The Neuropsychiatry of Epilepsy

CHAPTER 10

Dr Lihle Mgweba-Bewana[1] MBChB, DMH, MMed, MPhil, FCPsych, Prof Leigh L. van den Heuvel[2] PhD, MPhil Neuropsychiatry, Cert Neuropsychiatry(SA), MMed (Psych), FC Psych(SA), MBChB, Prof John Joska[4] MBChB, PhD, FCPsych, Dr Maria Oto[3] LMS, Phd, MRCPsych, Dr Matthew Lennon[5,6] MD, MSc, PhD

[1] Division of Neuropsychiatry, Weskoppies Hospital, Pretoria, South Africa.
[2] Department of Psychiatry, Stellenbosch University, South Africa
[3] Scottish Epilepsy Centre, Glasgow, United Kingdom
[4] Division of Neuropsychiatry, University of Cape Town, South Africa
[5] Centre for Healthy Brain Aging (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, University of New South Wales, Sydney NSW, Australia
[6] Royal North Shore Hospital, Northern Sydney Local Health District, Sydney NSW, Australia

Definition and Aetiology

A seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures are not synonymous with epilepsy. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures; it is also characterised by the neurobiological, cognitive, psychological, and social consequences of this condition. The International League Against Epilepsy (ILAE) defines someone as having epilepsy if they meet any of the following conditions[1,2]**:**

1. *"At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.*
2. *One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.*
3. *Diagnosis of an epilepsy syndrome."*

They furthermore state: *"Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years."*

The classification of epilepsies according to the International League Against Epilepsy (ILAE) was updated in 2017 and again in 2025, reflecting developments in the science. The classification approach is now an operational/practical classification. The classification system has three levels: Seizure type (see Figure 1), Epilepsy type and Epilepsy syndrome.

In addition to characterizing, and therefore classifying the type of seizure and epilepsy, an attempt to understand cause is helpful. The majority of seizures fall into genetic, structural (congenital or acquired), and metabolic groups. A significant number, though, will remain of unknown cause (Table 1).

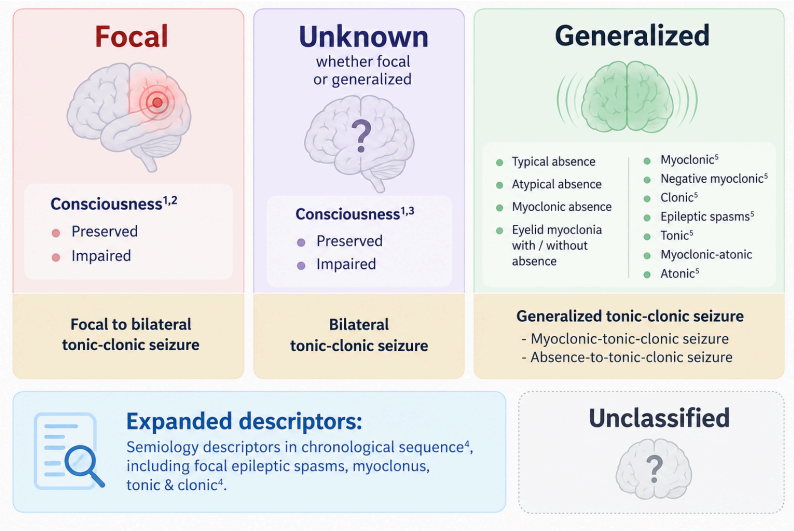


Figure 1: Classification of seizure types according to the International League Against Epilepsy (ILAE). Figure and description taken directly from Beniczky et al., 2025[2] *and reused under* Creative Commons CC-BY 4.0 license.

1. Operationally defined by awareness and responsiveness.
2. If the state of consciousness is unknown, classify as focal (without specifying the sub-classification)
3. If the state of consciousness is unknown, classify as unknown whether focal or generalized (without specifying the sub-classification)
4. Described using the terms in the ILAE semiology glossary (see reference Beniczky et al., 2025)
5. These phenomena may occur also in focal seizures (usually unilaterally or asymmetrically) as part of the semiology of a focal seizure.

Table 1: Classification of Epilepsy according to aetiology

Aetiology	Description	Examples
Genetic (~20–40%)	Epilepsy is the direct result of a known or presumed genetic defect - Seizures are the core symptom of the disorder	Childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy
Structural (~30%)	Congenital – structural abnormalities on imaging from pre-natal phase	Cortical dysplasia, tuberous sclerosis
	Acquired – structural abnormalities acquired because of events during life	Stroke, trauma, infection, immune-based
Metabolic (~5%)	biochemical (genetic or acquired) errors disrupt CNS metabolism, cause a shortage of vital cofactors, or allow toxic substances to build up	Disorders including Glucose Transporter 1 (GLUT1) Deficiency Syndrome, Cerebral Folate Deficiency, Maple Syrup Urine Disease
Unknown (~20–30%)	Epilepsy in cases where diagnostic, imaging and genetic tests are normal - May involve as yet unidentified microscopic changes, synaptic abnormalities, or rare/interacting genetic abnormalities	

