BMJ Best Practice

Focal seizures

Straight to the point of care

Last updated: Apr 08, 2025

Table of Contents

Summary

Focal seizures are the transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain originating within networks limited to one hemisphere.

Focal seizures can be caused by overt brain lesions (e.g., stroke, tumor), but neuroimaging studies often do not identify any underlying pathology.

History-taking is the most important aspect of diagnosis. Supportive tests, although helpful, need not be abnormal for a diagnosis of focal seizures.

Monotherapy with anticonvulsant medication is the initial and preferred treatment. Choice of medication should be tailored to the needs of the individual patient, taking into account factors such as age, sex, and comorbidities.

When at least two monotherapy trials fail to achieve seizure remission, dual therapy may be tried; use of drugs with different mechanisms of action should be considered to maximize efficacy and minimize toxicity.

Patients in whom seizure remission is not achieved with two monotherapy trials followed by dual therapy are considered to have refractory focal seizures. They should be evaluated to confirm the diagnosis and for consideration of resective epilepsy surgery and/or neuromodulation therapies.

Definition

Focal seizures (formerly known as partial seizures) refer to the electrical and clinical manifestations of seizures that arise from one portion of the brain. An electroencephalogram typically indicates a localized discharge over the area of onset, or regions beyond the initial onset as the abnormal electrical activity propagates. Focal seizures can originate from any lobe in the brain. Focal epilepsy of temporal lobe origin is the most frequently recognized focal epilepsy.

Focal aware seizures (formerly known as simple focal seizures) are those in which consciousness is preserved. Focal impaired awareness seizures (formerly known as complex focal seizures) are characterized by loss of awareness, memory loss for the clinical event, and impaired responsiveness at the time of the event.

Focal seizures may evolve into bilateral tonic-clonic seizures (formerly known as secondarily generalized tonic-clonic seizures). The clinical manifestations of a particular seizure depend on the clinically eloquent structures of the brain that are activated.[1]

The clinical definition of epilepsy includes any of the following conditions: 1) at least two unprovoked seizures occurring >24 hours apart; 2) one unprovoked 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.[1] [2]

Epidemiology

Focal seizures are the most common seizure type in adults. Overall, more than half of seizures in the epilepsy population are focal; this applies across all age groups.

In 2016, the estimated number of people globally with active epilepsy was 45.9 million.[4] A 2017 systematic review and meta-analysis of international studies reported an incidence rate of epilepsy of 61.4 in 100,000 person-years.[5] In high-income countries, age-specific incidence of epilepsy is highest in people under age 20 years (especially those in the first few months of life), and in adults >60 years, with the lowest incidence in the intervening years.[6] The incidence of epilepsy is somewhat higher for men.

The 2016 Global Burden of Disease study reported an age-standardized prevalence of epilepsy of 622 in 100,000 population.[4] A similar estimate of 638 in 100,000 was reported in a 2017 review, with a pooled point prevalence of 299 in 100,000 for focal seizures.[5] Prevalence is reported to increase with age, with peaks at 5-9 years and >80 years.[4]

The reported incidence and prevalence of epilepsy is higher in low/middle-income countries than in high-income countries.[4] [5] Prevalence in the Global Burden of Disease study varied from a low of 311 in 100,000 population in Japan to a high of 1288 in 100,000 population in Cape Verde. These differences may be due in part to differences in factors such as mortality, etiology (e.g., number of central nervous system infections), treatment, and study methodology.[4] [5]

Etiology

Despite improvements in diagnostic technologies, the etiology of focal seizures is identified in only about one third of cases.

Any insult to the brain may result in the development of focal epilepsy. Examples include:

- Traumatic brain injury.[7] Penetrating head injuries have the highest risk for the development of epilepsy.[8] Closed head injury (skull fracture or >30 minutes of unconsciousness or amnesia) leads to a significantly increased risk for the development of seizures.[9] Risk may be slightly elevated even if amnesia lasts less than 30 minutes.[10]
- Central nervous system (CNS) infection.[11] The presumed mechanism is an inflammatory process involving the CNS. The more severe the CNS infection, the more likely it is to contribute to seizure development.
- Brain tumors. Epilepsy is common in patients with glioneuronal tumors and glioma, and is also associated with meningioma and brain metastases.[12] Low-grade tumors seem more epileptogenic than high-grade tumors.[12] [13] One case series suggested that 28% of patients undergoing surgery for brain tumors experience seizures.[14]
- Malformations of cortical development (MCDs). These are characterized by abnormal cortical structures or heterotopic gray matter resulting from disrupted cerebral cortex formation. The cause is mostly genetic, but infectious, vascular, and metabolic etiologies have also been reported. It is estimated that 25% to 40% of treatment-resistant childhood epilepsy is attributable to MCDs, and that at least 75% of patients with MCDs have epilepsy.[15] [16]
- Intracranial vascular malformations. Seizures are a common presentation in patients with intracranial vascular malformations such as arteriovenous malformations and cavernous angiomas. Seizures may occur de novo or be secondary to intracerebral hemorrhage.[17]

- Stroke. Risk of seizure activity is at least 3 times higher after stroke, but prophylactic anticonvulsant drug therapy is typically not recommended.[18] [19]
- Alzheimer disease and non-Alzheimer dementia. Both have been associated with seizure development.[20]
- Perinatal injury. This seems to be particularly the case when there is coexistent neurologic handicap with concomitant intellectual disabilities (e.g., cerebral palsy).[21]
- Family history. Related to the development of focal epilepsy, although this is not a simple relationship. Some syndromes are thought to be due to inheritance of a single gene (familial temporal lobe epilepsy), while others have a complex inheritance (idiopathic focal epilepsies and cryptogenic/symptomatic focal epilepsies).[22] [23]

Benign focal epilepsies of childhood are a group of idiopathic syndromes known to cause focal seizures in developmentally and neurologically normal children. They include benign childhood epilepsy with centrotemporal spikes and childhood epilepsy with occipital paroxysms.[24] These syndromes follow a benign course and usually remit prior to adulthood.

Neurocutaneous syndromes such as neurofibromatosis, Sturge-Weber syndrome, and tuberous sclerosis may result in focal or generalized seizures.

Pathophysiology

The pathophysiology of human epilepsy is complex and not completely understood. Experimental studies in animal models of epilepsy have elucidated potential pathophysiologic mechanisms; e.g., kindling, a process by which repeated subthreshold electrical stimulation of specific neuroanatomic structures (e.g., amygdala, hippocampus) leads to the development of electrographic and then focal clinical seizures, which worsen in severity over time. The kindling model has been used to study the process of epileptogenesis related to certain types of focal epilepsy.[25]

After a causative event (e.g., significant head trauma) there may be a latent period (and sometimes a second "hit") before clinical development of seizures.

Neurochemical and neurophysiologic features thought to be relevant to the development of focal seizures include:

- Neurotransmitter disturbances (e.g., an imbalance between inhibitory gamma-aminobutyric acid [GABA]-ergic and excitatory glutaminergic neurotransmitters)
- Alterations in neuronal and glial cell structures, such as voltage-gated sodium channels, voltage-gated calcium channels, gap junctions (connexins), SV2A synaptic protein vesicles, G-protein-coupled receptors, A or M voltage-gated potassium channels, and ionotropic glutamate receptors.[26] [27] [28]

Several anticonvulsant medications target these mechanisms. Identifying other targets presents an opportunity for new drug development.

Classification

International League Against Epilepsy (ILAE) report of the Commission on Classification and Terminology, 2017[1] [3]

1. Focal-onset seizures

- Aware/impaired awareness (optional)
    - Motor-onset
        - Automatisms
        - Atonic
        - Clonic
        - Epileptic spasms
        - Hyperkinetic
        - Myoclonic
        - Tonic
    - Nonmotor-onset
        - Autonomic
        - Behavior arrest
        - Cognitive
        - Emotional
        - Sensory
- Focal to bilateral tonic-clonic

2. Generalized-onset seizures
3. Unknown-onset seizures.

In 2017, ILAE guidelines for seizure classification were revised to include the following:

- "Partial" becomes "focal"
- Awareness is used as a classifier of focal seizures
- The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated
- New focal seizure types include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional
- Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset
- Focal to bilateral tonic-clonic seizure replaces secondarily generalized seizure
- New generalized seizure types are: absence with eyelid myoclonia, myoclonic absence, myoclonic-atonic, myoclonic-tonic-clonic
- Seizures of unknown onset may have features that can still be classified.

Case history

Case history #1

An 18-year-old girl presents with several episodes of confusion over the past several months. Typically, she experiences a warning signal, which she describes as a rising sensation within her abdomen that travels upward through her chest. She is usually unaware for a few minutes, but others have told her that during these episodes she smacks her lips, picks at her clothing, and is unable to speak. After the event, she feels tired, has a headache, and prefers to lie down. She notes that her memory has not been as good as it was in the past, and her school grades have declined. Her medical history is notable for several febrile seizures as a young child, although she was not treated for seizures at that time. An aunt was diagnosed with seizures many years ago.

Case history #2

A 70-year-old man presents with a tonic-clonic seizure. His wife states that during the past month there have been times when he does not respond when spoken to, mumbles words that do not make sense, and stares in a motionless way. After several minutes, he is usually responsive. His past medical history includes hypertension and hypercholesterolemia. He had a stroke during the preceding year, which resulted in weakness of the right extremities and loss of expressive language. Although he recovered most motor and language deficits, he still walks with a limp on the right side and sometimes uses the wrong word.

Other presentations

Patients may present complaining of features consistent with auras, such as memory-related phenomena (déjà vu, jamais vu), emotional changes (fear, panic, anxiety), autonomic changes (flushing, pallor, sweating, piloerection, warmth, coolness), visual distortions (changes in depth perception, shapes, or colors) or hallucinations (seeing formed and unformed shapes, objects, or people), auditory hallucinations (ringing sensations, tunes), or gustatory or olfactory changes. These symptoms may or may not be followed by alteration of awareness.

An alternative presentation is repeated focal impaired awareness seizures without recovery between them. These may or may not evolve to bilateral tonic-clonic seizures, and can present as behavioral changes only, which can be interpreted as a confused state. This constitutes status epilepticus (please refer to our topic "Status epilepticus").

Approach

History is the mainstay of the diagnosis of focal epilepsy. Clinical examination often reveals no obvious abnormality.

Electroencephalogram (EEG) and various imaging techniques may be helpful, although results are frequently normal and these tests mainly serve as supportive investigations.

History

History-taking is the most important aspect of focal seizure diagnosis, yet probably the most difficult to do. As the person experiencing the focal seizure is often unaware of what happens during the seizure, it is important to ask a witness, such as a partner, parent, sibling, or friend, to describe the events. This can be assisted by the witness videoing the events with a smartphone.

Warning symptoms and limb movements

When questioning the patient it is important to ask about warning symptoms, such as abnormal sensations of taste, smell, touch, psychic phenomena (including déjà vu [the sensation of having previously experienced something new] and jamais vu [temporarily not recognizing a familiar object or person]), abdominal sensations, and the inability to speak. It should be established whether the episodes involve movements of one or both limbs on one side of the body or all four limbs, in order to distinguish a focal seizure from a generalized event.

Focal impaired awareness seizure

To investigate the possibility of a focal impaired awareness seizure (seizure with impaired consciousness), the physician should ask about purposeless actions known as automatisms (picking at clothes, smacking of the lips), inability to follow commands, and whether the patient stares and becomes unaware of their surroundings. Whether memory loss occurred should also be established. The duration of the spells should be clarified, as most focal impaired awareness seizures last 30-90 seconds.

Medical history

A detailed medical history should be sought. History of head injury, recent central nervous system (CNS) infection, and previous stroke or brain tumor should be established.

Family history of a seizure disorder or any neurocutaneous syndromes (e.g., tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome) should also be discussed.

Physical exam

The physical exam is often normal; however, the possibility of focal seizures increases if abnormalities are detected on neurologic exam. For example, the patient may have a postictal hemiparesis (Todd paralysis), suggestive of a focus in the opposite hemisphere. For patients who are not postictal, a fixed neurologic deficit (hemiparesis, unilateral facial weakness) often suggests an underlying structural CNS lesion, which may be associated with focal seizures.

Skin exam should be performed to look for evidence of neurocutaneous syndromes. For instance, the presence of ash-leaf spots, shagreen patches, facial angiofibromas, and/or periungual fibromas is often

indicative of tuberous sclerosis. Café au lait spots, axillary freckling, and/or fibromas are suggestive of neurofibromatosis. Port-wine stain is associated with Sturge-Weber syndrome.

Laboratory studies

After a first-time seizure, possible provoking stimuli should be investigated.[36] Laboratory tests include:

- Electrolyte panel (including sodium, magnesium, and calcium levels): can identify electrolyte disturbances, uremia, and other metabolic abnormalities that may precipitate a seizure episode
- Blood glucose: to detect glucose derangements
- Complete blood count: may reveal signs of systemic or CNS infection
- Toxicology screen: useful if use of illicit substances is suspected
- Lumbar puncture: helpful if patient has fever, and CNS infection is suspected; contraindicated without prior neuroimaging if the patient has a depressed level of consciousness.

EEG

All patients with a suspected seizure should have an EEG. Although not necessarily diagnostic, it helps support a diagnosis of focal epilepsy.[37] Other indications include worsening seizure control, new seizure type, patients who have recently switched medication and continue to have seizures, and unknown epilepsy type.

All EEG studies for evaluating suspected epileptic seizures should include awake and sleep recordings, because epileptiform activity is more likely to be recorded during sleep.

Interictal epileptiform discharges (IEDs)

IEDs, represented by spikes or sharp waves, are the most frequent electrographic abnormality identified in routine EEG studies for people with a history of epilepsy.

The sensitivity of the first routine EEG to identify IEDs is approximately 50%, with sensitivity approaching 90% by the fourth EEG or following a 24- to 48-hour continuous EEG study.[38] Therefore, approximately 10% of patients with epilepsy do not demonstrate IEDs on EEG.

Of note, IEDs are seen in 3% of children and 0.5% of adults who do not have a history of epilepsy.[38] The yield of the EEG may be increased by sleep, sleep deprivation, hyperventilation, or photic stimulation, or by placement of additional electrodes to the standard international 10-20 system.

Neuroimaging

CT head

In the emergency department, on an urgent basis, a computed tomography (CT) scan of the head is performed.[39] This is of value in determining acute causes of seizures, such as traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, or large structural brain lesions. However, CT results may provide limited information, as a bony streak artifact obscures the temporal lobe, which is the most epileptogenic region of the brain. In patients with a known diagnosis of epilepsy, it is not necessary to repeat CT head if they experienced a seizure and were taken to the emergency department.

MRI brain

In the nonacute setting, magnetic resonance imaging (MRI) of the brain is performed with and without gadolinium contrast.[40] [41] [42] 3-Tesla MRI may lead to increased diagnostic yield. MRI (especially

with thin sections through the temporal lobe) identifies small but physiologically important anatomical abnormalities, including mesial temporal sclerosis, neoplastic lesions, vascular malformations (e.g., cavernous malformations), and developmental lesions (e.g., focal cortical dysplasia, nodular heterotopia, schizencephaly and polymicrogyria, as well as hemimegalencephaly).[43] The identification of these pathologies in patients with treatment-resistant focal epilepsy is essential in the planning of surgery.

Other imaging studies

Positive emission tomography (PET) scan, single photon emission computed tomography (SPECT) scan, functional MRI scan, and magnetoencephalography (MEG) scan are mainly used in the detailed planning for epilepsy surgery. While not required in the initial workup of epilepsy, these techniques provide important complementary information toward the identification of the epileptogenic zone and valuable functional localization of language and motor cortex.

Functional MRI may be used for language lateralization prior to epilepsy surgery.[44] [45] [46] It may also be used to predict memory decline.[47] [48]

Video/EEG long-term monitoring

May be useful for those who have had workup as outpatients and for whom the diagnosis of focal seizures remains uncertain.

