, raising free levels
- B Phenytoin blocks carbamazepine autoinduction
- C No clinically relevant interaction
- D Mutual induction at the same target, so neither level stabilises
- E Synergy through complementary mechanisms, making this a preferred refractory combination

123 REDUNDANCY

•••

A 70-year-old on carbamazepine for focal epilepsy has lacosamide added. Which outcome is most likely, and which is most dangerous?

- A Sedation is most likely; respiratory depression most dangerous
- B Hyponatraemia is most likely; SJS most dangerous
- C No interaction is expected
- D Neurotoxicity is most likely; bradyarrhythmia is most dangerous
- E Weight gain is most likely; pancreatitis most dangerous

124 REDUNDANCY

•••

A patient partly controlled on levetiracetam has brivaracetam added. What is the problem?

- A Same SV2A target: no new mechanism, same behavioural burden
- B No problem: adding brivaracetam is rational polytherapy in partial responders
- C Brivaracetam induces levetiracetam metabolism
- D The combination prolongs the QT interval
- E Brivaracetam displaces levetiracetam from albumin

125 REDUNDANCY

•••

A child on topiramate and zonisamide is starting the ketogenic diet. Which shared risk will compound?

- A QT prolongation and torsades de pointes
- B Dose-dependent hepatotoxicity
- C Irreversible visual field constriction
- D Symptomatic hyponatraemia and confusion
- E Kidney stones, acidosis and oligohidrosis

126 KINETIC COLLISION

•••

A man well controlled on valproate is admitted with pneumonia and started on meropenem. Two days later he has a GTCS, and his valproate level is 12 mg/L. What is the best management?

- A Continue meropenem and recheck the level in a week
- B Double the valproate dose
- C Change the antibiotic or cover with another ASM
- D Add carbamazepine for the duration of antibiotics
- E Give a valproate IV load of 40 mg/kg

127 KINETIC COLLISION

...

A patient on phenytoin has valproate added. Total phenytoin is 11 mg/L, but he now has nystagmus and ataxia. What is happening?

- A Laboratory error in the total phenytoin assay
- B Phenytoin induces valproate clearance, causing withdrawal
- C Valproate toxicity, unrelated to phenytoin
- D Free phenytoin is raised although the total is normal
- E Valproate induces phenytoin metabolism, lowering both

128 INDUCERS

...

A 55-year-old with glioblastoma on dexamethasone and temozolomide has seizures. Which ASM is the best initial choice?

- A Levetiracetam
- B Phenobarbital
- C Phenytoin
- D Carbamazepine
- E Primidone

129 ORGAN TOXICITY

...

A child on valproate starts cannabidiol. Which organ is at additive risk?

- A Kidney
- B Heart valves
- C Liver
- D Retina
- E Pancreas

130 ORGAN TOXICITY

...

A 15-year-old on levetiracetam is to start perampanel. What should the family be told?

- A Perampanel will roughly halve the levetiracetam level
- B The combination prolongs the PR interval in adolescents
- C Additive irritability and aggression risk from the first dose
- D No additive risk is expected
- E Additive kidney stone risk from carbonic anhydrase inhibition

131 ORGAN TOXICITY

...

An 80-year-old with COPD on oxycodone is prescribed pregabalin for neuropathic pain. What is the key risk?

- A QT shortening and arrhythmia
- B Hyponatraemia
- C Hepatic failure
- D Respiratory depression
- E Agranulocytosis

132 FOUR KINDS

...

Carbamazepine given to a child with SCN1A-related Dravet syndrome is an example of which kind of harmful combination?

- A Mechanistic opposition
- B Pharmacodynamic redundancy
- C Additive organ toxicity
- D Pharmacokinetic collision
- E Idiosyncratic hypersensitivity

11 The Patient Modifies the Drug

14 QUESTIONS

133 PREGNANCY

...

A 28-year-old with JME, seizure-free on valproate 1500 mg/day, discovers she is ten weeks pregnant. She wants to stop the valproate today. What is the best advice?

- A Continue for now and arrange urgent specialist review and scanning
- B Stop valproate today, since every further day adds fetal risk
- C Switch to full-dose lamotrigine this week and stop valproate
- D Advise termination, as the malformation risk is already fixed
- E Halve the valproate dose today and make no other changes

134 LAMOTRIGINE IN PREGNANCY

...

A woman's lamotrigine was increased from 200 to 500 mg/day during pregnancy as levels fell. On postpartum day five she has dizziness, diplopia and unsteadiness. What is the cause?

- A Sleep deprivation
- B Postpartum pre-eclampsia
- C Lamotrigine-induced aseptic meningitis
- D Postpartum depression
- E Lamotrigine toxicity after delivery

135 CONTRACEPTION

...

A woman on lamotrigine and a combined oral contraceptive reports dizziness and double vision only in the pill-free week each month. What explains this?

- A Withdrawal bleeding and falling progesterone lower the seizure threshold
- B Lamotrigine induces oestrogen metabolism
- C Catamenial seizure exacerbation
- D Oestrogen halves lamotrigine; levels rebound off the pill
- E Hypoglycaemia during the pill-free week

136 CONTRACEPTION

...

A 25-year-old on carbamazepine wants reliable contraception. Which option avoids the enzyme-induction problem?

- A An intrauterine device or depot progestogen
- B Contraceptive patch
- C Combined oral contraceptive at standard dose
- D Vaginal ring
- E Progestogen-only pill

137 CROSS-REACTIVITY

•••

A patient developed Stevens–Johnson syndrome on carbamazepine and needs an alternative. Which is the safest choice?

- A Eslicarbazepine
- B Levetiracetam
- C Lamotrigine
- D Oxcarbazepine
- E Phenytoin

138 CATAMENIAL EPILEPSY

•••

A 26-year-old feels her seizures cluster around menstruation. What is the best first step?

- A Perimenstrual clobazam
- B Referral for hormonal suppression
- C A seizure diary against cycle days
- D Acetazolamide from day –3 to +3
- E A 50% increase in her baseline ASM

139 OLDER ADULTS

•••

A 78-year-old on warfarin, a statin and amlodipine has new-onset focal epilepsy. Which approach is best?

- A No treatment until a third seizure
- B Levetiracetam, started low and titrated slowly
- C Carbamazepine at the standard adult dose, titrated weekly
- D Low-dose phenobarbital at night
- E Phenytoin loading then maintenance

140 DRUG LEVELS

•••

A patient has been seizure-free for three years on valproate 1000 mg/day. A routine level is 38 mg/L, below the 50–100 mg/L range. What should be done?

- A No change — treat the patient, not the level
- B Add a second ASM
- C Switch to a different agent
- D Increase to bring the level into range
- E Repeat the level weekly until it is in range

141 DRUG LEVELS

•••

A patient on carbamazepine has nystagmus, diplopia and ataxia. The level is 10 mg/L, within the 4–12 mg/L range. What is the correct interpretation?

- A The level must be checked for laboratory error
- B He is clinically toxic, whatever the level
- C He needs more drug to reach the top of the range
- D The level is therapeutic, so look for another cause
- E The symptoms are post-ictal

142 ELIMINATION

•••

An ICU patient on a midazolam infusion for five days develops acute kidney injury. The infusion is stopped, but he takes several days to wake. Why?

- A Midazolam metabolism saturates during long infusions
- B AKI induces hepatic CYP3A4, generating more drug
- C Its active metabolite is renally cleared and accumulates
- D AKI releases midazolam stored in adipose tissue
- E Midazolam itself is renally excreted unchanged

143 ELIMINATION

•••

A patient on oxcarbazepine develops chronic kidney disease (eGFR 25). What is the key concern?

- A Accumulation of the parent drug
- B No adjustment is needed
- C Loss of efficacy from faster clearance
- D Hepatic accumulation of an epoxide
- E Accumulation of the active MHD metabolite

144 WITHDRAWAL

•••

A man on clonazepam 2 mg twice daily for ten years is admitted, kept nil by mouth, and his regular medicines are omitted. On day three he is tremulous, tachycardic and has a seizure. What is the most likely cause?

- A Benzodiazepine withdrawal syndrome
- B Hypoglycaemia
- C Breakthrough of his underlying epilepsy
- D Alcohol withdrawal
- E Serotonin syndrome

145 STOPPING TREATMENT

•••

A 34-year-old delivery driver, seizure-free for three years, asks to stop his ASM. Which statement belongs in the counselling?

- A He can stop abruptly if his EEG is normal
- B Any relapse would be milder than his original seizures
- C Stopping carries no additional risk once he has been seizure-free for over two years
- D Relapse risk depends only on time since the last seizure
- E Relapse risk rises, mostly in the first year, with licence and job at stake

146 BREASTFEEDING

•••

A breastfeeding mother takes phenobarbital. What should be monitored in the infant?

- A Rash
- B Sedation and poor feeding
- C Hyponatraemia
- D Jaundice from hepatotoxicity
- E Visual tracking

147 BENZODIAZEPINE DOSING

•••

An 82 kg man has been seizing for seven minutes. He received lorazepam 2 mg IV three minutes ago and is still seizing. What is the next step?

- A Wait until 20 minutes before escalating
- B Intubate and start propofol
- C Move straight to levetiracetam 60 mg/kg, since lorazepam has failed
- D Give phenytoin 20 mg/kg
- E Give more lorazepam to complete the 4 mg dose

148 NO IV ACCESS

•••

A woman is convulsing at home in front of paramedics, who cannot obtain IV access. Which first-line treatment is appropriate?

- A Rectal paraldehyde
- B Wait for IV access, since IM benzodiazepines are too slow to be useful
- C IM midazolam 10 mg (or buccal/intranasal midazolam)
- D Oral clobazam
- E IM phenytoin

149 SECOND LINE

•••

A woman 30 weeks pregnant remains in convulsive status after two full doses of lorazepam. Which second-line agent is preferred?