Epidemiology

In 2021 there were an estimated 51.7 million prevalent cases of epilepsy worldwide[3] , affecting approximately 0.7% of all adults. Of these cases 42% were attributable to idiopathic epilepsy, while 58% were secondary epilepsy cases. Over the last 30 years, the prevalence of epilepsy has increased by approximately 10% while the death and disability rates have substantially decreased, meaning that there are an increasing number of people living with epilepsy as a chronic condition. There are no significant sex differences in the prevalence of epilepsy (males 0.68% and females 0.63%). The prevalence of epilepsy increases from birth to around 19 years of age, followed by a gradual decline up to the age of 55 years, after which there is a steep increase (Figure 2). There is substantial geographical variation in the prevalence of epilepsy (3 – 4x differences in rates), with

low- and middle-income countries (LMIC) bearing a substantially greater burden than high-income countries. The World Health Organisation (WHO) estimates that 80% of people with epilepsy live in LMIC. This is attributed to an increased prevalence of infectious conditions such as malaria and neurocysticercosis. Birth related injuries and access to medical interventions is also variable and limited[4].

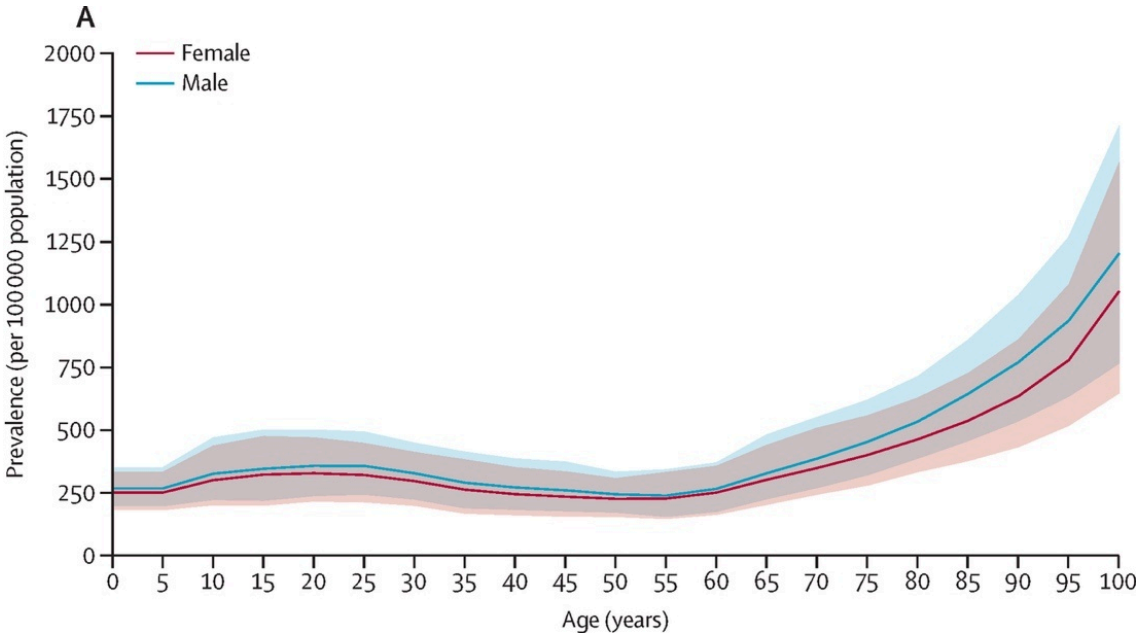


Figure 2: Global age-specific prevalence of epilepsy from idiopathic and secondary epilepsy, by age and sex, 2021. Figure taken directly from Fegin et al 2025 and reused under the Creative Commons CC-BY 4.0 license.

People with epilepsy have a 2 – 5 times elevated risk of any incident psychiatric condition, with a third of those with epilepsy having a lifetime psychiatric diagnosis[5]. Psychiatric diagnoses more common in those with epilepsy than those without include attention deficit hyperactivity disorder (ADHD, 13%; OR 3.93), autism spectrum disorders (ASD, 10.9%; OR 10.67), psychotic disorders (14.8%; OR 3.98), generalised anxiety disorder (GAD, 10.7%; OR 2.34), depression (13.7%; OR 2.45), and bipolar disorder (1.2%; OR 3.12)[6].

Pathophysiology

The core pathology of epilepsy is neuronal hyperexcitability, an imbalance of excitation over inhibition creating a cycle of focal or widespread synchronised neuronal network firing. As mentioned above this imbalance can be created through a range of innate or acquired mechanisms including genetic defects, ion channel abnormalities, synaptic reorganisation, brain injuries (e.g. traumatic brain injury [TBI], stroke), and inflammation amongst other contributors[7]. Rather than the pathophysiology of epilepsy generally, this chapter will focus on the mechanisms underlying psychiatric disorders in those with epilepsy including biological, psychological, and social contributors (Figure 2).



Figure 2: Biological, psychological and social contributors to psychiatric disorders in those living with epilepsy.