The patient is admitted to the epilepsy monitoring unit for continuous video and simultaneous EEG monitoring. The goal is to record the patient's typical clinical events. In addition, the increased EEG sampling may reveal evidence of interictal abnormalities (spikes and sharp waves), which may make the diagnosis of focal seizures more likely.

Alternatively, video/EEG long-term monitoring (LTM) may be used as part of the workup for localization of seizure onset in patients with treatment-resistant focal epilepsy who are being considered for epilepsy surgery. The yield of video/EEG LTM in patients with a normal routine EEG is 25% to 40%.[39] If video/EEG LTM is required for presurgical evaluation, it is important to record all of the patient's seizure types, and to record multiple seizures in an attempt to localize the seizure focus.

Supportive tests

Neuropsychologic testing is a comprehensive evaluation of cognitive function (including the various modalities of memory, language, and attention) and visual spatial processing. Deficits in any of these spheres may be observed in patients with treatment-resistant focal epilepsy. For example, memory disturbances may be identified in patients with temporal lobe epilepsy, while attention problems are more common in patients with frontal lobe epilepsy. Patterns of deficits may emerge, which may support the results of the other tests, and help localize the epileptogenic focus prior to surgery.

The Wada test (intracarotid amobarbital test), which is used to confirm the lateralization of language and to discern memory dominance prior to epilepsy surgery, has increasingly been replaced by functional MRI.[46] [47] The Wada test may, however, be indicated when there is a high risk of postsurgical global amnesia (despite its reliability for this purpose being questioned) or when functional MRI fails to show clear left-lateralization.[44] [45] [48]

History and exam

Key diagnostic factors

movement of one side of the body or one specific body part (common)

- A focal seizure is characterized by localized brain activity, which is represented by motor activity of the head (presenting as forced head and gaze deviation to one side) or dystonic posturing of a hand. The epileptogenic area is in the hemisphere contralateral to the side of the head/gaze deviation and/or the dystonic hand.

premonitory sensation or experience (fear, epigastric sensation, déjà vu, jamais vu) (common)

- A premonitory sensation or sequence of sensations more likely indicates a focal seizure most often associated with temporal lobe origin.

automatisms (picking at clothes, smacking of the lips) (common)

- Suggests a focal impaired awareness seizure.

temporary aphasia (common)

- A postictal aphasia can be seen after focal seizures that involve the language centers. This does not necessarily imply that the seizure originated in the dominant hemisphere, as a seizure can originate in the nondominant hemisphere and propagate to the dominant hemisphere, causing a postictal aphasia.
- If the first symptom is expressive and/or receptive aphasia, the epileptogenic area most likely originated in the dominant hemisphere. If the patient speaks during the seizure, the epileptogenic area is likely to be in the nondominant hemisphere.

staring and being unaware of surroundings (common)

- Suggests a focal impaired awareness seizure.

Other diagnostic factors

postictal focal neurological deficit (Todd paralysis, aphasia) (common)

- A postictal paralysis or weakness on one side of the body suggests a focal seizure, and generally indicates that the seizure focus is contralateral to the side of the deficit.

persistent focal neurological deficit (common)

- Associated with central nervous system dysfunction, and suggests the presence of focal seizures.
- May also indicate a recent or previous stroke. On examination, there may be visual loss, language dysfunction, and sensory neglect, associated with weakness or numbness of one side of the body.

poor memory (uncommon)

- Although there are many causes of poor memory, one possibility is the presence of undiagnosed or uncontrolled focal impaired awareness seizures.

stigmata of neurocutaneous syndromes (uncommon)

- Some physical signs (neurocutaneous findings) may suggest an underlying neurologic disease associated with seizures. For instance, the presence of ash-leaf spots, shagreen patches, facial

angiofibromas, and/or periungual fibromas is often indicative of tuberous sclerosis. Café au lait spots, axillary freckling, and/or fibromas are suggestive of neurofibromatosis. Port wine stain is associated with Sturge-Weber syndrome.

Risk factors

Strong

febrile seizure

- The risk of developing epilepsy is greater if there is a history of febrile seizures.[29] [30]
- A distinction is often made between simple febrile seizures (generalized, <15 minutes, in a neurologically normal child aged between 6 months and 6 years, not due to meningoencephalitis) and complex febrile seizures (multiple or focal, and lasting >15 minutes). Unprovoked focal-onset seizures are more likely to be associated with complex febrile seizures.[31]
- Febrile seizures may contribute to the development of mesial temporal sclerosis (loss of neurons and scarring of the temporal lobe associated with certain brain injuries, closely related to temporal lobe epilepsy), but it has not yet been determined if this is causative or a result of the seizures.[32]

traumatic brain injury

- The more severe the head injury, the greater the risk of developing seizures. Penetrating head injuries carry the greatest risk.[8] Closed head injury (skull fracture or >30 minutes of unconsciousness or amnesia) leads to a significantly increased risk for the development of seizures.[9] Risk may be slightly elevated even if amnesia lasts less than 30 minutes.[10]
- The presumed mechanism is trauma-induced injury or scar that sets up an epileptogenic focus.

central nervous system (CNS) infection

- The more complicated the CNS infection, the more likely it is to contribute to seizure development. Meningoencephalitis has been associated with a 16-fold increased risk for focal seizure, bacterial meningitis a fourfold increased risk, and aseptic meningitis a twofold increased risk.[33] The presumed mechanism is an inflammatory process involving the CNS.
- Focal epilepsy can result from infections with parasites such as neurocysticercosis, toxoplasmosis, and malaria. Neurocysticercosis is a common cause of epilepsy worldwide; it should be considered in any patient who grew up or has spent time in an area of the world known to have high rates of neurocysticercosis, notably Latin America, Africa, and India.[11] [34]

stroke

- Risk of developing focal epilepsy is at least 3 times higher after a stroke.[18]
- The presumed mechanism is central nervous system cortical injury. The risk is higher with hemorrhagic than with ischemic stroke.[19] Clinically undetectable cerebrovascular disease can present with seizures, and these may be a warning sign for a future stroke.[35]

brain tumor

- The tumor (especially if infiltrative) may result in the development of an epileptogenic focus.
- Epilepsy is common in patients with glioneuronal tumors and glioma, and is also associated with meningioma and brain metastases.[12] Low-grade tumors seem more epileptogenic than high-grade tumors.[12] [13] One case series suggested that 28% of patients undergoing surgery for brain tumors experience seizures.[14]

intellectual disability and/or cerebral palsy

- One study found that in children with intellectual disability alone, the cumulative risk of developing seizures by age 22 years was 5%. In children with intellectual disability and cerebral palsy, the cumulative risk rose to 38%.[21] Children with a postnatal injury in addition to intellectual disability had a cumulative risk for seizure development (postinjury) of 66%.[21] The more severe the brain insult, the more likely the development of an epileptogenic focus.

dementia

- Both Alzheimer disease and non-Alzheimer dementia have been associated with seizure development.[20]

family history of seizures

- Family history is related to the development of focal epilepsy, although this is not a simple relationship. Some syndromes are thought to be due to inheritance of a single gene (familial temporal lobe epilepsy), while others have a complex inheritance (idiopathic focal epilepsies and cryptogenic/symptomatic focal epilepsies).[22] [23]

intracranial vascular malformations

- Seizures are a common presentation in patients with intracranial vascular malformations such as arteriovenous malformations and cavernous angiomas. Seizures may occur de novo or be secondary to intracerebral hemorrhage.[17]

malformations of cortical development (MCDs)

- MCDs are characterized by abnormal cortical structures or heterotopic gray matter resulting from disrupted cerebral cortex formation. The cause is mostly genetic, but infectious, vascular, and metabolic etiologies have also been reported. It is estimated that 25% to 40% of treatment-resistant childhood epilepsy is attributable to MCDs, and that at least 75% of patients with MCDs have epilepsy.[15] [16]

Weak

male sex

- Slightly more common in males.

Tests

1st test to order

Test	Result
blood glucose • An important initial test. Hypoglycemia and hyperglycemia should be excluded in patients presenting with a first seizure episode.[36]	**extreme hypoglycemia or hyperglycemia can cause provoked focal seizures**
CBC • Helpful in establishing an underlying systemic or central nervous system infection.[36]	**elevated WBC can indicate a central nervous system infection**
electrolyte panel • Electrolyte disturbances (including uremia, decreased/elevated sodium, and magnesium or calcium abnormalities) should be excluded in patients presenting with a first seizure episode.[36]	**possible electrolyte disturbances**
toxicology screen • Indicated if use of illicit substances is suspected.[36]	**variable**
lumbar puncture and cerebrospinal fluid analysis • Indicated when a central nervous system infection is suspected (fever present) as the underlying cause of the seizure episode.[36] • Contraindicated without prior neuroimaging if the patient has a depressed level of consciousness.	**evidence of excessive WBCs; elevated protein and/or low glucose may be present if central nervous system infection**
CT head • Usually ordered when a patient presents in the emergency department with a first seizure episode.[39] It is useful for identifying acute causes of seizures, but is less sensitive for smaller abnormalities often seen on MRI.	**intracranial hemorrhage; skull fracture; presence of structural lesion**
MRI brain • Regarded as the test of choice in the workup of focal seizures.[40] [41] It can be ordered initially (usually first test ordered when patient presents in the office), or obtained after head CT (usually first test ordered when patient presents in the emergency room). • Sensitivity of the MRI may be increased by using gadolinium enhancement or thin coronal sections without skips through the temporal lobes, with fluid-attenuated inversion recovery (FLAIR) sequences. • Developmental lesions include focal cortical dysplasia, nodular heterotopia, schizencephaly, polymicrogyria, and hemimegalencephaly.	**anatomic temporal lobe abnormalities (mesial temporal sclerosis, neoplastic lesions, vascular malformations, and developmental lesions)**
electroencephalogram (EEG) • Useful in the initial workup of focal seizures. Overall, the sensitivity of the first routine EEG is about 50%; this increases to 90% after 4 EEGs or following a 24- to 48-hour continuous EEG study.[38] However, a normal EEG does not exclude a diagnosis of epilepsy.	**focal spikes or sharp waves with associated slowing of the electrical activity in the area of the spikes**

Other tests to consider

Test	Result
video/electroencephalogram (EEG) long-term monitoring (LTM) • Not required in the initial investigation, but may be useful in a number of clinical situations; for example, to confirm the diagnosis when there is uncertainty (and when there is no response to usual therapy), as well as in the surgical workup for treatment-resistant focal epilepsy.	**capturing seizure activity simultaneously on video recording and EEG; increased EEG sampling may reveal evidence of interictal abnormalities (spikes and sharp waves), which may make the diagnosis of focal seizures more likely**
PET scan • Performed as part of the surgical evaluation of treatment-resistant focal epilepsy.[49]	**ictal: hypermetabolic; interictal: hypometabolic**
single photon emission computed tomography (SPECT) scan • Performed as part of the surgical evaluation of treatment-resistant epilepsy. For an ictal SPECT scan, a radioactive tracer such as 99m-Tc-HMPAO is injected at the onset of the seizure, and the patient is scanned. This is compared with a scan taken when the patient is seizure-free (interictal scan).	**ictal SPECT shows increased vascular perfusion in the region of seizure onset compared with interictal SPECT**
functional MRI scan • Not required in the initial workup of seizures. • Functional MRI may be used for language lateralization prior to epilepsy surgery.[44] [45] [46] It may also be used to predict memory decline.[47] [48]	**area of seizure activity and brain functions localized**
magnetoencephalography (MEG) scan • Not required in the initial workup of seizures. • May provide important complementary information toward the identification of the epileptogenic zone and possible functional localization of language and motor cortex, so used mainly in detailed planning for epilepsy surgery.	**epileptic focus localized**
neuropsychological testing • A comprehensive evaluation of memory, language, and intellectual function. Deficits in all these spheres are common in patients with treatment-resistant epilepsy. Patterns of deficits may emerge, which may support the results of the other tests, and help to localize the epileptogenic focus.	**deficits in language or memory, localized to an area of the brain**
Wada test • The Wada test (intracarotid amobarbital test), which is used to confirm the lateralization of language and to discern memory dominance prior to epilepsy surgery, has increasingly been replaced by functional MRI.[46] [47] • The Wada test may, however, be indicated when there is a high risk of postsurgical global amnesia (despite its reliability for this purpose being questioned) or when functional MRI fails to show clear left-lateralization.[44] [45] [48] • The test involves inactivating one hemisphere of the brain at a time for a 3- to 5-minute period with an intracarotid administered barbiturate agent (e.g., methohexital), and testing the "awake" side	**language localized to the left hemisphere; memory intact on the right, but reduced on the left, in a patient with presumed left mesial temporal sclerosis**

Test	Result
using cards with images and words. It is important to demonstrate that memory is supported by the side of the brain opposite the suspected seizure focus. The presence of a poor memory function on the side presumed to be the epileptogenic focus suggests that additional memory deficit post surgery is less likely.	

Emerging tests

Test	Result
7T MRI scan • Studies have demonstrated the added value of 7T MRI (compared with 1.5 and/or 3T MRI) in patients with and without known epileptogenic lesions.[50] • Currently used mostly as a research tool; not commonly available in clinical practice.	**identifies structural brain lesions**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Syncope	• Refers to the sudden loss of muscle tone, posture, and consciousness associated with reduced systemic BP. • There is often a prodrome with a feeling of nonspecific sickness, which may be associated with nausea, vertigo, and skin pallor. • Typical attacks last about 10 seconds, without a postictal period. • Tussive syncope is brought about by a coughing spell. • Convulsive syncope is similar to syncope, but is followed by spasm of the torso and limbs, clenching of the fists, brief shaking, and, rarely, tongue biting and incontinence. • Family history may be positive for syncope. Documentation of low BP during an attack is often helpful.	• Electroencephalogram often shows nonspecific diffuse slowing or attenuation. • ECG may show an arrhythmia, premature ventricular contractions, or even asystole. • A tilt table test may reproduce the patient's symptoms, and therefore be diagnostic. However, occasionally patients with seizures may also have abnormal tilt table tests.
Transient ischemic attack (TIA)	• May involve sensory, motor, speech, vestibular, or memory symptoms, and lasts <20 minutes. • There may rarely be brief limb shaking. • TIAs last longer than focal seizures and may be associated with an increase in BP; the symptoms can follow a particular arterial distribution (e.g., middle cerebral artery or vertebral artery).	• MRI brain may reveal presence of small vessel ischemic disease or past stroke. • The electroencephalogram (EEG) is often normal but not infrequently may reveal intermittent focal slowing. • Abnormalities in other aspects of the stroke evaluation including carotid artery patency, echocardiogram, and lipid profile.
Sleep disorders	• Sleepwalking or somnambulism starts 1 to 2 hours after sleep. The person walks about in a trance and may carry out purposeful activity. • Sleep terrors present with manifestations of fear during an arousal from slow-wave	• Simultaneous electroencephalogram is normal without evidence of epileptiform discharges or seizure activity.

Condition	Differentiating signs / symptoms	Differentiating tests
	sleep. Often heralded by a loud vocalization.	
Tic disorders	• Tics usually involve the head, neck, and shoulders, and may be complex movements. They may be temporarily suppressed. • Physical exam is typically normal, except for observed tics.	• Diagnostic studies in tic disorders are often normal. • Electroencephalogram features associated with epileptic seizures are absent.
Chorea	• Continuous, involuntary, rapid, random movements that tend not to be repeated stereotyped movements. • Chorea is commonly due to Sydenham chorea (one of the clinical manifestations of acute rheumatic fever).[51] [52]	• Diagnosis is usually based on history and physical exam.
Tremor	• Involuntary, oscillatory movement of a body part that is rhythmic compared with the movements due to focal seizures.	• Diagnosis is usually based on history and physical exam.
Migraine	• Suggestive features include a more severe, unilateral pulsatile headache, photo- and phonophobia, nausea, vomiting, and family history of migraine. • The aura of migraine is often longer (>5 minutes) and has a more gradual onset and offset.	• Brain MRI is either normal or reveals small, scattered white matter signal changes that do not enhance with gadolinium. • An electroencephalogram may reveal focal slowing (theta and delta) and is usually normal between headaches.
Transient global amnesia (TGA)	• Usually occurs in people older than 50 years. • Sudden onset of amnesia that lasts for several hours. • Patients maintain alertness, but are confused and ask questions repeatedly.	• MRI of the brain may be normal, or may show evidence of past pathology (e.g., old ischemic disease). Occasionally, unilateral or bilateral punctate restricted diffusion is seen in the hippocampus, but this is not necessary for diagnosis.[53] [54] [55] • The electroencephalogram is usually normal; slowing is also possible. • No test can definitively make the diagnosis of TGA.