- A Lacosamide
- B Valproate
- C Phenobarbital
- D Levetiracetam
- E Fosphenytoin

150 SECOND LINE

•••

An 84-year-old on bisoprolol and digoxin, with second-degree AV block, remains in status after benzodiazepines. Which second-line agent should be avoided?

- A Valproate
- B Any of them — all are contraindicated
- C Levetiracetam
- D Fosphenytoin
- E None — choice makes no difference

151 FIVE-MINUTE RULE

•••

Why was the operational definition of status epilepticus moved from 30 to 5 minutes?

- A Seizures lasting over 5 minutes rarely stop on their own
- B Guidelines needed a shorter audit standard
- C Benzodiazepines stop working after 5 minutes
- D Mortality doubles with each additional minute of seizure activity after 5
- E Neuronal death begins at 5 minutes

152 RECEPTOR TRAFFICKING

•••

Why do benzodiazepines become less effective the longer status epilepticus continues?

- A Synaptic GABA-A receptors are internalised
- B The blood–brain barrier closes during status
- C Benzodiazepines become sequestered in muscle
- D Seizures induce hepatic benzodiazepine clearance
- E Benzodiazepines are metabolised faster during seizures

153 REFRACTORY STATUS

•••

A 45-year-old has received two full doses of lorazepam and levetiracetam 60 mg/kg, and is still seizing at 45 minutes. What is the next step?

- A Load phenobarbital orally
- B Start ketamine without intubation
- C Give a third dose of lorazepam and reassess at 60 minutes
- D Intubate and start a midazolam or propofol infusion with cEEG
- E Give a second second-line agent and wait 30 minutes

154 SUPER-REFRACTORY STATUS

•••

A previously well 22-year-old has new-onset status epilepticus that recurs each time anaesthesia is weaned after 48 hours. Infection screen is negative. Which steps are most appropriate?

- A Load valproate 40 mg/kg as the next antiseizure agent before any other step
- B Proceed to emergency resective epilepsy surgery
- C Stop all anaesthesia and observe off sedation
- D Add ketamine; seek autoimmune or POLG causes; avoid valproate
- E Increase propofol indefinitely and await resolution

155 NCSE AFTER CONVULSIVE STATUS

•••

A patient's convulsions stop after lorazepam and levetiracetam. An hour later he remains unresponsive with no visible movements. What is the next step?

- A Give flumazenil to reverse sedation
- B Repeat CT and wait
- C Attribute it to post-ictal state and recheck tomorrow
- D Extubate and observe
- E Continuous EEG to exclude non-convulsive status epilepticus

156 ESETT

•••

Which statement about ESETT is correct?

- A Three agents gave ~45–47% cessation with no difference; lacosamide untested
- B Valproate was most effective but caused more hypotension and intubation
- C Levetiracetam stopped seizures significantly more often than fosphenytoin
- D Lacosamide was non-inferior to levetiracetam in the second-line setting
- E It enrolled patients before any benzodiazepine had been given

157 STABILISATION

•••

A malnourished man with alcohol dependence is brought in seizing. Glucose is 2.6 mmol/L. Besides airway and IV access, what should be given?

- A Glucose alone
- B Thiamine and withhold glucose until a seizure-free interval
- C Bicarbonate
- D Thiamine together with glucose
- E Phenytoin before glucose

158 NCSE

•••

Roughly how often are non-convulsive seizures found in comatose ICU patients when continuous EEG is applied?

- A About 60–80%
- B Under 1%
- C About 1–2%
- D Almost never without convulsions
- E Roughly 8–48%

13 Seizures in the ICU

8 QUESTIONS

159 ICH

•••

A patient with lobar intracerebral haemorrhage was started on phenytoin prophylaxis in the ED. He has had no seizures. What is the best course?

- A Continue phenytoin for six months, then review
- B Stop it; prophylaxis is not recommended in ICH
- C Add valproate for broader cover while in hospital
- D Switch to levetiracetam and continue it long-term
- E Continue phenytoin, targeting a total level of 15–20 mg/L

160 TBI

•••

A 30-year-old with a severe traumatic brain injury is admitted to ICU. Which seizure prophylaxis strategy is evidence-based?

- A Prophylaxis only after a second seizure
- B Valproate for six months
- C Lifelong levetiracetam to prevent epilepsy
- D Levetiracetam for 7 days against early seizures
- E No prophylaxis in any circumstance

161 SAH

•••

If seizure prophylaxis is used after aneurysmal subarachnoid haemorrhage without seizures, what is the usual approach?

- A Valproate until the aneurysm is secured, then lifelong
- B Phenytoin for 6 months
- C Prophylaxis is mandatory for 3 months
- D Short-term levetiracetam for 3–7 days
- E Lifelong levetiracetam

162 HSV ENCEPHALITIS

•••

A 58-year-old with suspected HSV encephalitis is in status epilepticus. Which statement is correct?

- A Wait for CSF PCR before giving aciclovir
- B Use only phenytoin, as other ASMs interact with aciclovir
- C Seizures in HSV encephalitis rarely need treatment
- D Give aciclovir now and treat seizures in parallel
- E Withhold aciclovir until the seizures are controlled

163 POST-ANOXIC

•••

After a cardiac arrest, a comatose patient develops generalised myoclonic status on day one. The family is told the prognosis is hopeless. Which statement is correct?

- A Myoclonic status reliably predicts death within days
- B Valproate is contraindicated after cardiac arrest
- C Myoclonic status alone is not a hopeless sign: treat, prognosticate later
- D Seizures after cardiac arrest should not be treated
- E Myoclonus proves severe hypoxic injury, so investigation and treatment should stop

164 CEEG

•••

Three days after aneurysm clipping, a 67-year-old is drowsy (GCS 12). Overnight a nurse documented a 90-second generalised “possible tremor”. What should be done?

- A Arrange a routine EEG next week
- B Start phenytoin without EEG
- C Attribute it to opioids and reduce analgesia
- D Repeat CT and reassess tomorrow
- E Start continuous EEG

165 CEEG

•••

How long should continuous EEG run in a comatose ICU patient to exclude non-convulsive seizures?

- A 30 minutes
- B Until the patient wakes fully, regardless of how many days that takes
- C 24–48 hours, extending to 48–72 hours if suspicion is high
- D 4 hours
- E 1 week minimum

166 DISPROPORTIONATE ENCEPHALOPATHY

•••

A patient with cirrhosis is far more obtunded than his modestly raised ammonia would explain, and he is not improving with lactulose. What should be considered?

- A Start valproate empirically
- B Increase lactulose and wait
- C Hepatic encephalopathy only — no further tests
- D Non-convulsive status epilepticus — arrange cEEG
- E Start flumazenil

14 Cutting Edge

9 QUESTIONS

167 DRUG RESISTANCE

•••

A 24-year-old with focal epilepsy failed levetiracetam at three months and carbamazepine at six months, both at adequate doses and well tolerated. Which statement is correct?

- A He must fail at least four drugs before referral
- B Drug resistance requires failure of a two-drug combination
- C He cannot be called drug-resistant until two years have passed
- D He should try lamotrigine before any referral is made
- E He is drug-resistant now and should be referred for surgical evaluation

168 PHARMACOLOGICAL PLATEAU

•••

In the Glasgow cohort data of Kwan and Brodie, roughly what proportion of patients become seizure-free on the first appropriate drug, and how much does a third drug add?

- A About 47% with the first; about 13% more with the third
- B About 47% with the first; about 4% more with the third
- C About 30% with the first; about 30% more with the third
- D About 90% with the first; under 1% with the third
- E About 70% with the first; about 20% more with the third

169 WIEBE TRIAL

•••

In the 2001 Wiebe randomised trial of temporal lobe epilepsy, what proportion were free of seizures impairing awareness at one year?

- A 100% with surgery versus 0% with medical therapy
- B 58% with surgery versus 8% with continued medical therapy
- C 58% with surgery versus 40% with medical therapy
- D 30% with surgery versus 25% with medical therapy
- E 90% with surgery versus 50% with medical therapy at one year

170 NEUROMODULATION

•••

A 38-year-old has drug-resistant bilateral mesial temporal lobe epilepsy with independent left and right onsets and bilateral hippocampal atrophy. He has 15–20 seizures a month and cannot have bilateral resection because of memory risk. Which device best fits?

- A Vagus nerve stimulation alone, allowing his medications to be withdrawn
- B Corpus callosotomy
- C Hemispherotomy
- D Unilateral anterior temporal lobectomy
- E Responsive neurostimulation (RNS) with bilateral hippocampal leads

171 TEMPORAL LOBECTOMY

•••

After a right anterior temporal lobectomy, which visual field defect is most expected?

- A Left superior quadrantanopia
- B Right homonymous hemianopia
- C Bitemporal hemianopia
- D Right superior quadrantanopia
- E Left inferior quadrantanopia

172 SURGICAL OPTIONS

•••

A 12-year-old with Lennox–Gastaut syndrome has frequent atonic drop attacks with facial injuries despite multiple drugs. No resectable focus exists. Which procedure most directly targets the drop attacks?

- A Anterior temporal lobectomy
- B Hemispherotomy
- C Corpus callosotomy
- D Lesionectomy
- E Laser ablation of the hippocampus

173 LASER ABLATION

•••

A child has gelastic (laughing) seizures from a hypothalamic hamartoma. Which approach has the highest reported seizure-freedom rate?

- A Laser interstitial thermal therapy
- B Long-term clobazam
- C Responsive neurostimulation targeting the hamartoma
- D Corpus callosotomy
- E Vagus nerve stimulation

174 VNS

•••

Which statement about vagus nerve stimulation is most accurate?

- A It makes most patients seizure-free within the first year
- B It records intracranial EEG continuously for review
- C About half achieve $\geq 50\%$ reduction; seizure freedom is uncommon
- D It is contraindicated in children under twelve
- E It requires a single identified seizure focus to work

175 DBS

•••

Which outcome did the SANTE trial report for anterior thalamic nucleus deep brain stimulation?