Biologically, psychiatric disorders and epilepsy have shared causes, as well as having bidirectional causative relationships. Psychiatric disorders and epilepsy have shared genetic architecture (e.g. ADHD and ASD)[8], and both can be caused by structural brain abnormalities (e.g. scarring, gliosis, TBI, and hippocampal sclerosis), neurotransmitter/neuroendocrine abnormalities (e.g. hypothalamic-pituitary-adrenal [HPA] axis dysregulation), and neuroinflammation[9]. Seizures also have direct biological effects on mood, psychosis and behaviour, observed most commonly in the effects of electroconvulsive therapy (ECT)[10]. In those with epilepsy the psychiatric effects vary widely by seizure phase, with sometimes opposing phenomena occurring in the pre-ictal, ictal, post-ictal, and interictal periods (see Table 2). Anti-seizure medications, discussed further below, are also significant contributors to psychiatric complications. Medications such as levetiracetam and brivaracetam can cause significant depression, irritability and other behavioural disturbances. The causative biological relationship between epilepsy and psychiatric disorders is bidirectional, and it has been well documented that psychiatric comorbidity worsens epilepsy outcomes through multiple avenues including poor sleep, reduced physical activity, and dietary changes, amongst other contributors[9].

Table 2: Psychiatric symptoms related to ictal phases

	Cognitive	Anxiety	Mood	Psychosis	Sleep & Vegetative	Other / Somatic
Pre-ictal "prodrome"			Irritability Dysphoria Depression			Headache Malaise

Ictal (inc. aura)		Ictal anxiety		Hallucinations- often inc. non auditory		Relatively stereo-typed
Post-ictal	Confusion common (<30min)		Anger and aggression common	Preceding lucid period (24 hrs), abrupt onset, agitation, behavioural disturbance	Drowsy	
Inter-ictal	Mild attention, executive function, or memory dysfunction - Can be progressive over years	Anxiety common (agoraphobia, GAD, social)	Depression common (irritability & somatic)	SCZ like psychosis: Associated with recurrent postictal psychosis	Hyposexuality common (medication, TLE)	Personality changes

Cogn imp, cognitive impairment; esp, especially; GAD, generalised anxiety disorder; SCZ, schizophrenia; TLE, Temporal lobe epilepsy

Psychologically, those living with epilepsy may be affected in myriad ways. Epilepsy is deeply unpredictable, which can lead to fear and avoidance of public or exposed environments contributing to agoraphobia, GAD, and social anxiety. The loss of autonomy (especially driving) may contribute to frustration, loss of identity, low self-esteem and depressed mood. Seizures resulting in injury (e.g. motor vehicle accident) can be a source of psychological trauma. Cognitive difficulties in memory, attention, concentration or executive function can impact education, employment and daily living, further contributing to distress [9]. Socially, those with epilepsy may become isolated because of stigma, loss of function, or inability to drive, amongst other contributors. They may have reduced employment opportunities and increased healthcare costs, resulting in greater financial strain. Beliefs about epilepsy vary widely by community, and cultural misconceptions may lead to discrimination, delayed diagnosis, or
undertreatment. Given the lack of predictability and limitations associated with epilepsy, those living with it may adopt the “sick role” within their family relationships.

Psychiatric Presentations, Assessment and Diagnosis

While the presentation of epilepsy will most commonly be with a motor seizure, in rare cases of focal epilepsy individuals can present with predominant or exclusive psychiatric symptoms. Focal epilepsy, which makes up around 60% of epilepsy cases, is most commonly localised in the temporal (60% of cases) and frontal (30%) lobes. Temporal lobe epilepsy (TLE) can present with aura, impaired awareness, motor automatisms (e.g. lip smacking, finger plucking) and generalising to a bilateral tonic-clonic seizure[11]. Psychiatric manifestations of temporal lobe seizures may include sudden overwhelming fear, abrupt mood shifts (depression or intense anger), hallucinations, illusions or delusions. Psychiatric presentations of frontal lobe seizures can include sudden affective

changes (intense fear, anger, explosive laughing) and bizarre hypermotor automatisms, including screaming, swearing, pelvic thrusting, or bicycle pedalling. These seemingly organised activities may be mistaken for a functional seizure or a psychiatric disorder. Useful features to help distinguish these psychiatric features of a seizure from psychiatric disorders are the very short duration (seconds to minutes vs days to months), the stereotyped episodes (highly predictable or identical), the preceding aura (e.g. epigastric rising sensation, visual auras, anxiety), the post-ictal confusion that often follows seizures, and the occurrence of these episodes during sleep (especially for frontal seizures)[11].

Differential diagnoses of epilepsy

A range of differential diagnoses should be considered when assessing those with presumed epilepsy, to avoid patients being misdiagnosed and wrongly treated with antiseizure medications (ASMs), with potentially serious adverse effects. Important differential diagnoses include:

- **Functional seizures or psychogenic non-epileptic seizures (PNES)** – involuntary/dissociative events that involve a seizure like presentation without corresponding electrical activity. This is discussed further below.
- **Transient ischaemic attack** – neurological symptoms lasting less than 24 hours caused by a temporary loss of blood flow to part of the brain.
- **Syncope** – temporary loss of consciousness and particularly in vasovagal events can present with some brief clonic movements.
- **Migraine** – form of severe headache that can present with temporary neurological symptoms (e.g. aura, partial visual loss, transient weakness/paralysis).
- **Sleep disorders** – narcolepsy may present with sudden paroxysms of reduced consciousness/awareness and sleept terrors or a REM sleep behaviour disorder may present with screaming or thrashing around in bed at night, similar to focal seizures.
- **Acute dystonia** – A period of sustained contraction of any muscle group (e.g. lip pursing, grimacing, tongue protrusion, torticollis) that may present similarly to a focal seizure.