Condition	Differentiating signs / symptoms	Differentiating tests
Meniere disease	• Episodic vertigo, tinnitus, nausea, and vomiting may occur. • A key differentiating factor is the presence of hearing loss, which exists even between attacks.	• Audiogram should be abnormal. • Electronystagmography is often abnormal.
Functional seizures (nonepileptic seizures)	• Episodes of altered movement, sensation, emotion, or experience that have the appearance of epileptic seizures, but are not caused by paroxysmal, hypersynchronous electrical activity of the brain.[56] • Functional seizures similar to focal impaired awareness seizures are common, but the clinical appearance of functional seizures may mimic virtually any seizure type. • Some features more likely to suggest functional seizures include: eyes being tightly closed, tearfulness, duration more than 2 minutes, hyperventilation during a seizure, and side-to-side head shaking.[57] • Functional seizures are usually considered a functional neurologic symptom disorder. Some patients will have had adverse life events, but, importantly, these are neither necessary nor sufficient for the diagnosis.[57] Psychological comorbidities - especially anxiety, panic, and depression - are common, affecting over 50% of patients.[58] • A significant minority of people with functional seizures will have coexistent epilepsy, so it is important to determine if the patient has a number of different types of spells.	• The only reliable diagnostic test to differentiate functional from epileptic seizures is video/electroencephalogram (EEG) (long-term monitoring). The EEG during functional seizures is either normal or obscured by movement or muscle artifact. The video during functional seizures allows the observer to view the details of the behaviors present. • Correct diagnosis is usually based on the semiology of the event and the absence of epileptiform EEG correlate.
Dissociative disorders	• Partial or complete loss of normal integration	• The electroencephalogram (EEG) is often normal

Condition	Differentiating signs / symptoms	Differentiating tests
	between past memories, immediate sensations, identity, and movements. Often senses derealization, depersonalization, and out of body experiences.	but may have nonspecific (nondiagnostic) findings, such as focal or diffuse slowing. • Video EEG may be helpful in characterizing the notion that the abnormal experience does not represent focal seizures.
Panic attacks	• Subjective sense of dread, with acute onset of autonomic symptoms such as palpitations, sweating, nausea, paresthesias, feeling faint, and abdominal or chest discomfort; often lasting 10 to 30 minutes. • Consciousness is rarely lost, and derealization, as well as depersonalization, is more common with panic attacks than with focal seizures. • Panic attacks are more common in younger age groups but may occur at any age.	• Clinical diagnosis. • Neuroimaging and electroencephalogram (EEG) are usually normal with panic attacks. • There should be no ictal EEG changes during video/EEG monitoring.

Approach

The main goal of treatment is to achieve maximum seizure control as efficiently as possible (preferably with monotherapy) with no or minimal adverse effects. A structured approach to treatment is helpful.

Acute management of status epilepticus (defined as either 5 minutes or more of continuous seizure activity, or two or more discrete seizures between which there is incomplete recovery of consciousness), is beyond the scope of this topic. See Status epilepticus .

Treatment of acute repetitive seizures

Acute repetitive seizures (also known as seizure clusters) affect up to half of patients with epilepsy, and can significantly disrupt patients' lives, but their prevalence is underappreciated and seizure action plans are often lacking.[62] [63]

There is no well-established definition of acute repetitive seizures, which adds to the challenge of recognizing them.[64] One frequently used clinical definition is three or more seizures within 24 hours for patients whose habitual seizure frequency is fewer than three seizures per day, with return to full alertness between seizures. Other definitions include two or more seizures in 6 hours, two or more seizures in 24 hours, or two to four seizures in less than 48 hours.[64]

Caregivers should be trained to administer treatments as soon as possible in the community when the seizure clusters are identified, without the need for the patient to attend the hospital. Treatment options include diazepam rectal gel, intranasal formulations of midazolam and diazepam, and a buccal formulation of midazolam (available only in Europe). These benzodiazepine formulations have shown reasonable efficacy, equal to or better than that of intravenous formulations, in most patients. Oral benzodiazepines (e.g., lorazepam) can be used if the above formulations are not available or in patients in whom the rectal route is less favored (adults), provided that the patient is awake and cooperative, and the risk of aspiration is low or not a concern.[62] [63]

In a hospital setting, intravenous benzodiazepines and intravenous formulations of anticonvulsant medications such as phenytoin/fosphenytoin, valproic acid, levetiracetam, lacosamide, and brivaracetam can be used to treat acute repetitive seizures.

The patient should be continued on a suitable oral formulation of an anticonvulsant once stabilized.

Long-term treatment with anticonvulsants: principles

The decision to start anticonvulsant drug treatment following a first unprovoked seizure should be individualized and based on the patient's preference and circumstances.[65] Treatment of the first unprovoked seizure reduces the risk of a subsequent seizure, but does not improve the likelihood of sustained, long-term seizure remission.[65] [66]

Treatment should always be tailored to the needs of the patient, taking into account factors such as age and sex, any comorbidities and other medications, and drug properties. Any anticonvulsant may be used as first-line monotherapy if it is the most suitable choice for a particular patient.

When changing from one anticonvulsant to another, current and new medications should be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). The pharmacokinetic profile of each drug should be researched before instructing the patient on how to switch. A written schedule helps patient adherence. Dose should

be adjusted according to response and serum drug level. Patients should be advised that there is an increased risk of seizures during the transition period.

Long-term treatment: choice of anticonvulsant

The efficacy of anticonvulsants has been established in multicenter, randomized, double-blind, placebo-controlled trials. However, the number of head-to-head trials is limited.[67] The available data suggest that anticonvulsants used to treat focal seizures have comparable efficacy. Therefore, the choice of anticonvulsant should focus on tolerability and be individualized. In particular, the following should be taken into account:[68]

- The age and sex of the patient (including, for women, whether they are of childbearing potential)
- The underlying etiology of the focal seizures
- The pharmacokinetic properties, mechanism of action, and available formulations of the drug (e.g., extended-release formulations)
- Comorbidities and any other medication the patient is taking.

Typically, newer anticonvulsants are associated with fewer, less severe adverse effects, as well as fewer drug-drug interactions.[68] [69]

Considerations in relation to comorbidities and drug properties include the following:

- For patients with psychiatric comorbidities: levetiracetam, brivaracetam, topiramate, zonisamide, and perampanel should only be used with great caution and with close monitoring for recurrence or exacerbation of psychiatric symptoms.
- For patients with cognitive problems: topiramate and zonisamide should only be used with great caution.
- For patients with renal impairment: levetiracetam should be used with caution and on the advice of a specialist neurologist, since this drug is cleared exclusively by the kidney.
- For patients who may have underlying liver disease or other comorbidities requiring multiple drug therapy, including P450 enzyme-inducing medication: levetiracetam, gabapentin, and pregabalin may help minimize effects on the liver and reduce the potential for drug-drug interactions. Valproic acid, phenobarbital, phenytoin, and felbamate should not be offered.
- For patients with migraine as well as focal seizures: topiramate and valproic acid are both effective as migraine prophylaxis.
- For patients with neuropathic pain: anticonvulsants with efficacy for certain neuropathic pain conditions (the most common of which is painful diabetic neuropathy) include gabapentin, pregabalin, oxcarbazepine, and carbamazepine.[70] [71] [72]
- Anticonvulsants associated with weight gain include valproic acid, gabapentin, and pregabalin, and these should be used with great caution in patients with obesity. Those associated with weight loss include topiramate and zonisamide. For the most part, other anticonvulsants are considered not to affect body weight.
- Anticonvulsant dose adjustment and/or slower titration may be needed (e.g., for people with renal or hepatic impairment).

Dual therapy

Considerations for choosing two anticonvulsants to use in combination include:

- Maximizing therapeutic efficacy by using drugs with different mechanisms of action
- Minimizing pharmacokinetic and pharmacodynamic drug interactions.

Few clinical trials provide data on which combinations may be more effective or preferable.

Adults <60 years old (long-term treatment)

Additional considerations for women of childbearing potential and pregnant women are discussed in a separate section below.

Anticonvulsant monotherapy (adults <60 years old)

A trial of anticonvulsant monotherapy is indicated if the patient has had at least two spontaneous seizures, or one seizure with one of the following: epileptiform activity on electroencephalogram (EEG); structural pathology on brain magnetic resonance imaging (MRI) or computed tomography (CT); seizure out of sleep; focal onset indicated by semiology (i.e., head turning or gaze deviation).[73]

Lamotrigine, levetiracetam, and oxcarbazepine are suitable first-line anticonvulsants for monotherapy.[74] [75] [76] [77] [78] [79] Results from a pragmatic randomized controlled trial suggest that the adverse reaction profile of lamotrigine may be superior to that of levetiracetam in patients (>5 years of age) with two or more unprovoked seizures.[80]

Other treatment options include lacosamide, eslicarbazepine, brivaracetam, zonisamide, carbamazepine, valproic acid, topiramate, perampanel, and cenobamate.[77] [81] [82] Brivaracetam is a derivative of levetiracetam with higher binding affinity for the presynaptic SV2 protein. Behavioral adverse events are likely to be less frequent and less severe with brivaracetam than with levetiracetam, except in patients with a history of psychiatric comorbidities.[83] [84] [85] [86]

Gabapentin and pregabalin are appropriate options for patients with particular comorbidities (e.g., psychiatric comorbidities, hepatic impairment, migraine, neuropathic pain).

Alternative anticonvulsant monotherapy (adults <60 years old)

If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that is suitable for this population. A drug with a different mechanism of action should be considered. If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance.

Anticonvulsant dual therapy (adults <60 years old)

If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated using:

- A combination of two monotherapy options, or
- An anticonvulsant that is used primarily for adjunctive treatment (e.g., clobazam) in combination with one of the monotherapy options.

A combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects, should be used.[72] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103]

Other adjunctive therapies are available, including rufinamide, vigabatrin, tiagabine, and felbamate.[104] [105] [106] [107] [108] However, rufinamide, vigabatrin, tiagabine, and felbamate are associated with severe adverse effects, and should only be considered when multiple other medications have been

attempted and surgery is deemed not to be an option. An epilepsy specialist should be involved if these agents are being considered.

Adults ≥60 years old (long-term treatment)

The incidence of new-onset seizures in older people is significant.[6] The decision to treat focal seizures in older people is often made after the first unprovoked seizure, because the likelihood of recurrence is higher, and the consequences for the patient of even a single seizure (e.g., falls/hip fracture) may be life-changing.

Anticonvulsant monotherapy (adults ≥60 years old)

Monotherapy administered at the lowest possible dose is preferred. Older patients are particularly susceptible to adverse effects and often have tolerability issues, especially at higher doses or with polytherapy. Age-related physiologic changes may contribute to lower rates of drug metabolism and erratic drug absorption, possibly leading to either toxicity or breakthrough seizures. In addition, many people over the age of 60 years have important medical comorbidities, and take a number of different medications.

Anticonvulsants with more favorable pharmacokinetics and adverse-effect profiles, such as lamotrigine, gabapentin, and levetiracetam, are usually the most appropriate choice for patients ≥60 years old. Other options include oxcarbazepine, lacosamide, eslicarbazepine, brivaracetam, pregabalin, carbamazepine, zonisamide, valproic acid, perampanel, and cenobamate.[77] [81] [82] Doses should be increased gradually according to patient response, and the patient should be closely monitored for signs of toxicity. Treatment should always be tailored to the individual patient.[109] [110] [111]

The pharmacokinetic properties of some anticonvulsants make them less desirable choices for treating focal seizures in older people. These anticonvulsants include drugs that are P450 enzyme inducers or inhibitors; have high protein binding; or are associated with cognitive adverse events.

Alternative anticonvulsant monotherapy (adults ≥60 years old)

If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that has proven efficacy for focal epilepsy in the older population. A drug with a different mechanism of action should be considered. If the first monotherapy agent is unsuitable due to intolerable adverse effects (which can be a particular issue in older patients), the alternative agent should be chosen with special consideration for the patient's health profile and tolerance.

Anticonvulsant dual therapy (adults ≥60 years old)

If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated after consultation with a specialist neurologist. Two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects, can be used.[72] [81] [82] [89] [90] [91] [93] [95] [96] [97] [98] [99] [102] [103] [105]

Women of childbearing potential and pregnant women (long-term treatment)

Care should be taken with anticonvulsant treatment for any woman of childbearing potential. A specialist should be consulted for guidance about choice of anticonvulsant for pregnant women. Women with epilepsy should receive preconception counseling.[112] [113] [114]

In particular:

- Avoid anticonvulsants with documented risks of major and minor fetal malformations or a negative impact on cognitive development, such as valproic acid, and its derivatives, topiramate, phenobarbital, and phenytoin.[114][115] [116] [117] The latest data on teratogenicity should be consulted.[114] Data on the teratogenic potential of newer anticonvulsants may not be available or may be limited.[118]
- For women taking birth control pills, avoid anticonvulsants with enzyme-inducing properties (e.g., carbamazepine, phenytoin, phenobarbital, primidone), as these can lower contraceptive efficacy and lead to an increased failure rate.[119]

Valproic acid and its derivatives

Valproic acid and its derivatives may cause major congenital malformations, including neurodevelopmental disorders and neural tube defects, after in utero exposure. These drugs are contraindicated in pregnancy; however, if it is not possible to stop them, treatment may be continued with appropriate specialist care.

- These agents must not be used in female patients of childbearing potential unless other options are unsuitable, there is a pregnancy prevention program in place, and certain conditions are met.
- Precautionary measures may also be required in male patients owing to a potential risk that use in the three months leading up to conception may increase the likelihood of neurodevelopmental disorders in their children.
- Regulations and precautionary measures for female and male patients may vary between countries, with some countries taking a more heightened precautionary stance, and you should consult your local guidance for more information.

If the patient is taking these drugs to prevent major seizures and is planning to become pregnant, the decision of continuing valproic acid versus changing to an alternate agent should be made on an individual basis.

Topiramate

One large cohort study reported an association between prenatal exposure to topiramate and increased risk of child neurodevelopmental disorders.[120] Topiramate exposure in pregnancy is associated with cleft lip and being small for gestational age.[114]

- In some countries, topiramate is contraindicated in pregnancy and in women of childbearing age unless the conditions of a pregnancy prevention program are fulfilled to ensure that women of childbearing potential: are using highly effective contraception; have a pregnancy test to exclude pregnancy before starting topiramate; and are aware of the risks associated with use of the drug.[121] [122]

Safety of other anticonvulsants in pregnancy

In 2021 the UK Medicines and Healthcare products Regulatory Agency (MHRA) published a review of the safety of the following anticonvulsants in pregnancy: carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide.