- A ~40% median reduction at one year, ~69% at five
- B A 75% median reduction at nine years of follow-up
- C No significant benefit over sham stimulation at any point
- D Benefit confined to genetic generalised epilepsy
- E Seizure freedom in about 60% of patients at one year

15 SUDEP and the Conversations You Must Have

6 QUESTIONS

176 SUDEP RISK

•••

Which is the dominant modifiable risk factor for SUDEP?

- A Daytime seizures
- B Use of levetiracetam
- C Frequency of tonic-clonic seizures
- D Use of a sodium-channel blocker
- E Female sex

177 SUDEP PREVENTION

•••

Which practical advice is supported to reduce SUDEP risk?

- A Sleep propped upright on several pillows each night
- B Avoid all aerobic exercise and exertion
- C Take ASMs only during periods of seizure clustering
- D Avoid sleeping prone; arrange night supervision or detection
- E Sleep alone in a quiet room to avoid sleep disruption

178 SUDEP RISK

•••

Approximately how much higher is SUDEP risk in Dravet syndrome than in epilepsy overall?

- A Not raised
- B About 100-fold
- C About two-fold
- D Raised only in adults
- E About ten-fold

179 SUICIDALITY WARNING

•••

How should the class-wide ASM suicidality warning be applied in practice?

- A Screen mood once at diagnosis; repeat screening adds nothing
- B Avoid all ASMs in anyone with a past psychiatric history
- C It applies to levetiracetam and perampanel, not the class
- D Ask about mood at each review; the absolute rise is about 1 in 500
- E Prescribe an antidepressant alongside every new ASM

180 SUDEP COUNSELLING

•••

When do the AAN and AES recommend discussing SUDEP?

- A Only in drug-resistant epilepsy
- B Only after a second GTCS
- C Never with the family present
- D Only if the patient or family raises the subject first
- E At diagnosis and periodically thereafter

181 SUDEP DEFINITION

•••

Which death would NOT meet the definition of SUDEP?

- A Unwitnessed death in bed with no seizure observed
- B Death in a young adult found prone in the morning
- C Death after a witnessed GTCS with normal autopsy
- D Sudden death with normal toxicology and no anatomical cause
- E Death during documented status epilepticus

16 How to Confirm You Are a Bad Epileptologist

3 QUESTIONS

182 RATIONALISING POLYTHERAPY

•••

A 40-year-old with refractory focal epilepsy takes five ASMs accumulated over 15 years and is sedated and unsteady. Seizure frequency has not changed in years. What is the best strategy?

- A Stop all five drugs and start cenobamate monotherapy
- B Keep every drug, as removing any one risks status epilepticus
- C Withdraw drugs that never clearly helped, slowly and one at a time
- D Stop the two most sedating drugs together this week
- E Add a sixth drug with a mechanism not yet covered

183 STOPPING FOR SIDE EFFECTS

•••

Three weeks into lamotrigine titration, a patient develops fever, a widespread rash and oral ulceration. What should be done with the lamotrigine?

- A Continue and add an antihistamine
- B Stop it immediately, accepting the withdrawal risk
- C Stop it after a slow four-week taper
- D Cross-taper to a structurally unrelated ASM over the next two weeks
- E Halve the dose and continue

184 WORSENING SEIZURES

•••

A patient well controlled on lamotrigine for years has more frequent seizures over two months. She insists she takes every dose. Which cause should be considered before assuming non-adherence?

- A Seasonal variation
- B A new combined pill halving her lamotrigine
- C Lamotrigine-induced hyponatraemia lowering the seizure threshold
- D Lamotrigine autoinduction
- E Tolerance to lamotrigine

17 What Is Coming

5 QUESTIONS

185 MACHINE LEARNING

•••

Which technology application is described as the strongest real, validated example in the field?

- A Smartphone seizure-prediction apps
- B Fully automated EEG reporting without review
- C Automated MRI lesion detection such as MELD
- D Wearable detection of subtle focal seizures
- E Automated surgical outcome prediction

186 NEUROSTEROIDS

•••

Ganaxolone is approved for CDKL5 deficiency disorder. What is the key pharmacological advantage of its site of action?

- A It irreversibly inhibits GABA-transaminase
- B It antagonises postsynaptic AMPA receptors
- C It acts at a site that does not develop tolerance
- D It blocks thalamic T-type calcium channels
- E It binds SV2A with far higher affinity than levetiracetam

187 PRECISION THERAPY

•••

An infant with early-onset epilepsy has a confirmed gain-of-function SCN8A variant. Which drug class is most likely to help?

- A Vigabatrin
- B Gabapentinoids
- C Sodium-channel blockers
- D They should be avoided, as in Dravet
- E Ethosuximide

188 MOLECULAR THERAPY

•••

Which molecular approach is described as nearest to clinical use in epilepsy?

- A CRISPR base editing of point mutations
- B RNA interference
- C Antisense oligonucleotides
- D Optogenetics
- E AAV gene delivery

189 WEARABLES

•••

What are the strengths and limits of wearable seizure detection?

- A Proven in randomised trials to prevent SUDEP in unsupervised patients
- B Good for convulsive seizures, poor for subtle focal events
- C Useful only in hospital
- D Reliable for all seizure types
- E Good for focal seizures, poor for convulsive ones

Answers and explanations

Number · correct option · explanation · take-home point

1 The Ancient Dance

1 **B** Bromide fell to phenobarbital because of psychosis and bromoderma; phenobarbital gave ground to phenytoin because of sedation; the second generation exists because the first was effective and unpleasant. Valproate and carbamazepine remain among the most effective drugs available. The modern advance is a wider menu of tolerability and interaction profiles, not efficacy.

The formulary is a menu of tolerability, not a ladder of efficacy.

2 **C** Before 1938 the available agents (bromide, phenobarbital) controlled seizures largely alongside sedation. Screening in the electroshock model selected for seizure suppression itself. Proof that a neurological disease could be pharmacologically modified belongs to Locock and bromide (1857); absence received a specific drug only with ethosuximide (1958) — and phenytoin can aggravate absence.

Phenytoin 1938: seizure control separated from sedation.

3 **C** Ibn Sina (c. 1025) classified seizures by origin, described non-convulsive events, and noted that fear and psychological change could precede a seizure. Galen gave us the word 'aura', Jackson the march and the modern definition of focal discharge, Tissot the return to the brain, and the Edwin Smith papyrus the first post-traumatic convulsions.

Ibn Sina: non-convulsive events and aura-based localisation, eleventh century.

4 **D** Ezogabine (retigabine) was discontinued in 2017 after retinal pigmentation and blue-grey skin discolouration had confined it to a last-line role. Vigabatrin causes irreversible visual field constriction but remains in use under a risk-management programme. Felbamate is restricted, not withdrawn. Fenfluramine was withdrawn as an anorectic in 1997 and re-approved for Dravet and Lennox–Gastaut at a fraction of the dose.

Ezogabine: discontinued 2017 after retinal pigmentation.

2 Making Sense of the Chaos

5 **E** 'Complex partial' became focal impaired awareness, and 'secondary generalisation' became focal to bilateral tonic-clonic. 'Simple partial' is focal aware. Know both vocabularies: the referral letter will use one and the trainee the other.

Complex partial = focal impaired awareness; secondarily generalised = focal to bilateral tonic-clonic.

6 **E** With unknown onset, choose a broad-spectrum agent until the epilepsy is classified. If this proves to be JME or another genetic generalised epilepsy, each of the narrow-spectrum alternatives could aggravate absence or myoclonic seizures. Levetiracetam suits a woman of childbearing potential better than valproate. There is no penalty for broad-spectrum first, and a real penalty for the reverse.

Unknown onset → broad-spectrum. The cost of being wrong runs one way.

7 **C** Seizure type tells you what to treat and epilepsy type sets the broad strategy, but the syndrome — the cluster of seizure type, EEG, imaging, age of onset and prognosis — is where precision treatment lives and where catastrophes such as carbamazepine in JME or Dravet are prevented.

Levels 1 and 2 choose a drug; level 3 prevents a catastrophe.

8 **A** In anti-NMDAR encephalitis the serum antibody can be negative while the CSF is positive, and the MRI is often normal. With new-onset refractory seizures, behavioural change and autonomic instability, send serum and CSF panels and start empirical immunotherapy where suspicion is high. Immune epilepsy needs immunotherapy urgently; ASMs alone will fail.

Serum-negative does not exclude NMDAR encephalitis. Treat on suspicion.

9 **D** Neurocysticercosis is the commonest infectious cause of epilepsy worldwide. In infectious epilepsy, treating the infection is the primary goal and ASMs are adjuncts.

Neurocysticercosis leads the infectious aetiologies globally.

10 **D** Metabolic epilepsies are treated by correcting the derangement. In pyridoxine-dependent epilepsy the drug is not the treatment; lifelong pyridoxine is. The same chapter notes that POLG disease, another metabolic cause, contraindicates valproate.

Metabolic aetiology: replace the cofactor.

11 **E** The six aetiological categories are therapeutic targets, not exclusive labels. A tuber is a resectable structural cause; the TSC2 variant opens genotype-directed treatment such as vigabatrin for spasms and everolimus. Both matter to management.

A patient can be structural and genetic at once.

12 **C** The 2017 language asks about awareness as behaviour. Two questions settle it: could the patient respond meaningfully, and do they remember? A patient may appear aware yet retain no memory; that is impaired awareness. Memory loss does not imply generalised onset.

Awareness = responds meaningfully AND remembers.

3 The Art of Watching

13 A Dystonic arm posturing lateralises contralateral (~90%): left arm → right hemisphere. Manual automatisms (~70%) and post-ictal nose-wiping (~80% in TLE) are ipsilateral: right hand → right. The epigastric aura and oroalimentary automatisms place it in the mesial temporal lobe. Every sign points the same way.