PNES is often misdiagnosed as epilepsy despite a range of important distinguishing features. PNES is more common in the 20–40-year age group, where epilepsy is most common in childhood and over 55 years of age. PNES has a female to male ratio of 3:1, whereas epilepsy has a 1:1 ratio. Individuals
with PNES may also have epilepsy, in studies using video electroencephalogram (vEEG) monitoring an estimated 9.4% - 32% of people with PNES also have epilepsy[12] .

For clinicians there are several case features that should raise the likelihood of PNES including: 1) atypical seizures or presentation with a new type of seizure 2) stressful events preceding the onset of the seizures, 3) poor response to adequate anti-epileptic treatment, 4) sudden increase in frequency of seizures, 5) pre-existing psychiatric history, or 6) childhood trauma. Aside from the case features, the episodes themselves have some key differences outlined in Table 3 below.

Table 3: Features that can help differentiate epileptic vs psychogenic seizures (adapted from R Duncan, 2006[14] and Muthusamy et al 2022[15])

Sign	Epileptic	Psychogenic non epileptic seizures (PNES)
Duration	Usually brief (< 1-2 min)	Usually > 2 mins
Eyes	Usually open	Often closed
Motor activity	Stereotyped, builds & progresses, synchronized	Variable, wax & wanes, pelvic thrusting, rolling side to side
Vocalization	Uncommon	May occur
Prolonged ictal atonia	Very rare	May occur
Incontinence	Common in convulsive seizures	Less common
Autonomic signs	Cyanosis & tachycardia common in major convulsions	Uncommon
Postictal symptoms	Headache common, confusion, drowsiness	Headache rare, can awaken & be fully orientated.

Assessing co-morbid psychiatric disorders in epilepsy

As previously mentioned, those with epilepsy have higher rates of GAD, depression, bipolar disorder, ADHD, ASD, and psychotic disorders, as well as higher suicide rates compared to both the general population and those with depression without epilepsy[16]. Depression and anxiety, in particular, remain underdiagnosed in those with epilepsy as they are considered to be understandable reactions to a highly impairing chronic condition. Depression should be assessed as in the general population with a focus on characterising the chronicity (brief or longer term), pervasiveness (unremitting or paroxysmal), diurnal variation (worse in the mornings), and functional impact of the mood and anhedonia. While physical symptoms such as fatigue, subjective weakness, and poor concentration may be caused by either depression or epilepsy, symptoms including guilt, low self-esteem, neurovegetative symptoms (insomnia, poor appetite, weight loss) and other melancholic features (early morning wakening, severe unrelenting low mood) are all more suggestive of a depressive disorder. Similarly, features suggestive of anxiety in those with epilepsy include ruminations, panic attacks, early wakening and sleep disruption. The Epilepsy Anxiety Survey Instrument-Brief (EASI)[17] and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)[18] are brief validated screening questionnaires for people with epilepsy. The EASI and NNDI-E are eight and six items respectively and take 1 – 3 minutes to complete. Assessment of these symptoms should be conducted during the inter-ictal phase, so that peri-ictal confusion, fatigue or anxiety do not confound assessment.

In addition to psychiatric symptoms there are certain personality features that are associated with epilepsy, including greater rates of cluster C obsessive-compulsive personality traits[19], and religious, highly ethical or spiritual traits, observed particularly in people with temporal lobe epilepsy[20].

Investigations

Investigations for those with epilepsy may include baseline blood tests, prolactin levels, anti-seizure medication levels, electrocardiogram (ECG), EEG and brain imaging. Additional tests may include pregnancy tests (β-hCG), toxicology, cerebrospinal fluid (CSF) studies (e.g. biochemistry and culture), autoimmune encephalitis testing, metabolic studies, and genetic testing. Table 4 outlines the rationale for the different tests.

Table 4: Investigations for epilepsy work-up and rationale

Investigation	Rationale
Full Blood Count	Identifies anaemia, infection etc; establishes baseline before antiseizure medications.
Electrolytes, Urea Creatinine	Na^{+}, Ca^{2+} and Mg^{2+} abnormalities, which can provoke seizures; establishes renal function for med selection/dosing.
Liver Function Tests	Assess for hepatic dysfunction; provides information on capacity to metabolise medications (e.g. valproate, carbamazepine, clobazam).
Blood Glucose	Hypoglycaemia can cause seizures /mimic epilepsy.
C-Reactive Protein	Systemic infection/inflammation when clinically suspected; in children may support diagnosis of febrile seizures
Serum prolactin	10 – 20 minutes following true bilateral tonic clonic seizure prolactin should rise. Lack of rise can suggest PNES rather than epileptic seizure[21]
β-hCG	Pregnancy determines antiseizure medication choice and dose
Electrocardiogram (ECG)	Cardiac arrhythmias (e.g. long-QT syndromes, heart block) can present with transient loss of consciousness and convulsive movements, mimicking epilepsy
Electroencephalogram (EEG)	Supports diagnosis and classification. Epileptiform discharges increase the likelihood of epilepsy. A normal EEG does not exclude epilepsy
MRI brain – epilepsy protocol	Preferred structural investigation. Identifies lesions such as hippocampal sclerosis, cortical dysplasia, tumour, vascular malformation, previous stroke, or traumatic injury
Antiseizure medication levels	Not routinely required, but useful when toxicity, non-adherence, drug interactions or treatment failure is suspected; meds including phenytoin, valproate, carbamazepine and phenobarbitone