The review concluded that lamotrigine and levetiracetam, at maintenance doses, are not associated with an increased risk of major congenital malformations. Available studies do not suggest an increased risk of neurodevelopmental disorders or delay associated with in-utero exposure to lamotrigine or levetiracetam, but data are more limited.[114][118] A later study suggested an association between prenatal exposure to levetiracetam and attention-deficit hyperactivity disorder.[123]

Data for other drugs showed: an increased risk of major congenital malformations associated with carbamazepine, phenobarbital, and phenytoin; possible adverse effects on neurodevelopment of children exposed in utero to phenobarbital and phenytoin; and an increased risk of fetal growth restriction associated with phenobarbital and zonisamide. Risks associated with other anticonvulsants are uncertain due to lack of or limitations in the data.[118] [124] One subsequent MHRA study suggested that pregabalin might slightly increase the risk of major congenital malformations.[125] One systematic review reported adverse fetal and neonatal outcomes following in utero exposure to oxcarbazepine.[126]

For lamotrigine, levetiracetam, and any anticonvulsant that can be used during pregnancy, the MHRA recommends using monotherapy at the lowest effective dose, and provides monitoring advice.[118]

Anticonvulsant monotherapy (women of childbearing potential or pregnant)

Suitable anticonvulsants for women of childbearing potential and in pregnancy include lamotrigine and levetiracetam.[114][118] Other options include oxcarbazepine, lacosamide, and zonisamide.[114]

Alternative anticonvulsant monotherapy (women of childbearing potential or pregnant)

If monotherapy does not give adequate seizure control in a pregnant woman, referral to a specialist neurologist is recommended.

If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that is suitable for a woman of childbearing potential or a pregnant woman. A drug with a different mechanism of action should be considered. If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance.

Anticonvulsant dual therapy (women of childbearing potential or pregnant)

If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated. For pregnant women, consultation with a specialist neurologist is required.[114][127]

Two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects, can be used for dual therapy.[89] [90] [93] [97] [98] [99] [128]

Folic acid supplementation

Women with epilepsy should be advised to take high-dose folic acid before conception and during pregnancy.[113][127]

Folic acid supplementation (to help prevent neural tube defects in the developing fetus) is a routine recommendation for all women planning pregnancy, and any risk associated with folic acid supplementation is low. Evidence about the benefits of high-dose folic acid supplementation before and during pregnancy for women with epilepsy is inconclusive.[112] [114][129] [130]

Care of pregnant women

Pregnant women with epilepsy should be under the care of a multidisciplinary team that includes a high-risk obstetric specialist, and care should be coordinated through joint obstetric and neurology clinics.[113] However, risk of cesarean delivery, late pregnancy bleeding, premature contractions, or premature labor and delivery are probably not substantially increased in women taking anticonvulsant drugs who do not smoke.[131]

Monitoring of blood anticonvulsant levels is recommended, as pharmacokinetics are affected during pregnancy, and significant declines in levels may occur. Increased drug doses may be required.[132] [133]

An anatomic ultrasound should be performed between 14 and 18 weeks of pregnancy, and serum alpha-fetoprotein level measured, to check for possible fetal abnormalities. The need for amniocentesis is on a case-by-case basis.

Children (long-term treatment)

Treatment should be managed initially by a specialist pediatric neurologist. Guidelines for the acute treatment of seizures in children are largely independent of etiology, though hypoglycemia should never be overlooked.[134]

Once focal seizures are diagnosed in a child, determination of etiology is important for long-term treatment decisions. For example, certain syndromes, such as the subtype of localization-related/idiopathic epilepsy known as benign childhood epilepsy with centrotemporal spikes, are often accompanied by few seizures, are age dependent, and are usually self-limited. For this reason, some have advocated that no anticonvulsant treatment is necessary.[135]

In some cases (e.g., if seizure episodes are infrequent), it may be appropriate for the parent or caregiver to treat only the prolonged seizure with an acute therapy for aborting the seizure, such as rectal diazepam.

For the localization-related/symptomatic epilepsies (where etiologies such as malformations and other lesions are identified), focal seizures are often difficult to control. Early anticonvulsant treatment, often with polytherapy, is the norm in these situations.

Anticonvulsant monotherapy (children)

When selecting an appropriate anticonvulsant for a child, potential effects on cognition, learning, and behavior should be taken into account. For this reason, long-term treatment with anticonvulsants such as phenobarbital and phenytoin should be avoided.

Levetiracetam and oxcarbazepine are suggested as first-line options; they are effective, and a network meta-analysis of individual patients' data indicates that they have favorable profiles with regard to cognitive adverse effects.[136] Data on the cognitive effects of newer anticonvulsants may not be available or may be limited.

Other options for monotherapy in children include lamotrigine, lacosamide, eslicarbazepine, brivaracetam, carbamazepine, zonisamide, topiramate, perampanel, clobazam, and (other than for girls of childbearing potential) valproic acid.[81] [136] [137] [138]

Younger children often have more rapid clearance and variability in elimination kinetics of anticonvulsants; this must be factored into dosing regimens. Younger children may require liquid and/or chewable anticonvulsant formulations.

Alternative anticonvulsant monotherapy (children)

If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that is suitable for children. A drug with a different mechanism of action should be considered. If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance.

Anticonvulsant dual therapy (children)

If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated after consultation with a specialist pediatric neurologist. Two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects, can be used.[97] [98] [99] [105] [139] [140]

Treatment effectiveness and adherence

Only a relatively small percentage (less than 5%) of patients with persistent focal seizures become completely seizure-free after two separate monotherapy trials and/or a dual therapy trial with appropriate anticonvulsant medications at optimal doses. The likelihood of achieving freedom from seizures is not increased by further trials.[141] [142]

Determining treatment failure depends largely on baseline seizure frequency: it is easier to judge a lack of response in a patient who has six seizures a month than in someone who has six seizures a year. Medication adherence, the time frame for reaching therapeutic dosing, and drug tolerability also have to be taken into account.

Adherence with therapy is a challenge for many patients. Patients with relatively few seizures may have no ill effects if a single dose is missed but, with time, occasional missed doses may result in recurrent seizures. Some patients are nonadherent because of adverse effects, especially drowsiness and nausea. Others may have memory problems and cannot follow the medication regimen. Some patients cannot afford the cost of their medication and may, therefore, under-dose so that it lasts longer. Others may not like to take medication or may fear medication in general.

Ancillary treatment options

Avoiding sleep deprivation, alcohol, and excessive stress may be helpful at any stage of treatment, but cannot substitute for anticonvulsant drug therapy.

Evidence about nonpharmacologic interventions is limited. One 2020 Cochrane review found that adjunctive psychologic and self-management interventions improved quality of life and emotional wellbeing and reduced fatigue in adults and adolescents with epilepsy.[143] One 2019 systematic review

reported limited evidence that self-management strategies modestly improved some patient outcomes that are important to people with epilepsy.[144]

The International League Against Epilepsy Psychology Task Force recommends that psychologic interventions targeting improvements in quality of life and medication adherence, and a decrease in comorbidity symptoms (anxiety, depression), should be incorporated into comprehensive epilepsy care.[145]

Treatment-resistant epilepsy

For adults and children, failure of at least two anticonvulsants in combination (treatment-resistant or intractable epilepsy) should result in reassessment of the diagnosis. If the diagnosis is not secure, then reinvestigation, possibly with video/EEG monitoring, may be helpful.

If the focal seizure diagnosis is correct, and the patient is truly refractory to anticonvulsants, consideration and workup for epilepsy surgery or neurostimulation should be performed.[146] [147]

Consideration of these advanced options should be pursued at an epilepsy specialty center only.

Surgery

Candidates for epilepsy surgery include patients with lesions on brain MRI, or in whom the epileptogenic area can be localized to one region by a variety of techniques, including EEG. One Cochrane review reported that 64% of people who had surgery for epilepsy achieved a good outcome; however, the quality of evidence was low and the estimate across studies varied from 13.5% to 92.5%.[148]

Minimally invasive alternatives to traditional resective surgery include laser interstitial thermal therapy (LITT), radiofrequency ablation, and stereotactic radiosurgery.[149] [150]

Neurostimulation

If the patient has more than one epileptogenic focus, neurostimulation may be considered an alternative to surgery.[151] Options include vagus nerve stimulation and deep brain stimulation.[152] [153] [154] [155] [156]

Responsive neurostimulation (RNS) therapy, neuromodulation via a cranially implanted device, may be appropriate for some medically refractory patients for whom resective surgery is not a viable option.[157] [158] [159] [160]

Ketogenic diet

An option predominantly, but not exclusively, for children (not to be used in adults ≥60 years old). The ketogenic diet is high in fat and low in carbohydrates, and has been shown to reduce seizure frequency.[161] [162] [163] The diet must be initiated in the hospital, under close medical supervision, with monitoring for metabolic acidosis and renal calculi.

Drug discontinuation

Seizure freedom for long periods of time can occur with anticonvulsant therapy or after surgical treatment. Patients taking anticonvulsants who achieve seizure freedom may eventually wish to discontinue their medication to avoid the adverse effects, psychological implications, and cost of ongoing treatment.

There is no statistically significant evidence to guide the timing of anticonvulsant discontinuation in adults. For adults who have been seizure-free for at least 2 years, clinicians should discuss the risks and benefits of medication discontinuation with the patient, including the risks of seizure recurrence and treatment resistance. Individual patient characteristics and preferences should be taken into account. Patients who are seizure-free after epilepsy surgery and are considering medication discontinuation should be informed that the risk of seizure occurrence is uncertain due to lack of evidence.[164] [165] Abrupt medication discontinuation is inadvisable, but, beyond this, there is little evidence to guide the speed of medication taper in adults.[166]

For children who have been seizure-free for at least 18-24 months, and who do not have an electroclinical syndrome suggesting otherwise, discontinuation of anticonvulsant medication may be considered, as this does not clearly increase risk of seizure recurrence. The risks and benefits of discontinuation should be discussed with the patient and family. Provided that an EEG does not show epileptiform activity, discontinuation should be offered at a rate no faster than 25% every 10-14 days.[164]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
acute repetitive seizures: in the community		
	1st	**benzodiazepine**
acute repetitive seizures: in the hospital		
	1st	**intravenous benzodiazepine or anticonvulsant**

Ongoing		(summary)
adults <60 years old: nonpregnant or no risk of pregnancy		
	1st	anticonvulsant monotherapy
	2nd	alternative anticonvulsant monotherapy
	3rd	anticonvulsant dual therapy
	4th	resective epilepsy surgery or neurostimulation or ketogenic diet
adults ≥60 years old		
	1st	anticonvulsant monotherapy
	2nd	alternative anticonvulsant monotherapy
	3rd	anticonvulsant dual therapy
	4th	resective epilepsy surgery or neurostimulation
women of childbearing potential		
	1st	anticonvulsant monotherapy
	2nd	alternative anticonvulsant monotherapy
	3rd	anticonvulsant dual therapy
	4th	resective epilepsy surgery or neurostimulation or ketogenic diet
pregnant		
	1st	anticonvulsant monotherapy
	plus	folic acid
	2nd	alternative anticonvulsant monotherapy
	plus	folic acid
	3rd	anticonvulsant dual therapy
	plus	folic acid
children		
	1st	anticonvulsant monotherapy
	2nd	alternative anticonvulsant monotherapy
	3rd	anticonvulsant dual therapy
	4th	resective epilepsy surgery or neurostimulation or ketogenic diet

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

acute repetitive seizures: in the community

1st **benzodiazepine**

Primary options

» diazepam rectal: children 2-5 years of age: 0.5 mg/kg rectally as a single dose; children 6-11 years of age: 0.3 mg/kg rectally as a single dose; children ≥12 years of age and adults: 0.2 mg/kg rectally as a single dose
May repeat dose in 4-12 hours. Maximum 1 treatment every 5 days or up to 5 treatments per month.

OR

» diazepam nasal: children ≥6 years of age: consult specialist for guidance on dose; adults body weight 51-75 kg: 15 mg intranasally (one 7.5 mg spray into each nostril); adults body weight ≥75 kg: 20 mg intranasally (one 10 mg spray into each nostril)
May repeat dose after at least 4 hours. Maximum 2 doses per single episode and 1 episode every 5 days or up to 5 episodes per month.

OR

» midazolam nasal: children ≥12 years of age and adults: 5 mg intranasally (as one spray into one nostril)
May repeat dose once in opposite nostril after 10 minutes. Maximum 2 doses per single episode and 1 episode every 3 days or up to 5 episodes per month.

Secondary options

» lorazepam: children: consult specialist for guidance on dose; adults: 4 mg orally as a single dose, may repeat once after 10-15 minutes

Acute

» There is no well-established definition of acute repetitive seizures. One frequently used definition is three or more seizures within 24 hours for patients whose habitual seizure frequency is fewer than three seizures per day, with return to full alertness between seizures. Other definitions include two or more seizures in 6 hours, two or more seizures in 24 hours, or two to four seizures in less than 48 hours.[64]

» Caregivers should be trained to administer treatments as soon as possible when the seizure clusters are identified, without the need for the patient to attend the hospital. Treatment options include diazepam rectal gel, intranasal formulations of midazolam and diazepam, and a buccal formulation of midazolam (available only in Europe). These benzodiazepine formulations have shown reasonable efficacy, equal to or better than that of intravenous formulations, in most patients. Oral benzodiazepines (e.g., lorazepam) can be used if the above formulations are not available or in patients in whom the rectal route is less favored (adults), provided that the patient is awake and cooperative, and the risk of aspiration is low or not a concern.[62] [63]

acute repetitive seizures: in the hospital

1st **intravenous benzodiazepine or anticonvulsant**

Primary options

» diazepam: children: consult specialist for guidance on dose; adults: 5-10 mg intravenously every 5-10 minutes according to response, maximum 30 mg/total dose

OR

» lorazepam: children: consult specialist for guidance on dose; adults: 4 mg intravenously as a single dose, may repeat once after 10-15 minutes

OR

» phenytoin: children: consult specialist for guidance on dose; adults: 15-20 mg/kg intravenously as a loading dose, followed by an additional dose of 5-10 mg/kg according to response, maximum 30 mg/kg/total loading dose

OR

Acute

» fosphenytoin: children: consult specialist for guidance on dose; adults: 15-20 mg (phenytoin equivalents)/kg intravenously as a loading dose, followed by an additional dose of 5-10 mg (phenytoin equivalents)/kg according to response, maximum 30 (phenytoin equivalents)/kg/total loading dose Fosphenytoin dose expressed as phenytoin equivalents.

OR

» valproic acid: children: consult specialist for guidance on dose; adults: 20-40 mg/kg intravenously as a single dose, may give an additional dose of 20 mg/kg according to response, maximum 3000 mg/dose

OR

» lacosamide: children and adults: consult specialist for guidance on dose

OR

» levetiracetam: children and adults: consult specialist for guidance on dose

OR

» brivaracetam: children and adults: consult specialist for guidance on dose

» There is no well-established definition of acute repetitive seizures. One frequently used definition is three or more seizures within 24 hours for patients whose habitual seizure frequency is fewer than three seizures per day, with return to full alertness between seizures. Other definitions include two or more seizures in 6 hours, two or more seizures in 24 hours, or two to four seizures in less than 48 hours.[64]

» In a hospital setting, intravenous benzodiazepines and intravenous formulations of anticonvulsants such as phenytoin/fosphenytoin, valproic acid, levetiracetam, lacosamide, and brivaracetam can be used. Choice of medication should take into account the age and sex of the patient, and any comorbidities. The patient should be continued on a suitable oral formulation of an anticonvulsant once stabilized.

Acute

» Pregnant women with epilepsy should be under the care of a multidisciplinary team that includes a high-risk obstetric specialist.[112] [113] [114] Choice of anticonvulsant needs to balance the risks of seizures to the health of the woman and fetus against potential teratogenic effects of the drug treatment, and should be guided by specialist advice.[114] Some anticonvulsants are contraindicated in pregnancy due to an increased risk of major congenital malformations and/or child neurodevelopmental disorders (e.g., valproic acid and its derivatives, topiramate, phenobarbital, phenytoin).[115] [116] [117] [118] [120][123] [124][126] The latest data on teratogenicity should be consulted.[114]

Ongoing

adults <60 years old: nonpregnant or no risk of pregnancy

1st **anticonvulsant monotherapy**

Primary options

» lamotrigine: consult specialist for guidance on dose

OR

» levetiracetam: 500 mg orally twice daily initially, increase gradually according to response, maximum 3000 mg/day

OR

» oxcarbazepine: 300 mg orally twice daily initially, increase gradually according to response, maximum 2400 mg/day

Secondary options

» lacosamide: 100 mg orally twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» eslicarbazepine acetate: 400 mg orally once daily initially, increase gradually according to response, maximum 1600 mg/day

OR

» brivaracetam: 50 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

Tertiary options

» zonisamide: 100 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

OR

» carbamazepine: 200 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 1600 mg/day

OR

Ongoing

» valproic acid: 10-15 mg/kg/day orally given in 1-3 divided doses initially, increase gradually according to response, maximum 60 mg/kg/day

OR

» topiramate: 25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» perampanel: 2 mg orally once daily at bedtime initially, increase gradually according to response, maximum 12 mg/day

OR

» gabapentin: 300 mg orally three times daily initially, increase gradually according to response, maximum 3600 mg/day

OR

» pregabalin: 75 mg orally twice daily or 50 mg orally three times daily initially, increase gradually according to response, maximum 600 mg/day

OR

» cenobamate: 12.5 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

» A trial of anticonvulsant monotherapy is indicated after two spontaneous seizures, or one seizure with one of the following: epileptiform activity on electroencephalogram; structural pathology on brain magnetic resonance imaging or computed tomography; seizure out of sleep; focal onset indicated by semiology (i.e., head turning or gaze deviation).