Dystonic arm = contralateral focus; automatisms and nose-wiping = ipsilateral.

14 E Post-ictal nose-wiping is ipsilateral in about 80% of temporal lobe seizures, as are unilateral manual automatisms (~70%). Dystonia, forced version, eye deviation and Todd's paralysis all lateralise contralateral.

Ipsilateral: nose-wiping and manual automatisms.

15 D In the figure-of-4 sign the focus is contralateral to the extended arm (~85% at the onset of secondary generalisation). The older teaching that the extended arm is ipsilateral is inverted, and the inverted version has sent patients for the wrong evaluation. Forced head version also turns away from the focus.

Figure-of-4: focus opposite the extended arm.

16 D Post-ictal aphasia lateralises to the language-dominant hemisphere with more than 90% reliability; in a right-handed patient that is almost always the left.

Post-ictal aphasia = dominant hemisphere (>90%).

17 B Ictal vomiting or spitting is associated with a non-dominant temporal focus, usually right. The reliability is moderate, so it supports rather than settles lateralisation.

Ictal vomiting → non-dominant temporal.

18 A Frontal lobe seizures are nocturnal, brief, bizarre, stereotyped and clustered, with almost immediate recovery and no post-ictal confusion — which is why they are misdiagnosed as parasomnia, panic or functional events for years. Orbitofrontal and frontopolar seizures give hypermotor bicycling. Scalp EEG is often unhelpful during these events.

Brief, stereotyped, clustered nocturnal hypermotor events = frontal until proven otherwise.

19 E Occipital seizures produce brief elementary visual phenomena — colours, shapes, flashes — typically moving and confined to one hemifield. Migraine aura tends to be monochromatic, hemianopic and slowly expanding over 20–30 minutes. Complex hallucinations such as faces suggest temporal rather than occipital involvement. Headache occurs after both.

Coloured, brief, moving → occipital seizure. Monochrome, slow-spreading → migraine.

20 B Parietal seizures are often purely sensory, with a march along the sensory homunculus. They are frequently labelled functional before anyone records an EEG during symptoms. A left-sided march points to the right hemisphere.

A sensory march is a parietal seizure, not a functional symptom.

21 B The first clinical change is the most localising; everything after it is spread. Trained epileptologists watch frame by frame from the very start. The dramatic part contains almost no localising signal.

Watch the beginning, not the climax.

22 D Forced ictal head version lateralises contralateral, with about 80% reliability when it occurs late in the seizure, just before generalisation. The head turns away from the focus.

Late forced version: the head turns away from the focus.

23 C Olfactory hallucinations, usually unpleasant, reflect mesial temporal or insular activation. Déjà vu arises from parahippocampal familiarity circuits, and fear or dread from the amygdala.

Olfactory aura → mesial temporal or insular.

4 Reading the Brain's Diary

24 B Alpha (8–13 Hz) is posterior, present awake with eyes closed and blocks with eye opening. Absent alpha in the expected state signals cortical dysfunction. You cannot call an EEG abnormal until you can say what normal looks like for that state and age.

No alpha when alpha should be there = cortical dysfunction.

25 C Beta is 13–30 Hz, frontal and central. Excess beta is usually a drug effect from benzodiazepines, barbiturates or propofol.

Excess beta = check the drug chart.

26 A Delta is normal in N3 and infancy. Focal delta in an awake adult means a structural lesion at that site; diffuse delta means encephalopathy. MRI with an epilepsy protocol is the next step.

Focal delta awake = structural lesion. Diffuse delta = encephalopathy.

27 B Triphasic waves suggest hepatic or metabolic encephalopathy but mimic NCSE. A benzodiazepine trial under EEG is positive only if both the pattern and the clinical state improve. A pattern that resolves while the patient remains unchanged has told you nothing except that you have sedated him. Continue monitoring and treat the cause.

A benzodiazepine trial counts only when the patient improves too.

28 E This is hypsarrhythmia in infantile epileptic spasms syndrome — an emergency measured in days, not weeks. Time to treatment is the strongest modifiable predictor of developmental outcome. Investigation of the cause proceeds in parallel.

Hypsarrhythmia: treat within days.

29 B LPDs occur after stroke, HSV encephalitis, tumour, post-ictally and in CJD. They carry high seizure risk and sit on the ictal–interictal continuum, where EEG alone cannot decide. Continuous EEG and clinical correlation guide treatment.

LPDs: not always seizures, never safe to ignore.

30 A Lateralised rhythmic delta activity (LRDA) is an at-risk pattern associated with structural lesions, cortical irritability and the post-ictal state. It is not itself a seizure. Keep monitoring.

LRDA is a warning sign, not a seizure.

31 C Burst-suppression (bursts separated by suppression under 10 μ V) is an iatrogenic target in refractory status. In a post-anoxic patient with absent brainstem reflexes it signals a very poor prognosis. The same pattern means different things in different contexts.

Context decides what burst-suppression means.

32 D Generalised 4–6 Hz polyspike-wave with photosensitivity indicates JME or another genetic generalised epilepsy. Sodium-channel blockers can aggravate myoclonic and absence seizures. Valproate or levetiracetam are appropriate.

Polyspike-wave → avoid sodium-channel blockers.

5 The Detective Work

36 B Under the ILAE 2014 definition, one unprovoked seizure with a recurrence risk of 60% or more is epilepsy; a structural lesion plus epileptiform EEG meets that threshold. Levetiracetam or lamotrigine are chosen for their interaction profile. Carbamazepine and phenytoin would induce apixaban's metabolism — the induction burden in a patient on cardiovascular therapy is the whole argument against them. A remote stroke makes the seizure unprovoked.

One unprovoked seizure + $\geq 60\%$ recurrence risk = epilepsy.

37 A Lateral tongue biting suggests a GTCS; tip biting suggests a functional event. No sign alone is decisive, and the definitive test for functional seizures is video-EEG capturing a typical event with a normal ictal EEG.

Lateral bite → seizure. Tip bite → functional.

38 D Fine tremulous movement in syncope is entirely different from large-amplitude rhythmic bilateral jerking in a GTCS. A ten-second demonstration settles what the word 'shaking' cannot, and saves months of uncertainty.

When a witness says 'shaking', ask them to show you.

39 E Warmth, nausea and visual greying when standing in heat, with brief jerks and rapid recovery without confusion, is vasovagal syncope. Post-ictal confusion is the most reliable pointer to a true seizure, and its absence points away from one. An ECG is still appropriate.

Rapid recovery without confusion → think syncope.

40 B Gradual onset, duration over five minutes, waxing and waning, eyes closed with resistance to opening and pelvic thrusting all suggest functional seizures. The definitive test is video-EEG with a captured event and a normal ictal EEG. A normal interictal EEG does not discriminate, and frontal seizures can also be bizarre.

Functional seizures are diagnosed by capturing one.

33 E Epileptiform discharges in someone who has never had a seizure do not establish epilepsy, and a normal interictal EEG does not exclude it. The EEG modifies a clinical probability; it does not create one. Treating a discharge in a seizure-free patient adds toxicity to a person who was well. Fitness-to-fly rules are a separate occupational question.

Treat the patient, not the EEG.

34 A Vertex waves appear at the N1–N2 transition, maximal at the vertex. They can mimic epileptiform discharges and are distinguished by state and location. They are not pathological.

Vertex waves: normal, and the commonest over-read.

35 C ACNS critical-care terminology combines a main term (LPDs, GPDs, LRDA, GRDA) with modifiers: +F superimposed fast activity, +R rhythmic, +S stimulus-induced — plus prevalence, duration and amplitude. The +F and +R modifiers mark patterns further toward the ictal end of the continuum.

+F fast, +R rhythmic, +S stimulus-induced.

41 B Sudden collapse without prodrome, during exertion, with a family history of sudden death, is a cardiac arrhythmia until proven otherwise. Brief jerks are common in any cerebral hypoperfusion and do not make it a seizure.

Exertional collapse + family sudden death → cardiac work-up first.

42 B A standard brain MRI misses hippocampal sclerosis, subtle focal cortical dysplasia and small cavernomas. A normal standard scan is the commonest reason a surgical candidate is told they are not one. The protocol must be requested by name.

Request the epilepsy protocol by name.

43 E Coronal T2 perpendicular to the hippocampal long axis shows the three signs: volume loss, T2/FLAIR signal increase and loss of internal architecture (the layered 'jellyroll' collapses). In bilateral disease, asymmetry remains the key finding.

HS: volume loss, T2 signal, lost architecture — on coronal oblique T2.

44 A Gradient echo and SWI detect blood products, calcium and iron — cavernous malformations, post-traumatic haemosiderin and calcified lesions.

Blood products → GRE/SWI.

45 D Emotion-triggered atonia with preserved consciousness plus excessive daytime sleepiness is narcolepsy with cataplexy. Polysomnography and MSLT (and orexin where available) confirm it. Atonic seizures impair awareness and are not triggered by laughter.

Laughter-triggered atonia, aware, sleepy → cataplexy.

6 When the Mind Plays Tricks

46 A Morning myoclonus, absences and a GTCS after sleep deprivation is JME. Carbamazepine aggravates myoclonic and absence seizures and can increase GTCS. Levetiracetam is preferred given valproate's teratogenicity in a woman of reproductive age; valproate remains an option with full counselling and pregnancy-prevention conditions if levetiracetam fails.

JME on carbamazepine: stop it.

47 C Valproate is the most effective agent for JME, and SANAD II confirmed its superiority over levetiracetam in generalised and unclassified epilepsy. Lamotrigine may worsen myoclonus; carbamazepine aggravates it; ethosuximide covers absence only. Since 2024, regulators have added precautions for men too: the EMA asks prescribers to discuss a possible risk to children fathered during treatment and to consider contraception, and in the UK valproate should not be started in anyone under 55 unless two specialists agree.

Generalised epilepsy in a man: valproate is still the best drug.