Electroencephalography (EEG)

The gold standard investigation for diagnosis is 7-day, 24-hour video electroencephalogram (vEEG) monitoring, with episodes captured during that period. In many low-resource settings this may not be feasible and thus alternatives may include more brief periods of EEG monitoring,

ambulatory EEG monitoring and requesting that carers/family video the episodes on their phone, so that an accurate semiology may be acquired. The EEG can help subtype and localise the seizure focus but importantly, a normal EEG does not exclude epilepsy. Standard cranial EEG leads can only detect electrical activity up to 2 – 3 cm below the skull and thus seizure activity in the deeper parts of the brain are unlikely to be detected.

MRI Imaging

MRI scans are the imaging modality of choice for epilepsy with specialised imaging settings for those with suspected or confirmed epilepsy. The MRI epilepsy sequence varies by institution, scanner and country, but the common feature is that it uses specialised coronal oblique views, perpendicular to the long-axis of the hippocampus to identify subtle changes of hippocampal sclerosis. Other features include thin slices (3mm or less), high resolution voxels (1mm cubes), T2/FLAIR imaging and the frequent inclusion of susceptibility weighted and diffusion weighted imaging. Figure 3 shows some examples of MRI findings in those with epilepsy.

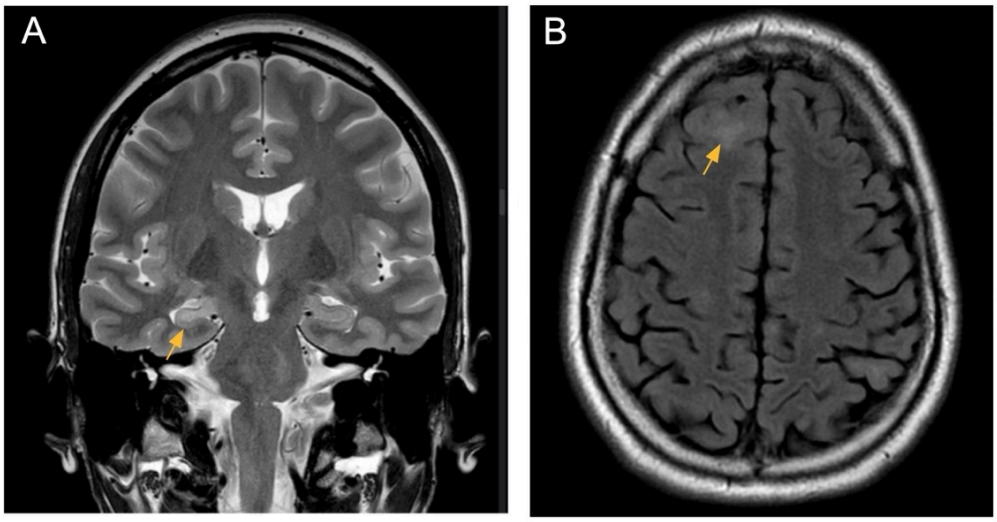


Figure 3: MRI case examples of patients with epilepsy. Images taken with permission from Radiopaedia.org. A – 35 year old female with temporal lobe epilepsy. Arrow highlights the right hippocampus, which is smaller than the left, shows T2/FLAIR hyperintensity with loss of internal architecture consistent with hippocampal sclerosis. (Case courtesy of Elena Filimonova – full scan available at radiopaedia.org/cases/hippocampal-sclerosis-4). B – 25 year old male with frontal lobe epilepsy. Arrow highlights cortical/subcortical hyperintense lesion (one of multiple) characteristic of tuberous sclerosis. (Case courtesy of RMH Neuropathology - full scan available at radiopaedia.org/cases/tuberous-sclerosis-17).

Genetic Testing

Genetic testing in epilepsy is a highly specialised field and is most often arranged by a subspecialty neurologist (epileptologist) or geneticist[22]. By providing an epilepsy subtype, genetic testing can inform the prognosis and management of psychiatric symptoms. For example, Dravet syndrome[23] (SCN1A defects) may present with intellectual disability, ADHD, ASD, severe mood swings and aggressive outbursts, with these symptoms likely to persist through life. Genetic testing has greater utility in those with neonatal onset seizures, developmental delay or intellectual disability, treatment resistant epilepsy, and epilepsy associated with worsening chronic neurological symptoms. It has less yield in those with late adolescent or adult-onset forms and those with extended family histories. Genetic testing may take many forms including

chromosomal microarrays (CMA) (i.e. single nucleotide polymorphisms), extended urine metabolic screens, gene panels, exome sequencing, and whole genome sequencing[22].