» Anticonvulsant options are listed based on established efficacy and optimal tolerability. However, treatment should always be tailored to the needs of the patient, taking into account age and sex; the underlying etiology of the seizures; the pharmacokinetic properties, mechanism of action, and available formulations of the drugs; and comorbidities and any other medications. Any anticonvulsant, including those not listed here, may be used as first-line monotherapy

Ongoing

if it is the most suitable choice for a particular patient.

» Lamotrigine, levetiracetam, and oxcarbazepine are suitable first-line anticonvulsants for monotherapy.[74] [75] [76] [77] [78] [79] Results from a pragmatic randomized controlled trial suggest that the adverse reaction profile of lamotrigine may be superior to that of levetiracetam in patients (>5 years of age) with two or more unprovoked seizures.[80]

» Other treatment options include lacosamide, eslicarbazepine, brivaracetam, zonisamide, carbamazepine, valproic acid, topiramate, perampanel, and cenobamate.[77] [81] [82] Behavioral adverse events are likely to be less frequent and less severe with brivaracetam than with levetiracetam, except in patients with a history of psychiatric comorbidities.[83] [84] [85] [86] Gabapentin and pregabalin are appropriate options for patients with particular comorbidities.

» For patients with psychiatric comorbidities: levetiracetam, brivaracetam, topiramate, zonisamide, and perampanel should only be used with great caution and with close monitoring for recurrence or exacerbation of psychiatric symptoms.

» For patients with cognitive problems: topiramate and zonisamide should only be used with great caution.

» For patients with renal impairment: levetiracetam should be used with caution and on the advice of a specialist neurologist.

» For patients who may have underlying liver disease or other comorbidities requiring multiple drug therapy, including P450 enzyme-inducing medication: levetiracetam, gabapentin, and pregabalin may help minimize effects on the liver and reduce the potential for drug-drug interactions. Valproic acid should not be offered (neither should phenobarbital or phenytoin).

» For patients with migraine as well as focal seizures: topiramate and valproic acid are both effective as migraine prophylaxis.

» For patients with neuropathic pain: anticonvulsants with efficacy for certain neuropathic pain conditions include gabapentin, pregabalin, oxcarbazepine, and carbamazepine.[70] [71] [72]

Ongoing

» Anticonvulsants associated with weight gain include valproic acid, gabapentin, and pregabalin, and these should be used with great caution in patients with obesity. Those associated with weight loss include topiramate and zonisamide. For the most part, other anticonvulsants are considered not to affect body weight.

» Anticonvulsant dose adjustment and/or slower titration may be needed (e.g., for people with renal or hepatic impairment).

» Avoiding sleep deprivation, alcohol, and excessive stress may be helpful at any stage of treatment, but cannot substitute for anticonvulsant therapy. There is some evidence that adjunctive psychologic and self-management interventions can improve quality of life and patient outcomes that are important to people with epilepsy.[143] [144] [145]

2nd **alternative anticonvulsant monotherapy**

» If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant from among the options available. A drug with a different mechanism of action should be considered. Any anticonvulsant, including those not listed for first-line monotherapy above, may be used as second-line monotherapy if it is the most suitable choice for a particular patient.

» If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance. Any new information that helps to define the epilepsy syndrome should be used to select the best-suited medication.

» When changing from one anticonvulsant to another, current and new medications should be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). Research the specific pharmacokinetic profiles for each of the drugs before instructing the patient on how to switch. A written schedule helps patient adherence. Dose should be adjusted according to response and serum drug level.

» Advise patients that there is an increased risk of seizures during this transition period.

3rd **anticonvulsant dual therapy**

Ongoing

Primary options

» lamotrigine: consult specialist for guidance on dose

OR

» oxcarbazepine: 300 mg orally twice daily initially, increase gradually according to response, maximum 2400 mg/day

OR

» levetiracetam: 500 mg orally twice daily initially, increase gradually according to response, maximum 3000 mg/day

OR

» brivaracetam: 50 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

OR

» valproic acid: 10-15 mg/kg/day orally given in 1-3 divided doses initially, increase gradually according to response, maximum 60 mg/kg/day

OR

» perampanel: 2 mg orally once daily at bedtime initially, increase gradually according to response, maximum 12 mg/day

OR

» clobazam: consult specialist for guidance on dose

OR

» gabapentin: 300 mg orally three times daily initially, increase gradually according to response, maximum 3600 mg/day

OR

» topiramate: 25 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 400 mg/day

Ongoing

OR

» zonisamide: 100 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

OR

» pregabalin: 75 mg orally twice daily or 50 mg orally three times daily initially, increase gradually according to response, maximum 600 mg/day

OR

» lacosamide: 100 mg orally twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» eslicarbazepine acetate: 400 mg orally once daily initially, increase gradually according to response, maximum 1600 mg/day

OR

» carbamazepine: 200 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 1600 mg/day

OR

» cenobamate: 12.5 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

OR

» phenytoin: 15-20 mg/kg orally as a loading dose given in 3 divided doses every 2-4 hours, followed by 4-7 mg/kg/day (or 300-400 mg/day) given in 2-3 divided doses

OR

» phenobarbital: 60 mg orally two to three times daily

OR

Ongoing

» primidone: 100-125 mg orally once daily at bedtime for 3 days, increase gradually according to response, maximum 2000 mg/day

» If two separate monotherapy trials at optimal doses do not result in seizure control, a dual therapy trial may be initiated using a combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects (such as valproic acid plus lamotrigine). These may be a combination of two monotherapy options, or an anticonvulsant that is used primarily as an adjunctive treatment (e.g., clobazam) in combination with one of the monotherapy options.[72] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103]

» Other adjunctive therapies are available, including rufinamide, vigabatrin, tiagabine, and felbamate.[104] [105] [106] [107] [108] However, rufinamide, vigabatrin, tiagabine, and felbamate are associated with severe adverse effects, and should only be considered when multiple other medications have been attempted and surgery is deemed not to be an option. An epilepsy specialist should be involved if these agents are being considered. These drugs are not detailed above.

» A dose adjustment may be required when using two anticonvulsants together; consult a specialist for guidance on dose.

» A list of suitable anticonvulsants for this patient group is detailed here; however, this list is not exhaustive. Two anticonvulsants may be chosen from this list.

4th **resective epilepsy surgery or neurostimulation or ketogenic diet**

» Failure of at least two anticonvulsant drugs in combination (treatment-resistant or intractable epilepsy) should result in reassessment of the diagnosis. If the diagnosis is not secure, then reinvestigation, possibly with video/electroencephalogram (EEG) monitoring, may be helpful.

» If the focal seizure diagnosis is correct, and the patient is truly refractory to anticonvulsants, consider and perform workup for epilepsy surgery or neurostimulation.

Ongoing

» Consideration of these advanced options should be pursued at an epilepsy specialty center only.

» Candidates for epilepsy surgery include patients with lesions on brain magnetic resonance imaging or in whom the epileptogenic area can be localized to one region by a variety of techniques, including EEG. Minimally invasive alternatives to traditional resective surgery include laser interstitial thermal therapy (LITT), radiofrequency ablation, and stereotactic radiosurgery.[149] [150]

» If the patient has more than one epileptogenic focus, neurostimulation may be considered an alternative to surgery.[151] Options include vagus nerve stimulation and deep brain stimulation.[152] [153] [154] [155] Responsive neurostimulation (RNS) therapy may be appropriate for some medically refractory patients for whom resective surgery is not a viable option.[157] [158] [159] [160]

» The ketogenic diet is high in fat and low in carbohydrates, and has been shown to reduce seizure frequency.[161] [162] [163] The diet must be initiated in the hospital, under close medical supervision, with monitoring for metabolic acidosis and renal calculi.

adults ≥60 years old

1st **anticonvulsant monotherapy**

Primary options

» lamotrigine: consult specialist for guidance on dose

OR

» gabapentin: 300 mg orally three times daily initially, increase gradually according to response, maximum 3600 mg/day

OR

» levetiracetam: 500 mg orally twice daily initially, increase gradually according to response, maximum 3000 mg/day

Secondary options

» oxcarbazepine: 300 mg orally twice daily initially, increase gradually according to response, maximum 2400 mg/day

Ongoing

OR

» lacosamide: 100 mg orally twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» eslicarbazepine acetate: 400 mg orally once daily initially, increase gradually according to response, maximum 1600 mg/day

OR

» brivaracetam: 50 mg orally twice daily initially, increase gradually according to response, maximum 200 mg/day

Tertiary options

» pregabalin: 75 mg orally twice daily or 50 mg orally three times daily initially, increase gradually according to response, maximum 600 mg/day

OR

» carbamazepine: 200 mg orally (immediate-release) twice daily initially, increase gradually according to response, maximum 1600 mg/day

OR

» zonisamide: 100 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

OR

» valproic acid: 10-15 mg/kg/day orally given in 1-3 divided doses initially, increase gradually according to response, maximum 60 mg/kg/day

OR

» perampanel: 2 mg orally once daily at bedtime initially, increase gradually according to response, maximum 12 mg/day

OR

Ongoing

» cenobamate: 12.5 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

» The decision to treat focal seizures in older people is often made after the first unprovoked seizure, because the likelihood of recurrence is higher, and the consequences of even a single seizure (falls/hip fracture) may be life changing.

» Anticonvulsant options are listed based on established efficacy and optimal tolerability. However, treatment should always be tailored to the needs of the patient, taking into account age and sex; the underlying etiology of the seizures; the pharmacokinetic properties, mechanism of action, and available formulations of drug; and comorbidities and any other medications. Any anticonvulsant, including those not listed here, may be used as first-line monotherapy if it is the most suitable choice for a particular patient.

» Older patients are particularly susceptible to adverse effects and often have tolerability issues, especially at higher doses or with polytherapy.

» Monotherapy at the lowest possible dose is preferred. Doses should be increased gradually according to patient response, and the patient should be closely monitored for signs of toxicity.

» The properties of some anticonvulsants make them less desirable choices for treating focal seizures in older people. These anticonvulsants include drugs that are P450 enzyme inducers or inhibitors; have high protein binding; or are associated with cognitive adverse events.

» Anticonvulsants with favorable pharmacokinetics and adverse-effect profiles, such as lamotrigine, gabapentin, and levetiracetam, are usually the most appropriate choice for patients ages 60 years or over. Other options include oxcarbazepine, lacosamide, eslicarbazepine, brivaracetam, pregabalin, carbamazepine, zonisamide, valproic acid, perampanel, and cenobamate. Treatment should always be tailored to the individual patient.[109] [110] [111]

» For patients with psychiatric comorbidities: levetiracetam, brivaracetam, zonisamide, and perampanel (as well as topiramate) should only be used with great caution and with close monitoring for recurrence or exacerbation of psychiatric symptoms.

Ongoing

» For patients with cognitive problems: zonisamide (and topiramate) should only be used with great caution.

» For patients with renal impairment: levetiracetam should be used with caution and on the advice of a specialist neurologist.

» For patients who may have underlying liver disease or other comorbidities requiring multiple drug therapy, including P450 enzyme-inducing medication: levetiracetam, gabapentin, and pregabalin may help minimize effects on the liver and reduce the potential for drug-drug interactions. Valproic acid (and phenobarbital, phenytoin, and felbamate) should not be offered.

» For patients with migraine as well as focal seizures: valproic acid is effective as migraine prophylaxis (as is topiramate).

» For patients with neuropathic pain: anticonvulsants with efficacy for certain neuropathic pain conditions include gabapentin, pregabalin, oxcarbazepine, and carbamazepine.[70] [71] [72]

» Anticonvulsants associated with weight gain include valproic acid, gabapentin, and pregabalin, and these should be used with great caution in patients with obesity. Zonisamide is associated with weight loss (as is topiramate). For the most part, other anticonvulsants are considered not to affect body weight.

» Avoiding sleep deprivation, alcohol, and excessive stress may be helpful at any stage of treatment, but cannot substitute for anticonvulsant drug therapy. There is some evidence that adjunctive psychologic and self-management interventions can improve quality of life and patient outcomes that are important to people with epilepsy.[143] [144] [145]

2nd **alternative anticonvulsant monotherapy**

» If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different drug that has proven efficacy for focal epilepsy in the older population. A drug with a different mechanism of action should be considered.

» Any anticonvulsant, including those not listed for first-line monotherapy above, may be used as second-line monotherapy if it is the most suitable choice for a particular patient.

Ongoing

» If the first monotherapy agent is unsuitable due to intolerable adverse effects (which can be a particular issue in older patients), an alternative agent should be chosen with special consideration for the patient's health profile and tolerance. Any new information that helps to define the epilepsy syndrome should be used to select the best-suited medication.

» Start treatment at the lowest possible dose, and increase dose gradually according to patient response. Monitor the patient closely for signs of toxicity.

» When changing from one anticonvulsant to another, the current and new medications should be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). Research the specific pharmacokinetic profiles for each of the drugs before instructing the patient on how to switch. A written schedule helps patient adherence. Dose should be adjusted according to response and serum drug level. Advise patients that there is an increased risk of seizures during this transition period.

3rd **anticonvulsant dual therapy**

» If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated after consultation with a specialist neurologist.

» Use a combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects.[72] [89] [90] [91] [93] [95] [96] [97] [98] [99] [102] [103] [105]

» Anticonvulsants listed for monotherapy above are also the most suitable options for dual therapy in this population; however, any anticonvulsants may be used in combination if that is the most suitable choice for a particular patient.

» A dose adjustment may be required when using two anticonvulsants together; consult a specialist for guidance on dose.

4th **resective epilepsy surgery or neurostimulation**

» Failure of at least two anticonvulsant drugs in combination should result in reassessment

Ongoing

of the diagnosis. If the diagnosis is not secure, then reinvestigation, possibly with video/electroencephalogram (EEG) monitoring, may be helpful.

» If the focal seizure diagnosis is correct, and the patient is truly refractory to anticonvulsants, consider and perform workup for epilepsy surgery or neurostimulation.

» Consideration of these advanced options should be pursued at an epilepsy specialty center only.