48 D JME is lifelong, with very high relapse rates when treatment stops. Any withdrawal decision weighs syndrome, EEG, MRI and what relapse would cost — licence, occupation, pregnancy — and must never be abrupt.

JME: lifelong; high relapse off treatment.

49 B The Glauser trial found ethosuximide and valproate equally effective in childhood absence, both better than lamotrigine, with ethosuximide causing significantly less attentional impairment. That makes ethosuximide first choice when absence is the only seizure type. Carbamazepine worsens absence.

Absence only → ethosuximide.

50 A Ethosuximide has no efficacy against tonic-clonic or focal seizures, so a patient with both absence and GTCS needs a different drug. Valproate covers both. The narrow-spectrum options would worsen the absences.

Absence + GTCS → valproate (ethosuximide misses the GTCS).

51 B Self-limited epilepsy with centrotemporal spikes has an excellent prognosis; virtually all remit by 16. With infrequent nocturnal seizures, monitoring is often the whole of management. The drug trap here is treating unnecessarily.

BECS: the trap is over-treatment.

52 B Prolonged or hemiclonic febrile seizures in the first year are the signature of Dravet syndrome, and the EEG is initially normal — which is why it is underestimated. Rule: send SCN1A genetics before prescribing any sodium-channel blocker. Carbamazepine, oxcarbazepine, phenytoin and lamotrigine can be catastrophic.

Prolonged febrile hemiclonic seizure in year one → SCN1A before any Na-channel blocker.

53 E Dravet is caused by loss of function in SCN1A (about 80% of cases), encoding Nav1.1, which is preferentially expressed in inhibitory interneurons. Blocking an already-failing channel removes inhibition while leaving excitatory networks relatively untouched, producing more seizures, status and faster cognitive decline.

Dravet: the drug fights the biology.

54 B Vigabatrin is first line in infantile spasms due to tuberous sclerosis and is often sufficient alone. Its unique efficacy here is what justifies its risk of permanent visual field loss. Start within days.

Spasms + TSC → vigabatrin.

55 D ICISS showed that hormonal therapy combined with vigabatrin was superior to hormonal therapy alone. Time to treatment is the strongest modifiable predictor of developmental outcome.

ICISS: hormones + vigabatrin beat hormones alone.

56 B In Lennox–Gastaut, valproate is the backbone, adding lamotrigine, rufinamide, clobazam, topiramate, cannabidiol or fenfluramine. Rufinamide is particularly useful for tonic-atonic drop attacks. Carbamazepine and vigabatrin may worsen tonic and atonic seizures. Move early to dietary and device therapy, as serial drug failures are the trap.

LGS drop attacks → rufinamide.

57 E Rasmussen encephalitis is progressive. Immunotherapy buys time, but only hemispherectomy (80–90% seizure-free) stops the seizures. It is a timed disease: delay is the intervention that harms.

Rasmussen: only surgery stops it.

58 E In sleep-related hypermotor epilepsy (ADNFLE), scalp EEG is often normal during events because the frontal generators are deep. The prognosis is often good with a sodium-channel blocker. The drug trap is years of psychiatric or parasomnia misdiagnosis.

Frontal seizures can have a normal scalp EEG.

7 One Synapse, Every Target

59 A Lamotrigine blocks fast inactivation of the sodium channel and also inhibits presynaptic glutamate and aspartate release — the likely reason its spectrum is broader than the rest of the class. Enhancement of slow inactivation belongs to lacosamide and cenobamate.

Lamotrigine: fast inactivation + glutamate release.

60 C Lacosamide and cenobamate act on slow rather than fast inactivation — a genuine pharmacological distinction, and probably a clinical one. Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine and rufinamide act on fast inactivation.

Slow inactivation: lacosamide, cenobamate.

61 C Benzodiazepines increase the frequency of chloride channel opening and require GABA — a ceiling effect. Barbiturates prolong the duration of opening and, at high concentration, open the channel directly.

Benzodiazepines: frequency, with a ceiling. Barbiturates: duration, without one.

62 A The 3 Hz spike-and-wave of absence is generated by a thalamocortical oscillation that depends on T-type calcium current. Valproate and zonisamide also modulate T-type channels; gabapentin and pregabalin act at $\alpha 2\delta$.

Absence → T-type calcium → ethosuximide.

63 D Despite its name, gabapentin has no action at GABA receptors. It binds $\alpha 2\delta$, reducing calcium entry and excitatory transmitter release. Pregabalin shares the target with higher affinity and linear absorption.

| *Gabapentin is not GABAergic.*

64 A Vigabatrin covalently and irreversibly inhibits GABA-transaminase, so its duration of action is uncoupled from plasma half-life. It is not a sodium-channel blocker; it is avoided in Dravet because it aggravates myoclonic seizures.

| *Vigabatrin: irreversible GABA-T inhibition.*

65 C Across levetiracetam's structural analogues, SV2A binding affinity tracks antiseizure potency — unusually good evidence that the target is the mechanism. Brivaracetam was rationally optimised from this, with 15–30 times the affinity.

| *For SV2A, affinity tracks potency.*

8 Spectrum, and the Drugs That Make Seizures Worse

69 C Lamotrigine is effective for focal and tonic-clonic seizures but can worsen myoclonus, and it is contraindicated in Dravet. Levetiracetam, valproate and perampanel are effective against myoclonic seizures.

| *Lamotrigine controls GTCS but may worsen myoclonus.*

70 A For focal epilepsy SANAD II found lamotrigine superior to levetiracetam and zonisamide on time to treatment failure. Carbamazepine, oxcarbazepine, lacosamide and zonisamide remain reasonable alternatives.

| *Focal epilepsy: lamotrigine first (SANAD II).*

71 A In generalised and unclassified epilepsy, valproate remained the most effective drug. That is what makes the reproductive question hard rather than simple: choosing an alternative is choosing a probably less effective drug.

| *Generalised epilepsy: valproate beat levetiracetam.*

72 C Oxcarbazepine, carbamazepine, phenytoin, gabapentin, pregabalin, tiagabine and vigabatrin can all aggravate absence. A boy with absences and GTCS needs valproate, which covers both.

| *Narrow-spectrum drugs worsen absence.*

73 D Vigabatrin, though not a sodium-channel blocker, aggravates absence and myoclonic seizures. That is why it is avoided in Dravet — for myoclonic aggravation, not because it shares a mechanism with carbamazepine.

| *Vigabatrin worsens absence and myoclonus.*

74 B Phenobarbital remains first line for neonatal seizures. NEOLEV2 found levetiracetam significantly less effective. Treat the cause in parallel.

| *Neonates: phenobarbital first (NEOLEV2).*

66 D Rational polytherapy combines across mechanism rows. Adding another sodium-channel agent gives the brainstem and cerebellum the full additive dose — diplopia, ataxia — while the epileptic network gets little extra. Carbamazepine also halves lamotrigine by induction. An SV2A or GABAergic partner is the logical choice.

| *Combine across mechanisms, not within them.*

67 C Perampanel was the first ASM built around AMPA antagonism. Felbamate acts at the NMDA glycine site; topiramate has AMPA/kainate activity among four mechanisms.

| *Perampanel = AMPA.*

68 E Lamotrigine with valproate is the one pairing with evidence of real synergy — at the cost of a halved lamotrigine titration, because valproate roughly doubles lamotrigine levels. The others are redundant pairs that add toxicity.

| *LTG + VPA: synergy, at half the titration.*

75 B Dravet treatment builds on valproate and clobazam, then adds stiripentol, fenfluramine or cannabidiol. Sodium-channel blockers are contraindicated, and vigabatrin is avoided for myoclonic aggravation. When stiripentol is added, reduce clobazam and valproate by 25–50%.

| *Dravet: VPA + CLB, then stiripentol, fenfluramine or CBD.*

76 A In a man, or a woman past childbearing potential, with generalised epilepsy, valproate is still the best drug per SANAD II. Lamotrigine may worsen myoclonus; carbamazepine and phenytoin can aggravate it.

| *No reproductive risk → valproate for generalised epilepsy.*

77 C Both the reflex prescription of valproate and the reflex refusal of it are failures of the same conversation. The alternative is chosen knowing it is probably less effective, and that trade-off is hers to understand and make. Valproate in women of childbearing potential requires a pregnancy prevention programme.

| *The valproate trade-off belongs to the patient.*

78 E In the Glauser trial ethosuximide and valproate were equally effective and both beat lamotrigine; ethosuximide caused less attentional impairment than valproate. Lamotrigine has some efficacy in absence but is inferior.

| *CAE: ethosuximide $\approx$ valproate > lamotrigine.*

79 A Pregabalin, licensed for generalised anxiety in some jurisdictions, aggravates myoclonic seizures, as does gabapentin. It also carries misuse potential and respiratory risk with opioids. The syndrome governs every prescription, not only the ASM.

| *Gabapentinoids aggravate myoclonus — even when prescribed for something else.*

80 A The three questions before any sodium-channel blocker: any morning myoclonus (undiagnosed JME), any absence or staring (narrow-spectrum drugs aggravate it), and could this be Dravet. If the syndrome is unclear, start broad-spectrum.

| *Ask about jerks, absences and Dravet first.*

9 The Formulary

81 E Phenytoin metabolism via CYP2C9 and 2C19 saturates within the therapeutic range, so a small dose increase can produce a large rise in level. A 50 mg increase near the top can double the level. Adjust in 25–50 mg steps and recheck.

Phenytoin: small dose change, large level change.

82 A Phenytoin is about 90% protein bound. In hypoalbuminaemia, renal failure, pregnancy or alongside valproate, the total underestimates free drug. His signs suggest toxicity. Increasing the dose on a low total makes a toxic patient more toxic. Target free level 1–2 mg/L.

Low albumin or renal failure: measure free phenytoin.

83 C Phenytoin should run no faster than 50 mg/min, or 25 mg/min in the elderly or in cardiac disease, because of hypotension and arrhythmia. Fosphenytoin can run up to 150 mg PE/min.