Neuropsychiatric aspects of treatment

Management of persons with epilepsy should occur within a multidisciplinary team including neurologists, psychiatrists, social workers, and occupational therapists amongst others. This section will focus particularly on the management of neuropsychiatric aspects of these cases. The primary goal in epilepsy treatment is to optimise seizure control. Those with poorly controlled, frequent seizures experience greater symptoms of anxiety, depression and stress [24] . In a substantial number of cases (20+%) patients will require more than one ASM, [25] and in those with treatment resistant focal epilepsy (>2 failed, adequate trials of ASMs), surgical ablation may be pursued.

Clinicians selecting anti-seizure medications should judiciously consider the neuropsychiatric side effects, the psychotropic medication interactions, and dual use psychiatric indications (see Table 5). For example, Levetiracetam is known to worsen irritability, aggression, low mood, and fatigue and should be avoided, if possible, in those with a significant psychiatric history[26]. Carbamazepine is known to induce a wide variety of CYP450 enzymes and increase the enzymatic breakdown of psychotropic medications, such as quetiapine, clozapine, olanzapine, tricyclic antidepressants, benzodiazepines and valproate. Valproate, while contraindicated in women of childbearing age, has a dual use as a mood stabiliser in bipolar disorder and may be the ASM of choice in those with comorbid bipolar disorder and epilepsy.

Table 5: Commonly prescribed antiseizure medications & their neuropsychiatric implications (adapted from S Karceski 2007[27] and Lyndon et al 2026[28])

Medication:	Mechanism of action	Type of epilepsy (Indication)	Neuropsychiatric indications	NB Drug-drug interactions	Neuropsychiatric Side-effects
Sodium Valproate (metabolised to valproic acid in GIT)	Indirectly increases GABA	Generalised tonic- clonic (GTC); Absence	Bipolar disorder (for mania & depression); aggression, agitation	Valproate can increase levels of TCAs, lamotrigine, quetiapine OCP co-admin can lower Na Valproate levels	Tremor, parkinsonism, associated with cognitive decline
Lamotrigine	May affect neurons that synthesise glutamate & aspartate	Focal onset seizures; GTC seizures	Bipolar depression; impulsivity and behaviour symptoms in borderline PD	Enzyme inducers (phenytoin, carbamazepine, phenobarbital, oestrogen-containing OCPs, rifampicin, protease inhibitors) can lower levels of lamotrigine	Neurotoxic side effects: dizziness and somnolence

Medication:	Mechanism of action	Type of epilepsy (Indication)	Neuropsychiatric indications	NB Drug-drug interactions	Neuropsychiatric Side-effects
Carbamazepine	Binds to voltage dependent Na channels	Focal and generalized seizures	Bipolar disorder and chronic pain syndromes e.g., trigeminal neuralgia.	Potent and broad-spectrum inducer of the CYP system	Sexual dysfunction, drowsiness, dizziness, blurred or double vision, lethargy, & headache
Phenytoin	Binds to voltage dependent Na channels	Focal & generalized seizures, status epilepticus Second-line agent for patients with mixed seizures	Nil	Potent inducer of CYP system	Confusion, slurred speech, double vision, ataxia, and neuropathy (with long-term use)
Levetiracetam	Unknown, in animals binds to the synaptic vesicle protein SV2A	Adjunctive therapy for focal-onset seizures Adjunctive therapy in treating myoclonic seizures; juvenile myoclonic epilepsy	Nil	Metabolism not related to CYP system	Fatigue, somnolence, dizziness, irritability, low mood and aggression.

Co-admin, co-administration; CYP, Cytochrome P450; GABA, Gamma aminobutyric acid (GABA); GIT, gastrointestinal tract; NA, sodium; NB, important; OCP, oral contraceptive pill; PD, personality disorder; SV2A, Synaptic vesicle glycoprotein 2A; TCAs, tricyclic antidepressants

Managing anxiety and depression in people with epilepsy

First line treatment for anxiety and depression in epilepsy is psychotherapy. A 2020 Cochrane review found that of the 27 studies examining psychological treatments in those with epilepsy most examined the effects of “skills-based” therapies with a cognitive behavioural therapy approach[29]. Skills included breathing exercises, mindfulness, reasoning, and visualisation. Others focussed on psychoeducation aimed at increasing understanding of epilepsy, what it means for individuals’ lives, and how they can continue living fulfilling lives with this chronic disease [29]. There is reasonable evidence to support that skills based and CBT approaches improve the quality of life of people living with epilepsy.

In cases with mild-moderate or severe depression or anxiety, particularly if not responsive to psychological therapies, antidepressant medication can be considered. There are few high quality studies examining the treatment of depression in those with epilepsy with only a handful of randomised controlled trials[26]. One randomised study of 64 individuals found that venlafaxine improved scores on a depression scale by more than 50% compared to no treatment, and a trial of sertraline suggested efficacy, but trials of paroxetine and amitriptyline were equivocal[30]. Moderate to low quality evidence indicates that antidepressant treatments do not increase frequency or severity of seizures in epilepsy.