» Candidates for epilepsy surgery include patients with lesions on brain magnetic resonance imaging or patients in whom the epileptogenic area can be localized to one region by a variety of techniques, including EEG. Minimally invasive alternatives to traditional resective surgery include laser interstitial thermal therapy (LITT), radiofrequency ablation, and stereotactic radiosurgery.[149] [150]

» If the patient has more than one epileptogenic focus, neurostimulation may be considered as an alternative to surgery. Options include vagus nerve stimulation and deep brain stimulation.[152] [153] [154] [155] Responsive neurostimulation (RNS) therapy may be appropriate for some medically refractory patients for whom resective surgery is not a viable option.[157] [158] [159] [160]

women of childbearing potential

1st **anticonvulsant monotherapy**

Primary options

» lamotrigine: consult specialist for guidance on dose

OR

» levetiracetam: 500 mg orally twice daily initially, increase gradually according to response, maximum 3000 mg/day

Secondary options

» oxcarbazepine: 300 mg orally twice daily initially, increase gradually according to response, maximum 2400 mg/day

Tertiary options

Ongoing

» lacosamide: 100 mg orally twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» zonisamide: 100 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

» Care should be taken with anticonvulsant treatment for any woman of childbearing potential. Women with epilepsy should receive preconception counseling.[112] [113] [114]

» The choice of anticonvulsant should be based upon the likelihood of pregnancy in the near future. The latest data available on teratogenicity should be consulted.[114] Data on the teratogenic potential of newer anticonvulsants may not be available or may be limited.[118]

» Some anticonvulsants are contraindicated in pregnancy due to an increased risk of major congenital malformations and/or child neurodevelopmental disorders (e.g., valproic acid and its derivatives, topiramate, phenobarbital,phenytoin).[115] [116] [117] [118] [120][123] [124]

» Inform women of childbearing potential that they must follow a pregnancy prevention program while on treatment with valproic acid and its derivatives. Some countries may also require that a pregnancy prevention program is in place for other anticonvulsants (e.g., topiramate).

» Suitable anticonvulsants for women of childbearing potential include lamotrigine and levetiracetam.[114] [118] Other options include oxcarbazepine, lacosamide, and zonisamide.[114] However, treatment should always be tailored to the needs of the patient, also taking into account the underlying etiology of the seizures; the pharmacokinetic properties, mechanism of action, and available formulations of the drugs; and comorbidities and any other medications. Any anticonvulsant, including those not listed here, may be used as first-line monotherapy if it is the most suitable choice for a particular patient.

» For women taking birth control pills, avoid anticonvulsants with enzyme-inducing properties (e.g., carbamazepine, phenytoin, phenobarbital, primidone), as these can lower contraceptive

Ongoing

efficacy and lead to an increased failure rate.[119]

» For patients with psychiatric comorbidities: levetiracetam and zonisamide (as well as brivaracetam and perampanel) should only be used with great caution and with close monitoring for recurrence or exacerbation of psychiatric symptoms.

» For patients with cognitive problems: zonisamide should only be used with great caution.

» For patients with renal impairment: levetiracetam should be used with caution and on the advice of a specialist neurologist.

» For patients who may have underlying liver disease or other comorbidities requiring multiple drug therapy, including P450 enzyme-inducing medication: levetiracetam (as well as gabapentin and pregabalin) may help minimize effects on the liver and reduce the potential for drug-drug interactions.

» For patients with neuropathic pain: anticonvulsants with efficacy for certain neuropathic pain conditions include oxcarbazepine and carbamazepine (as well as gabapentin and pregabalin).[70] [71] [72]

» Anticonvulsants associated with weight gain include gabapentin and pregabalin, and these should be used with great caution in patients with obesity. Zonisamide is associated with weight loss. For the most part, other anticonvulsants are considered not to affect body weight.

» Avoiding sleep deprivation, alcohol, and excessive stress may be helpful at any stage of treatment, but cannot substitute for anticonvulsant therapy. There is some evidence that adjunctive psychologic and self-management interventions can improve quality of life and patient outcomes that are important to people with epilepsy.[143] [144] [145]

2nd **alternative anticonvulsant monotherapy**

» If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that is suitable for a woman of childbearing potential. A drug with a different mechanism of action should be considered.

Ongoing

» Any anticonvulsant, including those not listed for first-line monotherapy above, may be used as second-line monotherapy if it is the most suitable choice for a particular patient.

» If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance. Any new information that helps to define the epilepsy syndrome should be used to select the best-suited medication.

» When changing from one anticonvulsant to another, current and new medications should be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). Research the specific pharmacokinetic profiles for each of the drugs before instructing the patient on how to switch. A written schedule helps patient adherence. Dose should be adjusted according to response and serum drug level.

» Advise patients that there is an increased risk of seizures during this transition period.

3rd **anticonvulsant dual therapy**

» If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated.

» Use a combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects.[89] [90] [93] [97] [98] [99] [128]

» Anticonvulsants listed for monotherapy above are also the most suitable options for dual therapy in this population; however, any anticonvulsants may be used in combination if that is the most suitable choice for a particular patient.

» A dose adjustment may be required when using two anticonvulsants together; consult a specialist for guidance on dose.

4th **resective epilepsy surgery or neurostimulation or ketogenic diet**

» Failure of at least two anticonvulsants in combination (treatment-resistant or intractable epilepsy) should result in reassessment of the diagnosis. If the diagnosis is not secure,

Ongoing

then reinvestigation, possibly with video/electroencephalogram (EEG) monitoring, may be helpful.

» If the focal seizure diagnosis is correct, and the patient is truly refractory to anticonvulsants, consider and perform workup for epilepsy surgery or neurostimulation.

» Consideration of these advanced options should be pursued at an epilepsy specialty center only.

» Candidates for epilepsy surgery include patients with lesions on brain magnetic resonance imaging or in whom the epileptogenic area can be localized to one region by a variety of techniques, including EEG. Minimally invasive alternatives to traditional resective surgery include laser interstitial thermal therapy (LITT), radiofrequency ablation, and stereotactic radiosurgery.[149] [150]

» If the patient has more than one epileptogenic focus, neurostimulation may be considered an alternative to surgery.[151] Options include vagus nerve stimulation and deep brain stimulation.[152] [153] [154] [155] Responsive neurostimulation (RNS) therapy may be appropriate for some medically refractory patients for whom resective surgery is not a viable option.[157] [158] [159] [160]

» The ketogenic diet is high in fat and low in carbohydrates, and has been shown to reduce seizure frequency.[161] [162] [163] The diet must be initiated in the hospital, under close medical supervision, with monitoring for metabolic acidosis and renal calculi.

pregnant

1st **anticonvulsant monotherapy**

Primary options

» lamotrigine: consult specialist for guidance on dose

OR

» levetiracetam: 500 mg orally twice daily initially, increase gradually according to response, maximum 3000 mg/day

Secondary options

MANAGEMENT

Ongoing

» oxcarbazepine: 300 mg orally twice daily initially, increase gradually according to response, maximum 2400 mg/day

Tertiary options

» lacosamide: 100 mg orally twice daily initially, increase gradually according to response, maximum 400 mg/day

OR

» zonisamide: 100 mg orally once daily initially, increase gradually according to response, maximum 400 mg/day

» Pregnant women with epilepsy should be under the care of a multidisciplinary team that includes a high-risk obstetric specialist, and care should be coordinated through joint obstetric and neurology clinics.[112] [113] [114] However, risk of cesarean delivery, late pregnancy bleeding, premature contractions, or premature labor and delivery are probably not substantially increased in women taking anticonvulsant drugs who do not smoke.[131]

» Particular care should be taken with anticonvulsant treatment for pregnant women. The latest data available on teratogenicity should be consulted.[114]

» Suitable anticonvulsants for pregnant women include lamotrigine and levetiracetam.[114] [118] Other options include oxcarbazepine, lacosamide, and zonisamide.[114]

» Some anticonvulsants are contraindicated in pregnancy due to an increased risk of major congenital malformations and/or child neurodevelopmental disorders (e.g., valproic acid and its derivatives, topiramate, phenobarbital, phenytoin).[115] [116] [117] [118] [120][123] [124][126]

» Monotherapy is preferable to polytherapy, but this is not always achievable. The lowest effective dose should be used.[118]

» Serum levels of anticonvulsants may decline during pregnancy, with a potential loss of seizure control.[129] Therefore, close monitoring of serum drug levels and clinical response is advised.[118]

» An anatomic ultrasound should be performed between 14 and 18 weeks of pregnancy, and serum alpha-fetoprotein level measured, to

Ongoing

check for possible fetal abnormalities. The need for amniocentesis is on a case-by-case basis.

plus **folic acid**

Treatment recommended for ALL patients in selected patient group

Primary options

» folic acid (vitamin B9): 4-5 mg orally once daily
Dose varies according to local guidelines. Lower doses may be recommended in some countries.

» Women with epilepsy should be advised to take high-dose folic acid before conception and during pregnancy.[113][127] Folic acid supplementation (to help prevent neural tube defects in the developing fetus) is a routine recommendation for all women planning pregnancy, and any risk associated with folic acid supplementation is low. Evidence about the benefits of high-dose folic acid supplementation before and during pregnancy for women with epilepsy is inconclusive.[112] [114][129] [130]

2nd **alternative anticonvulsant monotherapy**

» Pregnant women with epilepsy should be under the care of a multidisciplinary team that includes a high-risk obstetric specialist, and care should be coordinated through joint obstetric and neurology clinics.[112] [113] [114]

» If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant from among suitable options for pregnant women. A drug with a different mechanism of action should be considered.

» Any anticonvulsant, including those not listed for first-line monotherapy above, may be used as second-line monotherapy if it is the most suitable choice for a particular patient (taking into account the latest data on teratogenicity).

» If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance. Any new information that helps to define the epilepsy syndrome should be used to select the best-suited medication.

» When changing from one anticonvulsant to another, the current and new medications should

Ongoing

be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). Research the specific pharmacokinetic profiles for each of the drugs before instructing the patient on how to switch. A written schedule helps patient adherence. Dose should be adjusted according to response and serum drug level. Advise patients that there is an increased risk of seizures during this transition period.

plus **folic acid**

Treatment recommended for ALL patients in selected patient group

Primary options

» folic acid (vitamin B9): 4-5 mg orally once daily
Dose varies according to local guidelines. Lower doses may be recommended in some countries.

» Women with epilepsy should be advised to take high-dose folic acid before conception and during pregnancy.[113][127] Folic acid supplementation (to help prevent neural tube defects in the developing fetus) is a routine recommendation for all women planning pregnancy, and any risk associated with folic acid supplementation is low. Evidence about the benefits of high-dose folic acid supplementation before and during pregnancy for women with epilepsy is inconclusive.[112] [114][129] [130]

3rd **anticonvulsant dual therapy**

» Pregnant women with epilepsy should be under the care of a multidisciplinary team that includes a high-risk obstetric specialist, and care should be coordinated through joint obstetric and neurology clinics.[112] [113] [114]

» If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated after consultation with a specialist neurologist.

» Use a combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects.[89] [90] [93] [97] [98] [99] [128]

» Anticonvulsants listed for monotherapy above are also the most suitable options for

Ongoing

dual therapy in this population; however, any anticonvulsants may be used in combination if that is the most suitable choice for a particular patient (taking into account the latest data on teratogenicity).

» A dose adjustment may be required when using two anticonvulsants together; consult a specialist for guidance on dose.

plus **folic acid**

Treatment recommended for ALL patients in selected patient group

Primary options

» folic acid (vitamin B9): 4-5 mg orally once daily
Dose varies according to local guidelines. Lower doses may be recommended in some countries.

» Women with epilepsy should be advised to take high-dose folic acid before conception and during pregnancy.[113][127] Folic acid supplementation (to help prevent neural tube defects in the developing fetus) is a routine recommendation for all women planning pregnancy, and any risk associated with folic acid supplementation is low. Evidence about the benefits of high-dose folic acid supplementation before and during pregnancy for women with epilepsy is inconclusive.[112] [114][129] [130]

children

1st **anticonvulsant monotherapy**

Primary options

» levetiracetam: consult specialist for guidance on dose

OR

» oxcarbazepine: consult specialist for guidance on dose

Secondary options

» lamotrigine: consult specialist for guidance on dose

OR

» lacosamide: consult specialist for guidance on dose

MANAGEMENT

Ongoing

OR

» eslicarbazepine acetate: consult specialist for guidance on dose

OR

» brivaracetam: consult specialist for guidance on dose

Tertiary options

» valproic acid: consult specialist for guidance on dose

OR

» carbamazepine: consult specialist for guidance on dose

OR

» zonisamide: consult specialist for guidance on dose

OR

» topiramate: consult specialist for guidance on dose

OR

» perampanel: consult specialist for guidance on dose

OR

» clobazam: consult specialist for guidance on dose

» Treatment should be managed initially by a specialist pediatric neurologist.

» Once focal seizures are diagnosed, determination of etiology is important for treatment decisions. For example, certain syndromes, such as the subtype of localization-related/idiopathic epilepsy called benign childhood epilepsy with centrotemporal spikes, often require no anticonvulsant drug treatment.[135]

» In some cases (e.g., if seizure episodes are infrequent), it may be appropriate for the parent or caregiver to treat only the prolonged seizure

Ongoing

with an acute therapy for aborting the seizure, such as rectal diazepam.

» Treatment should always be tailored to the needs of the individual patient, taking into account age and sex; the underlying etiology of the seizures; the pharmacokinetic properties, mechanism of action, and available formulations of drug; and comorbidities and any other medications. Any anticonvulsant, including those not listed here, may be used as first-line monotherapy if it is the most suitable choice for a particular patient.

» When selecting an appropriate anticonvulsant for a child, potential effects on cognition, learning, and behavior should be taken into account. For this reason, long-term treatment with anticonvulsants such as phenobarbital and phenytoin should be avoided. Data on the cognitive effects of newer anticonvulsants may not be available or may be limited.

» Levetiracetam and oxcarbazepine are suggested as first-line options; they are effective and appear to have favorable profiles with regard to cognitive adverse effects.[136]

» Other options for monotherapy in children include lamotrigine, lacosamide, eslicarbazepine, brivaracetam, carbamazepine, zonisamide, topiramate, perampanel, clobazam, and (other than for girls of childbearing potential) valproic acid.[136] [137] [138]

» Care should be taken with anticonvulsant treatment for any girl of childbearing potential. The choice of anticonvulsant should be based upon the likelihood of pregnancy in the near future. The latest data available on teratogenicity should be consulted.[114] Inform girls of childbearing potential that they must follow a pregnancy prevention program while on treatment with valproic acid and its derivatives. Some countries may also require that a pregnancy prevention program is in place for other anticonvulsants (e.g., topiramate).

» For patients with psychiatric comorbidities: levetiracetam, brivaracetam, topiramate, zonisamide, and perampanel should only be used with great caution and with close monitoring for recurrence or exacerbation of psychiatric symptoms.

» For patients with migraine as well as focal seizures: topiramate is effective as migraine prophylaxis (as is valproic acid).

Ongoing

» Anticonvulsants associated with weight gain include valproic acid, gabapentin, and pregabalin, and these should be used with great caution in patients with obesity (they are not generally recommended for children anyway). Those associated with weight loss include topiramate and zonisamide. For the most part, other anticonvulsants are considered not to affect body weight.

» Younger children often have more rapid clearance and variability in elimination kinetics of anticonvulsants; this must be factored into dosing regimens. Younger children may require liquid and/or chewable anticonvulsant formulations.

» Avoiding sleep deprivation, alcohol, and excessive stress may be helpful at any stage of treatment, but cannot substitute for anticonvulsant therapy. There is some evidence that adjunctive psychologic and self-management interventions can improve quality of life and patient outcomes that are important to people with epilepsy.[143] [144] [145]

2nd **alternative anticonvulsant monotherapy**

» If the initial anticonvulsant is not effective or not tolerated, a second monotherapy trial is indicated, choosing a different anticonvulsant that is suitable for children. A drug with a different mechanism of action should be considered.

» Any anticonvulsant, including those not listed for first-line monotherapy above, may be used as second-line monotherapy if it is the most suitable choice for a particular patient.

» If the first monotherapy agent is unsuitable due to intolerable adverse effects, the alternative agent should be chosen with special consideration for the patient's health profile and tolerance. Any new information that helps to define the epilepsy syndrome should be used to select the best-suited medication.

» When changing from one anticonvulsant to another, current and new medications should be cross-titrated slowly; agents should not be started or stopped abruptly (the concomitant anticonvulsant is gradually reduced as the new agent is introduced). Research the specific pharmacokinetic profiles for each of the drugs before instructing the patient, and their parents or caregivers if appropriate, on how to switch. A written schedule helps patient adherence.

Ongoing

Dose should be adjusted according to response and serum drug level. Advise patients and their parents or caregivers that there is an increased risk of seizures during this transition period.