Phenytoin: ≤ 50 mg/min; ≤ 25 mg/min elderly or cardiac.

84 E Purple glove syndrome is a serious complication of IV phenytoin. Fosphenytoin is less irritant and is preferred when available.

IV phenytoin $\rightarrow$ watch for purple glove syndrome.

85 C HLA-B*15:02 is strongly associated with carbamazepine SJS/TEN. Screen before starting in patients of Han Chinese, Thai, Malay, Filipino or South Asian ancestry. Also check sodium and blood count at baseline.

*Asian ancestry + carbamazepine $\rightarrow$ HLA-B*15:02 first.*

86 A HLA-B*15:02 is linked mainly to SJS/TEN; HLA-A*31:01 to DRESS and hypersensitivity. HLA-B*57:01 relates to abacavir, B*58:01 to allopurinol, and DQB1*06:02 to narcolepsy.

*CBZ: B*15:02 $\rightarrow$ SJS/TEN; A*31:01 $\rightarrow$ DRESS.*

87 D Carbamazepine induces its own CYP3A4 metabolism over 2–4 weeks; expect to need a dose increase in the first month. Its 10,11-epoxide is active and contributes to efficacy and toxicity.

Carbamazepine autoinduces in the first month.

88 A Oxcarbazepine is often chosen to escape carbamazepine's induction or epoxide toxicity, but it is the worse drug for hyponatraemia, especially in the elderly and with thiazides or SSRIs. Switching to it for hyponatraemia is a common error; eslicarbazepine shares the problem.

Don't switch to oxcarbazepine to fix hyponatraemia.

89 E Eslicarbazepine is converted to S-licarbazepine, which is part of oxcarbazepine's MHD. Combining them adds hyponatraemia and toxicity without a new mechanism — with two prescriptions and two copayments. Use one at an adequate dose.

OXC + ESL = one drug prescribed twice.

90 B Valproate inhibits glucuronidation and roughly doubles lamotrigine, so every step is halved. Rapid titration with valproate is the commonest antecedent of lamotrigine-associated SJS. With inducers and no valproate, double the rate and the target.

LTG with valproate: halve everything.

91 D If more than five half-lives are missed, restart from the beginning of the schedule rather than resuming the previous dose. The titration schedule is the safety intervention against SJS/TEN.

Missed >5 half-lives of lamotrigine $\rightarrow$ retitrate.

92 E Lamotrigine can rarely cause HLH, presenting as persistent fever with cytopenias and very high ferritin. It is potentially fatal. Lamotrigine also causes SJS/TEN, DRESS and aseptic meningitis.

Lamotrigine + fever + cytopenias + high ferritin $\rightarrow$ HLH.

93 C Lacosamide prolongs the PR interval and can cause AV block or bradyarrhythmia, particularly with conduction disease or other PR-prolonging drugs. Get a baseline ECG before starting in anyone with cardiac history, on rate-controlling drugs, or receiving an IV load.

Lacosamide: PR interval. ECG first.

94 A Rufinamide shortens the QT and is contraindicated in familial short QT syndrome — the opposite of the concern with almost every other drug you prescribe. Cenobamate also shortens QT.

Rufinamide: check for short QT.

95 A After a prolonged interruption, re-titrate rather than resume the previous dose. Early trials with fast escalation produced DRESS; with the current slow schedule (start 12.5 mg, increase every two weeks) no DRESS occurred in the large open-label safety study of more than 1,300 patients. The temptation to catch up is exactly what produced the signal.

Cenobamate: the titration is the drug.

96 A Cenobamate inhibits CYP2C19, raising phenytoin and phenobarbital — reduce those by 25–50% as it is introduced. It induces CYP3A4, lowering hormonal contraceptives. It also raises clobazam's active metabolite substantially.

Cenobamate: $\uparrow$ phenytoin/phenobarbital, $\downarrow$ contraceptive.

97 E In the pivotal trial, about half to two-thirds of patients on 200–400 mg had a $\geq 50\%$ reduction in seizures, but maintenance-phase seizure freedom was about 11% at 200 mg and 21% at 400 mg. Quoting '~50% seizure freedom' conflates responder rate with freedom. There is no head-to-head trial, and cenobamate is licensed as adjunctive (and in the US monotherapy) treatment for focal seizures in adults.

Cenobamate: ~50% responders, ~20% seizure-free at 400 mg.

98 D Long-term phenobarbital causes Dupuytren contracture and frozen shoulder, along with osteomalacia, bone loss and dependence. It is cognitively the worst drug in the book and still among the most important — cheap and effective.

Phenobarbital long-term: Dupuytren and frozen shoulder.

99 D Primidone has a characteristic first-dose reaction out of proportion to the dose. Warn the patient specifically. It is effectively a prodrug of phenobarbital and PEMA; monitor the derived phenobarbital level.

Primidone: warn about the first dose.

100 B Diazepam is fastest on and fastest to redistribute, giving a brief clinical effect despite its long half-life. Lorazepam is less lipophilic and lasts longer in brain.

| *Diazepam: fast on, fast off. Lorazepam lasts in brain.*

101 B Cannabidiol is a potent CYP2C19 inhibitor and raises N-desmethyclobazam several-fold. The sedation is routinely blamed on the new drug. The answer is almost always to reduce clobazam — ideally by 25–50% before the child becomes drowsy.

| *CBD + clobazam sedation → reduce clobazam.*

102 B Vigabatrin causes permanent bilateral concentric visual field constriction in a substantial proportion of long-term users, usually asymptomatic until advanced. The toxicity is irreversible and silent.

| *Vigabatrin: visual fields, before and during.*

103 B Tiagabine carries an FDA warning for new-onset seizures and non-convulsive status in people without epilepsy prescribed it off-label. Get an EEG. It should be tapered rather than stopped abruptly, even when prescribed for something other than epilepsy.

| *Tiagabine can cause NCSE in people without epilepsy.*

104 A Stiripentol potentially inhibits CYP3A4, 2C19 and 1A2 by design. Reduce the partner drugs before the patient becomes toxic, not after. It also causes neutropenia and thrombocytopenia.

| *Stiripentol: cut the partners first.*

105 B Hyperammonaemic encephalopathy occurs at normal valproate levels and responds to L-carnitine. Valproate plus topiramate is a recognised additive pair — both raise ammonia. Confusion on this pair is an ammonia measurement, not a dose increase.

| *Valproate + confusion + normal level → check ammonia.*

106 B Epilepsy with ataxia, neuropathy, occipital migraine-like features, liver dysfunction — and refractory status of unclear cause in a young person — should raise POLG disease. Valproate carries a very high risk of fatal hepatotoxicity there. Test before prescribing; if testing is impossible in an emergency, choose another drug.

| *Possible POLG → no valproate.*

107 B Fatal hepatotoxicity concentrates under two years, on polytherapy, and in mitochondrial disease. Valproate also causes pancreatitis, hyperammonaemia and teratogenicity.

| *Valproate liver risk: <2 years, polytherapy, mitochondrial disease.*

108 B Regulatory restriction has replaced advice. A pregnancy prevention programme is a requirement for women and girls of childbearing potential. In 2024 the EMA added precautionary measures for men (discussing a possible risk of neurodevelopmental disorders in children fathered during treatment, and contraception), and the UK MHRA required two specialists to agree before valproate is started in anyone under 55.

| *Valproate: PPP is a requirement, not a suggestion.*

109 B Gabapentin is not metabolised and is renally excreted, but its absorption is saturable — a ceiling no other ASM has. Doubling the dose does not double the level. Pregabalin has linear, non-saturable absorption.

| *Gabapentin: double the dose ≠ double the level.*

110 D Topiramate causes acute angle-closure glaucoma, typically within a month of starting, requiring immediate discontinuation. Zonisamide shares the sulfonamide and carbonic anhydrase profile, and acetazolamide adds carbonic anhydrase inhibition.

| *Topiramate + acute eye pain = stop now.*

111 E Topiramate and zonisamide cause oligohydrosis and hyperthermia in children — most important in hot climates and during febrile illness. Counsel families about hydration and heat exposure.

| *Zonisamide/topiramate in children: watch heat.*

112 C Cross-reactivity between antibiotic and non-antibiotic sulfonamides is weaker than once believed, but a history of SJS to any sulfonamide is still a reason to choose something else.

| *Prior sulfonamide SJS → avoid zonisamide.*

113 D Felbamate is genuinely effective, which is why it still exists. Aplastic anaemia and fulminant hepatic failure, both with substantial mortality, appeared within a year of launch. It is the reason modern ASM approval relies on post-marketing surveillance: trials of a few hundred patients cannot exclude a one-in-several-thousand reaction.

| *Felbamate: consent, counts and LFTs.*

114 E Brivaracetam binds SV2A with 15–30 times the affinity, and roughly half of patients improve after the switch. Conversion is about 10:1 to 15:1, done overnight. Pyridoxine is widely used but the evidence is thin. Perampanel carries its own boxed warning for aggression. Do not run levetiracetam and brivaracetam together.

| *LEV behaviour problem → switch to BRV.*

115 D Levetiracetam has essentially no pharmacokinetic interactions — no CYP metabolism, negligible protein binding — which is why it is the default in transplantation, oncology, hepatic disease and polypharmacy. It is renally cleared, so dose by creatinine clearance. Inducers would drop tacrolimus levels.

| *Transplant or chemotherapy → levetiracetam.*

116 E Perampanel carries a dedicated boxed warning for serious psychiatric and behavioural reactions, including aggression and homicidal ideation — dose-related and commoner in adolescents and with rapid titration. Its 105-hour half-life means problems take weeks to appear and weeks to clear. Bedtime dosing reduces dizziness.

| *Perampanel: warn about behaviour, dose at night.*

117 D Perampanel is effective in myoclonus, including progressive myoclonic epilepsies. Carbamazepine, gabapentin and vigabatrin aggravate myoclonus, and lamotrigine may worsen it.