ADHD symptoms in people with epilepsy

There is a considerable overlap between epilepsy and ADHD. Given the mechanism of action of first-line stimulant ADHD medication (e.g. dexamphetamine, methylphenidate) there is concern that such treatment may decrease seizure threshold. Two large population based studies (n = 801,838 and n = 21,000) compared individuals within themselves when taking and not taking stimulant medications and found that ADHD medications were not associated with higher seizure frequency, and in fact that treating
ADHD may improve seizure control[31,32]. While treatment should proceed cautiously, diagnosis of epilepsy should not preclude adequate treatment of co-morbid ADHD.

Psychosis in people with epilepsy

Psychotic disorders in persons with epilepsy were found to be associated with longer duration of epilepsy[33]. There is similarly little high quality evidence to guide management of psychosis in those with epilepsy, with no large, randomised trials. A 2024 Cochrane review identified that in four case series psychotic symptoms improved on antipsychotic medications for most patients with epilepsy, and in a handful of cohort studies seizure frequency either decreased or did not change with antipsychotic medications[34]. There are several antipsychotic medications that are known to decrease seizure threshold including clozapine, olanzapine, and chlorpromazine, that should ideally be avoided, while others have much lower risk of inducing seizures (e.g. haloperidol, risperidone, quetiapine, and aripiprazole).

Chapter Summary

- **Definition and Aetiology:** Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate seizures and associated neurobiological, cognitive, psychological and social consequences.
- **Epidemiology:** Epilepsy is a common neurological disorder affecting more than 50 million people worldwide, with prevalence varying substantially by age and geographic region. Psychiatric comorbidity is also highly prevalent.
- **Pathophysiology:** Epilepsy arises from neuronal hyperexcitability and abnormal synchronised neuronal network activity. Psychiatric disorders and epilepsy have overlapping biological mechanisms, while seizures, ASMs and psychiatric illness can each contribute to neuropsychiatric symptoms.
- **Psychiatric presentations, assessment and diagnosis:** Epilepsy may present with psychiatric symptoms, particularly in focal epilepsy. Brief, stereotyped episodes of fear, mood change, hallucinations, delusions or unusual behaviour should prompt consideration of an ictal or peri-ictal phenomenon rather than assuming a primary psychiatric disorder.
- **Differential diagnoses of epilepsy:** Psychogenic non-epileptic seizures, syncope, transient ischaemic attacks, migraine, sleep disorders and movement disorders can mimic epileptic seizures. Careful attention to episode duration, stereotypy, motor features, triggers and post-ictal state is essential, recognising that epilepsy and PNES may coexist.
- **Assessing co-morbid psychiatric disorders in epilepsy:** Depression, anxiety, psychosis, bipolar disorder, ADHD and ASD are more common in people with epilepsy and should be actively assessed rather than attributed simply to the burden of chronic neurological illness. Screening tools such as the NDDI-E and EASI can assist assessment.
- **Investigations:** Investigation should be guided by the clinical presentation and may include blood tests, ECG, EEG, epilepsy-protocol MRI, ASM levels and, where indicated, autoimmune, metabolic, and genetic testing. A normal EEG does not exclude epilepsy, and video-EEG monitoring is particularly valuable when the diagnosis remains uncertain.
- **Neuropsychiatric aspects of treatment:** Management should be multidisciplinary and aim to optimise seizure control while considering the neuropsychiatric effects and drug interactions of ASMs. Medication choice should take comorbid psychiatric disorders into account.
- **Managing anxiety and depression in epilepsy:** Psychological interventions, particularly skills-based and cognitive behavioural approaches, are important first-line treatments for anxiety and depression. Antidepressant medication can be considered when psychological treatment is insufficient, symptoms are more severe or in settings where psychotherapeutic interventions are not available or accessible.
- **ADHD symptoms in those with epilepsy:** ADHD is substantially more common in people with epilepsy, and epilepsy should not automatically preclude appropriate stimulant treatment. Available population-based evidence suggests that ADHD medications do not increase seizure frequency and may improve seizure control.
- **Psychosis in those with epilepsy:** Psychosis requires careful assessment of its temporal relationship to seizures and consideration of ASM effects. Antipsychotic treatment can be effective, but medication choice should account for differences in seizure-threshold effects.

References

1. Fisher, R. S. *et al.* Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* **58**, 522–530 (2017).

2. Beniczky, S. *et al.* Updated classification of epileptic seizures: Position paper of the International League Against Epilepsy. *Epilepsia* **66**, 1804–1823 (2025).

3. Feigin, V. L. *et al.* Global, regional, and national burden of epilepsy, 1990 - 2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Public Health* **10**, e203–e227 (2025).

4. World Health Organisation. Epilepsy. *Fact Sheets* (2024).

5. Lin, J. J., Mula, M. & Hermann, B. P. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *The Lancet* **380**, 1180–1192 (2012).

6. Kwon, C.-S. *et al.* Psychiatric Comorbidities in Persons With Epilepsy Compared With Persons Without Epilepsy. *JAMA Neurol.* **82**, 72 (2025).

7. Devinsky, O. *et al.* Epilepsy. *Nat. Rev. Dis. Primers* **4**, 18024 (2018).

8. Wu, Y., Li, Y., Zhu, J. & Long, J. Shared genetics and causality underlying epilepsy and attention-deficit hyperactivity disorder. *Psychiatry Res.* **316**, 114794 (2022).

9. Mula, M., Kanner, A. M., Jetté, N. & Sander, J. W. Psychiatric Comorbidities in People With Epilepsy. *Neurol. Clin. Pract.* **11**, (2021).

10. Espinoza, R. T. & Kellner, C. H. Electroconvulsive Therapy. *New England Journal of Medicine* **386**, 667–672 (2022).

11. Ghulaxe, Y. *et al.* Understanding Focal Seizures in Adults: A Comprehensive Review. *Cureus* https://doi.org/10.7759/cureus.48173 (2023) doi:10.7759/cureus.48173.

12. Benbadis, S. R., Agrawal, V. & Tatum, W. O. How many patients with psychogenic nonepileptic seizures also have epilepsy? *Neurology* **57**, 915–917 (2001).

13. Duncan, R. The withdrawal of antiepileptic drugs in patients with non-epileptic seizures: safety considerations. *Expert Opin. Drug Saf.* **5**, 609–613 (2006).

14. Muthusamy, S., Seneviratne, U., Ding, C. & Phan, T. G. Using Semiology to Classify Epileptic Seizures vs Psychogenic Nonepileptic Seizures: A Meta-analysis. *Neurol. Clin. Pract.* **12**, 234–247 (2022).

15. Fazel, S., Wolf, A., Långström, N., Newton, C. R. & Lichtenstein, P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *The Lancet* **382**, 1646–1654 (2013).

16. Scott, A. J. *et al.* Design and validation of two measures to detect anxiety disorders in epilepsy: The Epilepsy Anxiety Survey Instrument and its brief counterpart. *Epilepsia* **60**, 2068–2077 (2019).

17. Friedman, D. E. *et al.* Identifying depression in epilepsy in a busy clinical setting is enhanced with systematic screening. *Seizure* **18**, 429–433 (2009).

18. Viola, V. *et al.* Personality disorders in people with epilepsy: a review. *Front. Psychiatry* **15**, (2024).

19. Devinsky, O. & Lai, G. Spirituality and Religion in Epilepsy. *Epilepsy & Behavior* **12**, 636–643 (2008).

20. Shimmura, M. & Takase, K. Clinical utility of serum prolactin and lactate concentrations to differentiate epileptic seizures from non-epileptic attacks in the emergency room. *Seizure* **95**, 75–80 (2022).

21. Habela, C. W., Schatz, K. & Kelley, S. A. Genetic Testing in Epilepsy: Improving Outcomes and Informing Gaps in Research. *Epilepsy Curr.* **25**, 153–157 (2025).

22. Anwar, A., Saleem, S., Patel, U. K., Arumaithurai, K. & Malik, P. Dravet Syndrome: An Overview. *Cureus* https://doi.org/10.7759/cureus.5006 (2019) doi:10.7759/cureus.5006.

23. Kwon, O.-Y. & Park, S.-P. Depression and Anxiety in People with Epilepsy. *Journal of Clinical Neurology* **10**, 175 (2014).

24. Stephen, L. J. & Brodie, M. J. Seizure freedom with more than one antiepileptic drug. *Seizure* **11**, 349–351 (2002).

25. Osimo, E. F., Fletcher, P. C. & Cope, T. E. Treating anxiety and depression in people with epilepsy. *Pract. Neurol.* **26**, 37 (2026).

26. Karceski, S. C. Seizure medications and their side effects. *Neurology* **69**, (2007).

27. Lyndon, S., Dworetzky, B. A. & Baslet, G. Psychiatric and behavioural side effects of anti-seizure medications in epilepsy. *Journal of Neurology* vol. 273 Preprint at https://doi.org/10.1007/s00415-025-13591-2 (2026).

28. Michaelis, R. *et al.* Psychological treatments for people with epilepsy. *Cochrane Database of Systematic Reviews* **2020**, (2020).

29. Maguire, M. J., Marson, A. G. & Nevitt, S. J. Antidepressants for people with epilepsy and depression. *Cochrane Database of Systematic Reviews* **2021**, (2021).

30. Wiggs, K. K. *et al.* Attention-deficit/hyperactivity disorder medication and seizures. *Neurology* **90**, (2018).

31. Brikell, I. *et al.* Medication treatment for attention-deficit/hyperactivity disorder and the risk of acute seizures in individuals with epilepsy. *Epilepsia* **60**, 284–293 (2019).

32. Gurgu, R., Ciobanu, A., Danasel, R. & Panea, C. Psychiatric comorbidities in adult patients with epilepsy (A systematic review). *Exp. Ther. Med.* **22**, 909 (2021).

33. Arora, A. *et al.* Effectiveness of antipsychotic drug therapy for treating psychosis in people with epilepsy: A systematic review. *Epilepsia* **65**, 3425–3440 (2024).