| *Perampanel works in myoclonus.*

118 E Cannabidiol causes dose-dependent transaminase elevation, markedly more frequent with valproate, plus thrombocytopenia. A high-fat meal raises exposure several-fold, so give it with consistent fat intake. It is a standardised pharmaceutical, unlike unregulated artisanal CBD.

| *CBD + valproate → watch the liver.*

119 C Fenfluramine was withdrawn as an anorectic in 1997 for valvular heart disease and pulmonary hypertension. At antiseizure doses no trial patient developed valvulopathy, but the mandatory monitoring stands. It is contraindicated within two weeks of an MAOI.

| *Fenfluramine: echo before, during and after.*

120 E Without stiripentol the maximum is 0.35 mg/kg twice daily (26 mg/day). Stiripentol raises fenfluramine exposure, so the maximum falls to 0.2 mg/kg twice daily, capped at 17 mg/day. For this child, 4 mg twice daily.

| *With stiripentol: fenfluramine max 0.2 mg/kg bd, 17 mg/day.*

10 Combinations That Do Harm

121 C This is pharmacodynamic redundancy plus a kinetic collision: the toxicity of one and the level of neither. Diplopia and ataxia are often misattributed to disease progression. Pair a sodium-channel blocker with an SV2A or GABAergic agent.

| *CBZ + LTG: double toxicity, half the lamotrigine.*

122 D No clinical situation requires both. Choose one.

| *CBZ + PHT: choose one.*

123 D Sodium-channel redundancy plus a conduction problem: lacosamide prolongs PR and the older agents have their own cardiac effects. Withdraw the older agent as lacosamide is introduced, and get a baseline ECG.

| *Lacosamide + older Na blocker: ataxia, and watch the PR.*

124 A Identical target. If brivaracetam is wanted, switch outright at roughly 10:1–15:1 with no cross-taper.

| *LEV + BRV: same target, switch instead.*

125 E Topiramate and zonisamide both inhibit carbonic anhydrase and both slow cognition. Stones, acidosis, oligohidrosis and word-finding difficulty compound, and the ketogenic diet adds to it. Pick one; if the diet is in use, prefer neither.

| *TPM + ZNS (+ diet): stones and acidosis.*

126 C Carbapenems drop valproate by 60–90% within a day, by a mechanism dose increases cannot overcome. Avoid the combination outright.

| *Valproate + carbapenem: avoid. Dose increases fail.*

127 D The total looks normal or low while free, active phenytoin rises. Measure the free level; increasing the dose on a total level here makes a toxic patient more toxic.

| *VPA + PHT: trust the free level.*

128 A The enzyme inducers lower corticosteroids, chemotherapy, anticoagulants, contraceptives, statins and immunosuppressants. In oncology, transplantation or HIV care, start from interaction-quiet agents: levetiracetam, brivaracetam, lacosamide or the gabapentinoids.

| *Oncology → interaction-quiet ASMs.*

129 C Transaminase elevation is substantially more frequent with valproate plus cannabidiol than with either alone. Check LFTs at baseline, one, three and six months and after every increase. Thrombocytopenia also clusters with this pair.

| *VPA + CBD → liver.*

130 C Both carry aggression and irritability signals, perampanel with its own boxed warning. In an adolescent, expect it and warn the family before the first dose. Families notice before patients do.

| *LEV + PER: behaviour stacks.*

131 D Gabapentinoid plus opioid is a documented mortality combination, worst in the elderly and in respiratory disease. Take a substance-use history before prescribing either gabapentinoid.

| *Gabapentinoid + opioid: respiratory drive.*

132 A Kind 4, the rarest and most damaging: the drug fights the biology. The three you must not get wrong are sodium-channel blockers in Dravet, narrow-spectrum agents in undiagnosed generalised epilepsy, and valproate where POLG disease is possible.

| *Kind 4: the drug fights the disease.*

11 The Patient Modifies the Drug

133 A Uncontrolled convulsive seizures are themselves dangerous to mother and fetus. The neural tube closes before most pregnancies are recognised, so switching at the first positive test achieves little for that risk. Do not stop an effective drug abruptly because a patient is pregnant; review urgently and counsel. Every consultation with a woman of childbearing potential is a pre-conception consultation.

Pregnant on valproate: don't stop abruptly. Plan before conception next time.

134 E Oestrogen-driven glucuronidation raises lamotrigine clearance steeply in pregnancy; levels can fall by more than half by the third trimester. Monitor and increase — then reduce within days of delivery, or the patient becomes toxic in the puerperium.

Lamotrigine: raise in pregnancy, reduce within days after delivery.

135 D Oestrogen-containing contraceptives halve lamotrigine, with rebound in the pill-free week. Contraception is bidirectional: starting or stopping the pill changes the epilepsy treatment. An IUD or depot progestogen sidesteps most of it.

Oestrogen halves lamotrigine — pill-free week brings toxicity.

136 A Enzyme-inducing ASMs reduce hormonal contraceptive efficacy. An IUD or depot progestogen sidesteps most of the interaction. Unplanned pregnancy is a foreseeable consequence of a conversation not had.

Inducer + contraception → IUD or depot.

137 B Phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, eslicarbazepine and lamotrigine share an aromatic structure; a serious rash with one predicts substantial risk with the others. Move to a structurally unrelated agent: levetiracetam, valproate, topiramate, gabapentin or a benzodiazepine.

After aromatic-ASM SJS → structurally unrelated agent.

138 C Catamenial epilepsy is diagnosed on paper, not on impression. Once a pattern is established, options include acetazolamide days −3 to +3, perimenstrual clobazam, and hormonal stabilisation with gynaecology.

Catamenial: prove the pattern with a diary first.

139 B In older adults, levetiracetam and lamotrigine are usually preferred, largely on interaction burden. Inducers interact with cardiovascular drugs and accelerate bone loss; sedating agents drive falls. Start at half dose, titrate slowly, target lower, monitor more often, and dose by renal function.

Elderly: start low, go slow, avoid inducers.

140 A A seizure-free patient with a level below range needs no change. Valproate's level–effect correlation is weak; don't chase the number. Ranges are population guidance, not targets.

Seizure-free below range: leave it.

141 B A patient with nystagmus and ataxia at a level inside the range is toxic. Ranges describe populations; this patient's ceiling is lower.

Toxic signs within range = toxic.

142 C Midazolam is the ICU example of a hepatic parent with an active, renally cleared metabolite; either organ failing prolongs the effect. Carbamazepine (10,11-epoxide) and fenfluramine (norfenfluramine) share the pattern.

Midazolam + AKI: active metabolite accumulates.

143 E Oxcarbazepine is reduced to MHD, which is renally cleared; renal impairment prolongs the active moiety rather than the parent. Reduce the dose. Eslicarbazepine shares the pattern.

Oxcarbazepine/eslicarbazepine: renal impairment prolongs MHD.

144 A Benzodiazepines and barbiturates carry a true physiological withdrawal syndrome — tremor, autonomic instability, seizures and occasionally delirium — and need tapers over weeks to months. Withdrawal seizures can be worse than the underlying epilepsy.

Never stop benzodiazepines abruptly.

145 E Withdrawal after remission is a decision about relapse risk, weighing seizure-free duration, syndrome, EEG, MRI and what relapse would cost — licence, occupation, pregnancy. Never stop abruptly.

Stopping is a relapse-risk conversation.

146 B Breastfeeding is generally supported with lamotrigine and levetiracetam. With phenobarbital, monitor the infant for sedation.

Breastfeeding on phenobarbital: watch for a sleepy infant.

12 Status Epilepticus

147 E Under-dosing the benzodiazepine is the commonest error in epileptology. Lorazepam is 0.1 mg/kg (max 4 mg per dose), repeated once. Give the full dose and the second dose, then escalate to second line if the seizure continues.

Full weight-based dose, then the second dose.

148 C With no IV access, give IM midazolam 10 mg, or buccal or intranasal midazolam in the community.

No IV? IM midazolam.

149 D ESETT found levetiracetam, fosphenytoin and valproate equivalent, so choose by comorbidity. Avoid valproate in pregnancy and hepatic disease. Levetiracetam is the default when no other factor decides. In eclampsia, magnesium is also needed.

Second line: pick by comorbidity. Pregnancy → not valproate.

150 D Avoid fosphenytoin in cardiac conduction disease and in the elderly on rate-control drugs. Levetiracetam or valproate are reasonable here, depending on hepatic status.

Conduction disease → avoid fosphenytoin.

151 A A seizure continuing past five minutes means the inhibitory mechanisms that normally end it have failed. T1 (5 min) is when to start treating; T2 (30 min) is when neuronal injury begins.

Five minutes is a biological threshold.

152 A From about 12 minutes, GABA-A receptors begin trafficking away from the synaptic membrane. Every minute of delay reduces the efficacy of the drug you are about to give — which is why early, full dosing matters.

Delay removes the benzodiazepine's target.

153 D Refractory status is failure of two lines. It needs ICU, anaesthesia — propofol 1–2 mg/kg then 2–12 mg/kg/h, or midazolam 0.2 mg/kg then 0.1–2 mg/kg/h — and continuous EEG, targeting seizure cessation or burst-suppression.

Two lines failed → ICU, anaesthetic, cEEG.

154 D This is super-refractory status: 24 hours of anaesthesia or recurrence on weaning. Options include ketamine, pentobarbital and the ketogenic diet. In a young person, consider immunotherapy for an autoimmune cause and avoid valproate where POLG disease is possible.

Refractory status in a young person: think autoimmune and POLG.

13 Seizures in the ICU

159 B Seizure prophylaxis is not recommended in ICH. Phenytoin is associated with worse neurological outcomes across observational studies. Treat only if seizures occur — levetiracetam if needed — and stop inherited prophylaxis.

ICH: no prophylaxis, and avoid phenytoin.

160 D Early post-traumatic seizure prophylaxis for 7 days is evidence-based; levetiracetam is preferred for tolerability. Late-epilepsy prophylaxis is not evidence-based and does not prevent epilepsy.

TBI: 7 days, not longer.

161 D Prophylaxis after aneurysmal SAH is controversial; most guidelines support short-term use only. Avoid long-term treatment unless a seizure occurs. Seizures complicate 8–20% of aneurysmal SAH.

SAH: short-term only, if at all.

162 D HSE has a high seizure burden, NCSE is common and post-encephalitic epilepsy is frequent. Give aciclovir immediately and run the full status protocol in parallel.

HSE: aciclovir now, seizures in parallel.

155 E Persistent NCSE after control of convulsive status is well described (DeLorenzo). NCSE is invisible without EEG. Order cEEG for any unexplained altered consciousness lasting more than ten minutes in a critically ill patient.

Not waking after status → cEEG.

156 A ESETT randomised patients still seizing after benzodiazepines. Cessation was 47%, 45% and 46%. The question 'which second-line drug?' now has one answer: whichever is safest for this patient. Lacosamide was not an arm.

ESETT: three drugs, one result.

157 D In the first five minutes: airway, breathing, circulation, glucose, and thiamine if at risk. Treat hypoglycaemia without delay; giving thiamine alongside glucose protects against Wernicke encephalopathy.

At risk of Wernicke: thiamine with the glucose.

158 E Non-convulsive seizures and status are common in a population that is almost never monitored: published cEEG series range from about 8% of unselected comatose patients (Towne) to 48% after apparently controlled convulsive status (DeLorenzo). Clues include encephalopathy disproportionate to the proposed cause.

Non-convulsive seizures: common in coma, invisible without EEG.

163 C Treat seizures detected on cEEG after cardiac arrest — levetiracetam, with or without phenobarbital for post-anoxic myoclonus — and prognosticate separately and later. Burst-suppression with absent brainstem reflexes is a different, ominous finding.

Post-anoxic myoclonus: treat now, prognosticate later.

164 E Drowsiness after a witnessed event may be post-ictal, and seizures in critically ill patients are mostly invisible without cEEG. In this book's scene the cEEG showed three seizures in six hours.

Unexplained drowsiness + a witnessed event → cEEG.

165 C Continuous monitoring for 24–48 hours (48–72 if suspicion is high) is indicated for comatose patients after cardiac arrest, unexplained altered consciousness, TBI or SAH with seizures, suspected NCSE, and encephalopathy disproportionate to its proposed cause.

cEEG: 24–48 h, longer if suspicious.

166 D The clue to NCSE is encephalopathy that does not fit its proposed cause: hepatic encephalopathy beyond what the ammonia justifies, or a septic patient not improving as expected. cEEG is the only way to exclude it. Valproate would be a poor empirical choice in liver disease.

Encephalopathy out of proportion → think NCSE.

14 Cutting Edge

167 E Drug-resistant epilepsy is failure of two adequate, well-tolerated, appropriately chosen trials — not years elapsed. He is drug-resistant at six months, not at ten years. That distinction is worth a decade of someone's life.

Two adequate failures = drug-resistant. Refer.

168 B About half become seizure-free on the first drug (47% in the 2000 report), the second adds about 13%, and in the long-term update the third added about 4%, with under 2% for each drug thereafter. After two well-chosen trials, the next intervention is reconsidering the diagnosis and evaluating for surgery — not a third prescription.

≈47% → +13% → +4% → <2% each.

169 B Wiebe and colleagues randomised 80 patients. The trial did not discover that surgery works; it produced the level of evidence that obligates us to offer it. Failing to arrange surgical evaluation after two drug failures is a failure of care.

Wiebe: 58% vs 8%.

170 E RNS detects activity from either focus independently and delivers responsive stimulation to whichever is active — exactly what it was designed for. VNS is a reasonable adjunct and bilateral ANT-DBS is evidence-based. Whatever is chosen is added to optimal medical therapy, not instead of it.

Bilateral independent mesial temporal foci → RNS.

171 A Resection disrupts Meyer's loop in the temporal lobe, producing a contralateral superior quadrantanopia. Dominant resections also carry verbal memory decline and naming deficits.

ATL → contralateral superior quadrantanopia.

172 C Corpus callosotomy reduces drop attacks by 50–80%, though complete seizure freedom is rare. Disconnection syndrome is usually transient with anterior two-thirds section.

Drop attacks → callosotomy.

173 A LITT achieves seizure freedom in roughly 80–90% of patients with hypothalamic hamartoma in experienced centres, and about 58–65% for mesial temporal epilepsy. It is operator-dependent, and retreatment is possible.

Hypothalamic hamartoma → LITT.

174 C VNS suits drug-resistant epilepsy without a resection option, in children and adults. About half achieve a ≥50% reduction after one to two years; seizure freedom is uncommon. Newer generators add heart-rate-triggered stimulation alongside the magnet. RNS is the device that also records intracranial EEG.

VNS: ~50% get ≥50% reduction; rarely seizure-free.

175 A SANTE reported a 41% median seizure reduction at one year, 56% at two years and 69% at five years — benefit grows with time. Depression and memory complaints are recognised adverse effects. ANT-DBS suits multifocal or poorly localised drug-resistant focal epilepsy. The 75% at nine years figure belongs to RNS.

SANTE: ~40% at one year, ~69% at five.

15 SUDEP and the Conversations You Must Have

176 C Three or more GTCS a year raises risk by roughly an order of magnitude. Complete seizure freedom brings risk close to the general population, making seizure control the most powerful lever.

SUDEP: control the convulsions.

177 D Prone position during and after a convulsion impairs breathing and is independently modifiable (MORTEMUS). Supervision at night is protective, and nocturnal seizures carry three- to five-fold risk. Wearable detection can alert caregivers.

Not prone; not alone.

178 E SUDEP incidence in Dravet syndrome is around 9 per 1,000 patient-years — roughly ten times that of epilepsy overall, and far higher than in other childhood epilepsies. Maximising control with stiripentol, fenfluramine or cannabidiol partly modifies it.

Dravet: SUDEP roughly ten times epilepsy overall.

179 D A pooled analysis of eleven ASMs found roughly double the rate of suicidal ideation or behaviour — an absolute increase of about one per 500 treated. It applies to the class. Ask the patient and the family, who often notice first.

Class warning: ask about mood, don't withhold.

180 E Most patients and families want to know when asked, and avoidance is experienced as a failure of care. Frame it around prevention. Patients who understand the risk adhere better.

Talk about SUDEP at diagnosis.

181 E SUDEP is sudden, unexpected, witnessed or unwitnessed, non-traumatic, non-drowning death in a person with epilepsy, with or without a preceding seizure, excluding documented status epilepticus, with no toxicological or anatomical cause at post-mortem.

SUDEP excludes documented status.

16 How to Confirm You Are a Bad Epileptologist

182 C Refractory epilepsy accumulates prescriptions. Withdraw ineffective drugs slowly, one at a time. Removing a drug is a clinical intervention, and patients often improve. Surgical evaluation should also be revisited.

Subtracting a drug is a treatment.

183 B ASMs should normally not be stopped abruptly, but a serious rash or organ injury is the exception: stop, and know you have made that choice. Choose a structurally unrelated replacement, not another aromatic ASM.

Serious rash = stop now; cross-tapering is for everything else.

17 What Is Coming

185 C Automated MRI surface analysis is peer-reviewed, multicentre and externally validated, and it changes surgical candidacy in patients previously called non-lesional. For every validated tool there are a hundred prediction apps with no published validation.

MELD: validated, and it changes management.

186 C Benzodiazepine tolerance develops within months. Neurosteroids act at the extrasynaptic site and avoid it. Trials continue in status epilepticus.

Ganaxolone: extrasynaptic, no tolerance.

184 B Worsening seizures are sometimes non-adherence, but also consider a new interacting drug (oestrogen halves lamotrigine), a switched generic, pregnancy, sleep deprivation, alcohol, intercurrent illness — or a drug aggravating a syndrome you did not identify.

Worse seizures? Look for what changed before blaming the patient.

187 C In gain-of-function SCN2A and SCN8A, sodium-channel blockers are precision therapy — the mirror image of loss-of-function SCN1A Dravet, where they are catastrophic. The genotype, not the seizure type, chooses the drug. Other examples: everolimus in TSC, ketogenic diet in GLUT1 deficiency, pyridoxine in pyridoxine-dependent epilepsy.

Gain-of-function SCN8A/SCN2A → Na-channel blockers help.

188 C Antisense oligonucleotides are in early-phase human trials and are the nearest to clinic. AAV delivery may be five to ten years from approvals, RNA interference beyond ten years, CRISPR ten to fifteen, and optogenetics remains a research tool.

Antisense is nearest to clinic.

189 B Cleared devices detect convulsive seizures well and can alert caregivers — useful for SUDEP prevention and a far better seizure diary than memory. Subtle focal events are poorly detected.

Wearables: GTCS yes, subtle focal no.



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FOUR THOUSAND YEARS OF THE FALLING SICKNESS

*A girl falls in a Babylonian marketplace,
and a priest names the god who seized her.*

Sumerian scribes recorded the fall and the froth with perfect accuracy and the wrong cause. Babylon classified some forty seizure types by 1050 BC. Hippocrates put the disease in the brain — and lost the argument for two thousand years, because he had no treatment and the priests had rituals. Galen gave us the word *aura*; Ibn Sina described seizures without convulsions nine centuries before video-EEG.

Then came the drugs: bromide in 1857, phenobarbital in 1912, Berger's first EEG in 1924, phenytoin from a screen of electroshocked cats in 1938 — and now antisense therapy aimed at the gene itself.

This book walks that road to the bedside — semiology, EEG, the syndromes, twenty-seven drugs in full, status epilepticus, the conversations about SUDEP, and twenty pitfalls written the wrong way round. With 189 questions to prove you were listening.