3rd **anticonvulsant dual therapy**

» If two separate monotherapy trials at optimal doses do not result in adequate seizure control, a dual therapy trial may be initiated after consultation with a specialist pediatric neurologist.

» Use a combination of two anticonvulsants with different mechanisms of action (with the aim of maximizing efficacy and minimizing toxicity), or a combination of two drugs that have been shown to have anticonvulsant agonistic effects.[97] [98] [99] [105] [139] [140]

» Anticonvulsants listed for monotherapy above are also the most suitable options for dual therapy in this population; however, any anticonvulsants may be used in combination if that is the most suitable choice for a particular patient.

» A dose adjustment may be required when using two anticonvulsants together; consult a specialist for guidance on dose.

4th **resective epilepsy surgery or neurostimulation or ketogenic diet**

» Failure of at least two anticonvulsants in combination (treatment-resistant or intractable epilepsy) should result in a reassessment of the diagnosis. If the diagnosis is not secure, then reinvestigation, possibly with video/electroencephalogram (EEG) monitoring, may be helpful.

» If the focal seizure diagnosis is correct, and the patient is truly refractory to anticonvulsants, consider and perform workup for epilepsy surgery or vagus nerve stimulation.

» Consideration of these advanced options should be pursued at an epilepsy specialty center only.

» Candidates for epilepsy surgery include patients with lesions on brain magnetic resonance imaging or in whom the epileptogenic area can be localized to one region by a variety of techniques, including EEG. Minimally invasive alternatives to traditional resective surgery include laser interstitial thermal therapy (LITT),

Ongoing

radiofrequency ablation, and stereotactic radiosurgery.[149] [150]

» If the patient has more than one epileptogenic focus, vagus nerve stimulation may be considered an alternative to surgery.[151] [156]

» The ketogenic diet is high in fat and low in carbohydrates, and has been shown to reduce seizure frequency.[161] [162] [163] The diet must be initiated in the hospital, under close medical supervision, with monitoring for metabolic acidosis and renal calculi.

Emerging

Losigamone

A b-methoxy-butenolide with an unknown mechanism of action. One Cochrane review of two randomized placebo-controlled trials (467 participants) found that losigamone can reduce seizure frequency when used as an add-on therapy for people with focal epilepsy.[167] Treatment withdrawals were significantly more common among participants receiving add-on therapy with losigamone.

Ganaxolone

A neurosteroid that acts through positive allosteric modulation of gamma-aminobutyric acid A receptor sites. Adjunctive ganaxolone reduced seizure frequency in a phase 2 trial of patients with uncontrolled focal-onset seizures despite taking up to three concomitant anticonvulsants.[168]

Topiramate (intravenous)

The Food and Drug Administration (FDA) has granted orphan-drug designation to intravenous topiramate for the treatment of focal-onset or primary generalized tonic-clonic seizures in hospitalized epilepsy patients who are unable to take oral topiramate.

Cannabidiol

Cannabidiol oral solution has been approved by the FDA and the European Medicines Agency for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome. Multicenter, randomized, placebo-controlled trials are required to investigate efficacy in patients with severe, treatment-resistant focal seizures.[169]

Primary prevention

The prevention of focal seizure development involves avoiding insults or injury to the brain; for example, wearing protective headgear in sports (helmets) and other physical activities (bicycle riding) will reduce the incidence and severity of traumatic brain injury.

Taking appropriate precautions to avoid central nervous system (CNS) infections (e.g., meningoencephalitis) by vaccination may be considered preventive. In addition, avoiding or limiting alcohol intake and abstaining from recreational drug use should reduce the risk of CNS injury.

Patient discussions

Provide patients with clear written instructions about medications and dosing. Patients often need to be reminded that they should take their medications at the same times every day.

If a generic bioequivalent anticonvulsant drug replaces a brand product, patients (and parents/caregivers if appropriate) should be reassured about equivalent effectiveness, and informed if there are any changes in color or shape.[177]

Encourage sufficient sleep and regular sleeping patterns, as sleep deprivation may trigger seizures in some patients.

Advise patients to check with their epilepsy doctor before starting over-the-counter, alternative, or prescribed medications, as some may interact with their anticonvulsant medication and lead to either breakthrough seizures or toxicity.

Patients with active seizures are not allowed to drive. The state driving regulations regarding duration of seizure freedom should be accessed. [Epilepsy Foundation: driver information by state] (https://www.epilepsy.com/driving-laws)

Explain to patients that they should not work from heights, operate heavy machinery, or engage in activities that might put them at risk from injury resulting from a seizure.

Advise patients with active epilepsy to exhibit caution with regard to swimming and bathing. Drowning is the most common accidental death in people with epilepsy. Therefore, they should not swim alone; a lifeguard or qualified buddy should be present. Extreme-contact sports should probably also be avoided.

A medical alert bracelet providing information about the patient's medical condition may be helpful. Alternately, a card with the patient's medical condition, the name and doses of medication, and the patient's medical doctor may be kept in the wallet.

If discontinuation of anticonvulsant medication is being considered for patients who have been seizure-free for 2 years or more, discuss the risks and benefits of discontinuation with the patient (and their family if appropriate), including the risks of seizure recurrence and treatment resistance. Individual patient characteristics and preferences, including quality of life considerations, should be taken into account.[164]

Contraception and pregnancy

Education about effective contraceptive options and potential adverse pregnancy outcomes should start in early adolescence and continue throughout a patient's reproductive life, because anticonvulsant medication, contraceptive needs, and desire for pregnancy are likely to change over time.[119]

Inform women of childbearing potential that they must follow a pregnancy prevention program while on treatment with valproic acid and its derivatives. Some countries may also require that a pregnancy prevention program is in place for other anticonvulsants (e.g., topiramate).

In the US and Canada, pregnant women with epilepsy can enroll in the North American AED (Antiepileptic Drug) Pregnancy Registry, which aims to obtain and publish information on the frequency of major malformations, such as heart defects, spina bifida, and cleft lip, among infants whose mothers had taken one or more anticonvulsants to prevent seizures or to treat any other medical condition. [The North American AED (Antiepileptic Drug) Pregnancy Registry] (https://www.aedpregnancyregistry.org)

Inform women that:

- Being seizure-free for at least 9 months before pregnancy is probably associated with a high rate of remaining seizure-free during pregnancy
- If they smoke they may have a substantially increased risk of premature contractions and premature labor and birth.[131]

FOLLOW UP

Monitoring

Monitoring

Patients taking anticonvulsant drugs for focal seizures should be followed up on a regular basis. The frequency of follow-up depends on several factors. Patients whose seizures are well controlled and who are not having adverse effects with medication may be seen every 6 months to 1 year. Patients having their medications adjusted or titrated should be seen every 1 to 2 months until they are stable. Intervening telephone or video follow-up may substitute for interval visits.

Patients should be encouraged to keep written seizure diaries. During a follow-up visit, patient seizure counts should be assessed, medication lists should be reviewed (and preferably the actual medication bottles), and an assessment for adverse events (continuous, peak dose) should be made. Patients should also be screened for mood disorders, which are common comorbidities. In addition, a quality-of-life assessment is often helpful: for example, the QOLIE10. [PROQOLID: Quality of Life in Epilepsy Inventory-10 (QOLIE-10)] (https://eprovide.mapi-trust.org/instruments/quality-of-life-in-epilepsy-inventory-10)

For patients on first-generation anticonvulsants, drug levels, complete blood count, and SMA-20 (total cholesterol, total protein, and various electrolytes) are often useful. These drugs have a narrow therapeutic index, and monitoring can assess adherence as well as provide surveillance of certain hematopoietic and hepatic toxicities. Laboratory testing for patients on second- and third-generation anticonvulsants may provide information about adherence, but a role in guiding dosing is less certain.

Patients with focal seizures who require chronic anticonvulsant therapy should be closely monitored for possible long-term adverse effects. These may include bone loss, weight changes, behavioral changes, renal calculi, and cerebellar dysfunction.

Patients who achieve seizure freedom may eventually wish to discontinue anticonvulsant medications. See Management approach .

Complications

Complications	Timeframe	Likelihood
head trauma	**variable**	**medium**
Head trauma may be a cause of seizures; people with seizures may experience head trauma as a result of a seizure episode.		
bone fracture	**variable**	**medium**
May be due to a fall precipitated by a seizure, a fall due to poor balance caused by anticonvulsant drug toxicity, or osteopenia/osteoporosis as a consequence of long-term anticonvulsant use (thought to be more common from the use of P450 enzyme-inducing anticonvulsants such as carbamazepine, phenytoin, phenobarbital, and primidone).		
memory loss	**variable**	**medium**
A common complaint in patients with epilepsy. It may be due to recurrent seizures, or adverse effects from a number of anticonvulsant agents. In patients with hippocampal pathology it may, in part, be related to cell/volume loss in the hippocampus.		
mood disorders	**variable**	**medium**
Mood disorders (e.g., depression, anxiety) are common among people with epilepsy, and can negatively impact on seizure outcome and quality of life.[174] [175] Patients should be monitored for mood disorders at each review, and referred for treatment as appropriate. Evidence to inform choice of antidepressant and anticonvulsant drugs in people with epilepsy and depression is very limited.[176]		
sudden unexpected death in epilepsy (SUDEP)	**variable**	**low**
This refers to the phenomenon of sudden, unexpected, unexplained death in people with epilepsy with no obvious cause on postmortem examination. Incidence in adults has been reported as 1.2 per 1000 patient-years, but may be underestimated.[170] [173] The major risk factor for SUDEP is the occurrence of generalized tonic-clonic seizures (GTCS); the risk of SUDEP increases in association with increasing frequency of GTCS.[170]		

Prognosis

Nearly two-thirds of patients with focal seizures achieve adequate seizure control with anticonvulsant drugs, either monotherapy or polytherapy. There is little evidence to guide the timing of medication withdrawal in seizure-free adults, but most patients are treated with anticonvulsants for at least 2 years.[165]

Up to 50% of patients have been reported to be drug-free at 5 years after surgery for focal seizures, with the likelihood higher among children. Factors that influence the outcomes of surgery include histopathologic diagnosis, age at surgery, and duration of epilepsy.[172]

Diagnostic guidelines

International

Reassessment: neuroimaging in the emergency patient presenting with seizure (https://www.aan.com/Guidelines/Home/ByTopic?topicId=23) [40]

Published by: American Academy of Neurology

Last published: 2007 (reaffirmed 2019)

Evaluating a first nonfebrile seizure in children (https://www.aan.com/Guidelines/Home/ByTopic?topicId=23) [59]

Published by: American Academy of Neurology

Last published: 2000 (reaffirmed 2023)

Guidelines for imaging infants and children with recent-onset epilepsy (https://www.ilae.org/guidelines/guidelines-and-reports) [41]

Published by: International League Against Epilepsy

Last published: 2009

Epilepsies in children, young people and adults (https://www.nice.org.uk/guidance/NG217) [60]

Published by: National Institute for Health and Care Excellence (UK)

Last published: 2022

Diagnosis and management of epilepsy in adults (https://www.sign.ac.uk/our-guidelines) [61]

Published by: Scottish Intercollegiate Guidelines Network

Last published: 2015 (reaffirmed 2019)

Treatment guidelines

International

Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication (https://www.aan.com/practice/guidelines) [114]

Published by: American Academy of Neurology, American Epilepsy Society, and Society for Maternal-Fetal Medicine

Last published: 2024

Antiseizure medication withdrawal in seizure-free patients: practice advisory update summary (https://www.aan.com/practice/guidelines) [164]

Published by: American Academy of Neurology

Last published: 2021

Gynecologic management of adolescents and young women with seizure disorders (https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/05/gynecologic-management-of-adolescents-and-young-women-with-seizure-disorders) [119]

Published by: American College of Obstetricians and Gynecologists

Last published: 2020 (reaffirmed 2024)

Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy (https://www.aan.com/practice/guidelines) [76]

Published by: American Academy of Neurology

Last published: 2018 (reaffirmed 2024)

Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy (https://www.aan.com/practice/guidelines) [103]

Published by: American Academy of Neurology

Last published: 2018 (reaffirmed 2024)

Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors (https://www.aan.com/practice/guidelines) [170]

Published by: American Academy of Neurology; American Epilepsy Society

Last published: 2017 (reaffirmed 2023)

Evidence-based guideline: management of an unprovoked first seizure in adults (https://www.aan.com/practice/guidelines) [66]

Published by: American Academy of Neurology; American Epilepsy Society

Last published: 2015 (reaffirmed 2024)

Update: vagus nerve stimulation for the treatment of epilepsy (https://www.aan.com/practice/guidelines) [156]

Published by: American Academy of Neurology

Last published: 2013 (reaffirmed 2019)

International

Update: management issues for women with epilepsy - focus on pregnancy: obstetrical complications and change in seizure frequency (https://www.aan.com/practice/guidelines) [131]

Published by: American Academy of Neurology **Last published:** 2009 (reaffirmed 2022)

Update: management issues for women with epilepsy - focus on pregnancy: vitamin K, folic acid, blood levels, and breastfeeding (https://www.aan.com/practice/guidelines) [129]

Published by: American Academy of Neurology **Last published:** 2009 (reaffirmed 2022)

Treatment of the child with a first unprovoked seizure (https://www.aan.com/practice/guidelines) [171]

Published by: American Academy of Neurology **Last published:** 2003 (reaffirmed 2024)

Temporal lobe and localized neocortical resections for epilepsy (https://www.aan.com/practice/guidelines) [147]

Published by: American Academy of Neurology **Last published:** 2003 (reaffirmed 2022)

Management of post-stroke seizures and epilepsy (https://eso-stroke.org/guidelines/eso-guideline-directory/#rehabilitation) [19]

Published by: European Stroke Organisation **Last published:** 2017

Epilepsies in children, young people and adults (https://www.nice.org.uk/guidance/NG217) [60]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2022

Diagnosis and management of epilepsy in adults (https://www.sign.ac.uk/our-guidelines) [61]

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2015 (revalidated 2019)

Online resources

1. PROQOLID: Quality of Life in Epilepsy Inventory-10 (QOLIE-10) (https://eprovide.mapi-trust.org/instruments/quality-of-life-in-epilepsy-inventory-10) *(external link)*

2. Epilepsy Foundation: driver information by state (https://www.epilepsy.com/driving-laws) *(external link)*

3. The North American AED (Antiepileptic Drug) Pregnancy Registry (https://www.aedpregnancyregistry.org) *(external link)*

REFERENCES

Key articles

- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-30. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13670) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28276060?tool=bestpractice.bmj.com)

- Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21. Full text (https://onlinelibrary.wiley.com/doi/10.1111/epi.13709) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28276062?tool=bestpractice.bmj.com)

- Leone MA, Giussani G, Nevitt SJ, et al. Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure. Cochrane Database Syst Rev. 2021 May 4;(5):CD007144. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007144.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33942281?tool=bestpractice.bmj.com)

- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr. 2018 Jul-Aug;18(4):260-8. Full text (https://journals.sagepub.com/doi/10.5698/1535-7597.18.4.260) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30254527?tool=bestpractice.bmj.com)

- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr. 2018 Jul-Aug;18(4):269-78. Full text (https://journals.sagepub.com/doi/10.5698/1535-7597.18.4.269) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30254528?tool=bestpractice.bmj.com)

- Royal College of Obstetricians and Gynaecologists. Epilepsy in pregnancy (Green-top Guideline No.68). Jun 2016 (updated May 2018) [internet publication]. Full text (https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg68_epilepsy.pdf)

- Nevitt SJ, Sudell M, Weston J, et al. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017 Dec 15;(12):CD011412. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011412.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29243813?tool=bestpractice.bmj.com)

- Boon P, De Cock E, Mertens A, et al. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Curr Opin Neurol. 2018 Apr;31(2):198-210. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29493559?tool=bestpractice.bmj.com)

References

1. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-30. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13670) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28276060?tool=bestpractice.bmj.com)

2. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014 Apr;55(4):475-82. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.12550) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24730690?tool=bestpractice.bmj.com)

3. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21. Full text (https://onlinelibrary.wiley.com/doi/10.1111/epi.13709) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28276062?tool=bestpractice.bmj.com)

4. GBD 2016 Epilepsy Collaborators. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Apr;18(4):357-75. Full text (https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30454-X/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30773428?tool=bestpractice.bmj.com)

5. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. 2017 Jan 17;88(3):296-303. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5272794) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27986877?tool=bestpractice.bmj.com)

6. Sen A, Jette N, Husain M, et al. Epilepsy in older people. Lancet. 2020 Feb 29;395(10225):735-48. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32113502?tool=bestpractice.bmj.com)

7. Rao VR, Parko KL. Clinical approach to posttraumatic epilepsy. Semin Neurol. 2015 Feb;35(1):57-63. Full text (https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0035-1544239) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25714868?tool=bestpractice.bmj.com)

8. Salazar AM, Jabbari B, Vance SC, et al. Epilepsy after penetrating head injury. I. Clinical correlates: a report of the Vietnam Head Injury Study. Neurology. 1985 Oct;35(10):1406-14. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3929158?tool=bestpractice.bmj.com)

9. Annegers JF, Grabow JD, Groover RV, et al. Seizures after head trauma: a population study. Neurology. 1980 Jul;30(7 Pt 1):683-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7190235?tool=bestpractice.bmj.com)

10. Annegers JF, Hauser WA, Coan SP, et al. A population-based study of seizures after traumatic brain injuries. N Engl J Med. 1998 Jan 1;338(1):20-4. Full text (https://www.nejm.org/doi/full/10.1056/NEJM199801013380104) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9414327?tool=bestpractice.bmj.com)

REFERENCES

11. Reddy DS, Volkmer R 2nd. Neurocysticercosis as an infectious acquired epilepsy worldwide. Seizure. 2017 Nov;52:176-81. Full text (https://www.seizure-journal.com/article/S1059-1311(17)30558-7/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29055271?tool=bestpractice.bmj.com)

12. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. Handb Clin Neurol. 2016;134:267-85. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803433) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26948360?tool=bestpractice.bmj.com)

13. Maschio M. Brain tumor-related epilepsy. Curr Neuropharmacol. 2012 Jun;10(2):124-33. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3386502) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23204982?tool=bestpractice.bmj.com)

14. Foy PM, Copeland GP, Shaw MD. The natural history of postoperative seizures. Acta Neurochir (Wien). 1981;57(1-2):15-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/7270268?tool=bestpractice.bmj.com)

15. Severino M, Geraldo AF, Utz N, et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain. 2020 Oct 1;143(10):2874-94. Full text (https://academic.oup.com/brain/article/143/10/2874/5890851) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32779696?tool=bestpractice.bmj.com)

16. Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. Dialogues Clin Neurosci. 2008;10(1):47-62. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181860) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18472484?tool=bestpractice.bmj.com)

17. Josephson CB, Rosenow F, Al-Shahi Salman R. Intracranial vascular malformations and epilepsy. Semin Neurol. 2015 Jun;35(3):223-34. Full text (https://www.thieme-connect.de/products/ejournals/html/10.1055/s-0035-1552621) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26060902?tool=bestpractice.bmj.com)

18. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 1993 May-Jun;34(3):453-68. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8504780?tool=bestpractice.bmj.com)

19. Holtkamp M, Beghi E, Benninger F, et al. European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy. Eur Stroke J. 2017 Jun;2(2):103-15. Full text (https://journals.sagepub.com/doi/10.1177/2396987317705536) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31008306?tool=bestpractice.bmj.com)

20. Subota A, Pham T, Jetté N, et al. The association between dementia and epilepsy: a systematic review and meta-analysis. Epilepsia. 2017 Jun;58(6):962-72. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13744) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28397967?tool=bestpractice.bmj.com)

21. Goulden KJ, Shinnar S, Koller H, et al. Epilepsy in children with mental retardation: a cohort study. Epilepsia. 1991 Sep-Oct;32(5):690-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1915178?tool=bestpractice.bmj.com)

22. Boillot M, Baulac S. Genetic models of focal epilepsies. J Neurosci Methods. 2016 Feb 15;260:132-43. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26072248?tool=bestpractice.bmj.com)

23. Ellis CA, Petrovski S, Berkovic SF. Epilepsy genetics: clinical impacts and biological insights. Lancet Neurol. 2020 Jan;19(1):93-100. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31494011?tool=bestpractice.bmj.com)

24. Tan HJ, Singh J, Gupta R, et al. Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes. Cochrane Database Syst Rev. 2014 Sep 5;(9):CD006779. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006779.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25190506?tool=bestpractice.bmj.com)

25. Bertram E. The relevance of kindling for human epilepsy. Epilepsia. 2007;48 Suppl 2:65-74. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17571354?tool=bestpractice.bmj.com)

26. Engelborghs S, D'Hooge R, De Deyn PP. Pathophysiology of epilepsy. Acta Neurol Belg. 2000 Dec;100(4):201-13. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11233674?tool=bestpractice.bmj.com)

27. Nemani VM. Binder DK. Emerging role of gap junctions in epilepsy. Histol Histopathol. 2005 Jan;20(1):253-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15578443?tool=bestpractice.bmj.com)

28. Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. Neurotherapeutics. 2007 Jan;4(1):18-61. Full text (https://link.springer.com/content/pdf/10.1016/j.nurt.2006.11.010.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17199015?tool=bestpractice.bmj.com)

29. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med. 1976 Nov 4;295(19):1029-33. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/972656?tool=bestpractice.bmj.com)

30. Dreier JW, Li J, Sun Y, et al. Evaluation of long-term risk of epilepsy, psychiatric disorders, and mortality among children with recurrent febrile seizures: a national cohort study in Denmark. JAMA Pediatr. 2019 Oct 7;173(12):1164-70. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31589251?tool=bestpractice.bmj.com)

31. Annegers JF, Hauser WA, Shirts SB, et al. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med. 1987 Feb 26;316(9):493-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3807992?tool=bestpractice.bmj.com)

32. Cendes F. Febrile seizures and mesial temporal sclerosis. Curr Opin Neurol. 2004 Apr;17(2):161-4. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15021243?tool=bestpractice.bmj.com)

33. Annegers JF, Hauser WA, Beghai E, et al. The risk of unprovoked seizures after encephalitis and meningitis. Neurology. 1988 Sep;38(9):1407-10. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3412588?tool=bestpractice.bmj.com)

34. White AC Jr, Coyle CM, Rajshekhar V, et al. Diagnosis and treatment of neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American

Society of Tropical Medicine and Hygiene (ASTMH). Clin Infect Dis. 2018 Apr 3;66(8):e49-75. Full text (https://academic.oup.com/cid/article/66/8/e49/4885412) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29481580?tool=bestpractice.bmj.com)

35. Shinton RA, Gill JS, Zezulka AV, et al. The frequency of epilepsy preceding stroke. Case-control study in 230 patients. Lancet. 1987 Jan 3;1(8523):11-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2879091?tool=bestpractice.bmj.com)

36. College of Emergency Medicine (UK). Evidence-based flowchart for the management of first seizure in the emergency department. Dec 2009 [internet publication]. Full text (https://rcem.ac.uk/wp-content/uploads/2021/10/First_Seizure_in_the_ED_Flowchart_Dec2009.pdf)

37. Koutroumanidis M, Arzimanoglou A, Caraballo R, et al. The role of EEG in the diagnosis and classification of the epilepsy syndromes: a tool for clinical practice by the ILAE Neurophysiology Task Force (Part 1). Epileptic Disord. 2017 Sep 1;19(3):233-98. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28984246?tool=bestpractice.bmj.com)

38. Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy: an operational curve. Epilepsia. 1987 Jul-Aug;28(4):331-4. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3622408?tool=bestpractice.bmj.com)

39. Boon P, De Reuck J, Drieghe C, et al. Long-term video-EEG monitoring revisited. The value of interictal and ictal video-EEG recording, a follow-up study. Eur Neurol. 1994;34 Suppl 1:33-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8001608?tool=bestpractice.bmj.com)

40. Harden CL, Huff JS, Schwartz TH, et al. Reassessment: neuroimaging in the emergency patient presenting with seizure (an evidence-based review). Neurology. 2007 Oct 30;69(18):1772-80. Full text (https://n.neurology.org/content/69/18/1772) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17967993?tool=bestpractice.bmj.com)

41. Gaillard WD, Chiron C, Cross JH, et al; ILAE, Subcommittee for Pediatric Neuroimaging. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009 Sep;50(9):2147-53. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/j.1528-1167.2009.02075.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19389145?tool=bestpractice.bmj.com)

42. American College of Radiology. ACR appropriateness criteria: seizures and epilepsy. 2019 [internet publication]. Full text (https://acsearch.acr.org/docs/69479/Narrative)

43. Kuzniecky R, Burgard S, Faught E, et al. Predictive value of magnetic resonance imaging in temporal lobe epilepsy surgery. Arch Neurol. 1993 Jan;50(1):65-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8418802?tool=bestpractice.bmj.com)

44. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: use of fMRI in the presurgical evaluation of patients with epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2017 Jan 24;88(4):395-402. Full text (https://n.neurology.org/content/88/4/395) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28077494?tool=bestpractice.bmj.com)

45. Bauer PR, Reitsma JB, Houweling BM, et al. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. J Neurol Neurosurg Psychiatry. 2014 May;85(5):581-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23986313?tool=bestpractice.bmj.com)

46. Massot-Tarrús A, Mousavi SR, Mirsattari SM. Comparing the intracarotid amobarbital test and functional MRI for the presurgical evaluation of language in epilepsy. Curr Neurol Neurosci Rep. 2017 Jul;17(7):54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28623489?tool=bestpractice.bmj.com)

47. Massot-Tarrús A, White KP, Mousavi SR, et al. Concordance between fMRI and Wada test for memory lateralization in temporal lobe epilepsy: a meta-analysis and systematic review. Epilepsy Behav. 2020 Jun;107:107065. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32276205?tool=bestpractice.bmj.com)

48. Massot-Tarrús A, White K, Mirsattari SM. Comparing the Wada test and functional MRI for the presurgical evaluation of memory in temporal lobe epilepsy. Curr Neurol Neurosci Rep. 2019 May 1;19(6):31. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31044310?tool=bestpractice.bmj.com)

49. Salamon N, Kung J, Shaw SJ, et al. FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. Neurology. 2008 Nov 11;71(20):1594-601. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19001249?tool=bestpractice.bmj.com)

50. Opheim G, van der Kolk A, Markenroth Bloch K, et al. 7T Epilepsy Task Force consensus recommendations on the use of 7T MRI in clinical practice. Neurology. 2021 Feb 16;96(7):327-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33361257?tool=bestpractice.bmj.com)

51. Jankovic J, Lang AE. Movement disorders: diagnosis and assessment. In: Bradley WG, Daroff RB, Fenichel GM, et al, eds. Neurology in clinical practice. Principles of diagnosis and management. 4th ed. Philadelphia, PA: Elsevier; 2004:313-5.

52. Fahn S, Jankovic J. Principles and practice of movement disorders. Philadelphia, PA: Elsevier; 2007:409-33.

53. Bartsch T, Butler C. Transient amnesic syndromes. Nat Rev Neurol. 2013 Feb;9(2):86-97. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23296343?tool=bestpractice.bmj.com)

54. Kim J, Kwon Y, Yang Y, et al. Clinical experience of modified diffusion-weighted imaging protocol for lesion detection in transient global amnesia: an 8-year large-scale clinical study. J Neuroimaging. 2014 Jul-Aug;24(4):331-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23551898?tool=bestpractice.bmj.com)

55. Scheel M, Malkowsky C, Klingebiel R, et al. Magnetic resonance imaging in transient global amnesia: lessons learned from 198 cases. Clin Neuroradiol. 2012 Dec;22(4):335-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22422060?tool=bestpractice.bmj.com)

56. Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J Neurol Neurosurg Psychiatry. 2010 Jul;81(7):719-25. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20581136?tool=bestpractice.bmj.com)

REFERENCES

57. Stone J, Burton C, Carson A. Recognising and explaining functional neurological disorder. BMJ. 2020 Oct 21;371:m3745. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33087335?tool=bestpractice.bmj.com)

58. Brown RJ, Reuber M. Psychological and psychiatric aspects of psychogenic non-epileptic seizures (PNES): A systematic review. Clin Psychol Rev. 2016 Apr;45:157-82. Full text (https://eprints.whiterose.ac.uk/98748) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27084446?tool=bestpractice.bmj.com)

59. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children (reaffirmed 2017). Neurology. 2000 Sep 12;55(5):616-23. Full text (https://n.neurology.org/content/55/5/616.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10980722?tool=bestpractice.bmj.com)

60. National Institute for Health and Care Excellence. Epilepsies in children, young people and adults. Apr 2022 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng217)

61. Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. May 2015 (revalidated Aug 2019) [internet publication]. Full text (https://www.sign.ac.uk/our-guidelines/diagnosis-and-management-of-epilepsy-in-adults)

62. Gidal B, Klein P, Hirsch LJ. Seizure clusters, rescue treatments, seizure action plans: unmet needs and emerging formulations. Epilepsy Behav. 2020 Nov;112:107391. Full text (https://www.epilepsybehavior.com/article/S1525-5050(20)30570-9/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32898744?tool=bestpractice.bmj.com)

63. Mesraoua B, Abou-Khalil B, Hosni Khodair R, et al. Seizure clusters. J Drug Assess. 2021 Aug 14;10(1):86-90. Full text (https://www.tandfonline.com/doi/full/10.1080/21556660.2021.1962671) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34408916?tool=bestpractice.bmj.com)

64. Jafarpour S, Hirsch LJ, Gaínza-Lein M, et al. Seizure cluster: definition, prevalence, consequences, and management. Seizure. 2019 May;68:9-15. Full text (https://www.seizure-journal.com/article/S1059-1311(18)30112-2/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29871784?tool=bestpractice.bmj.com)

65. Leone MA, Giussani G, Nevitt SJ, et al. Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure. Cochrane Database Syst Rev. 2021 May 4;(5):CD007144. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007144.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33942281?tool=bestpractice.bmj.com)

66. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (reaffirmed 2018). Neurology. 2015 Apr 21;84(16):1705-13. Full text (https://n.neurology.org/content/84/16/1705) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25901057?tool=bestpractice.bmj.com)

67. Thieffry S, Klein P, Baulac M, et al. Understanding the challenge of comparative effectiveness research in focal epilepsy: a review of network meta-analyses and real-world evidence on antiepileptic

drugs. Epilepsia. 2020 Apr;61(4):595-609. Full text (https://onlinelibrary.wiley.com/doi/10.1111/epi.16476) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32201951?tool=bestpractice.bmj.com)

68. Perucca E, Brodie MJ, Kwan P, et al. 30 years of second-generation antiseizure medications: impact and future perspectives. Lancet Neurol. 2020 Jun;19(6):544-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32109411?tool=bestpractice.bmj.com)

69. Palleria C, Cozza G, Khengar R, et al. Safety profile of the newest antiepileptic drugs: a curated literature review. Curr Pharm Des. 2017;23(37):5606-24. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28799510?tool=bestpractice.bmj.com)

70. Tassone DM, Boyce E, Guyer J, et al. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther. 2007 Jan;29(1):26-48. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17379045?tool=bestpractice.bmj.com)

71. Delahoy P, Thompson S, Marschner IC. Pregabalin versus gabapentin in partial epilepsy: a meta-analysis of dose-response relationships. BMC Neurol. 2010 Nov 1;10:104. Full text (https://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-10-104) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21040531?tool=bestpractice.bmj.com)

72. Panebianco M, Bresnahan R, Marson AG. Pregabalin add-on for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2022 Mar 29;3:CD005612. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005612.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35349176?tool=bestpractice.bmj.com)

73. Kim LG, Johnson TL, Marson AG, et al; MRC MESS Study Group. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. Lancet Neurol. 2006 Apr;5(4):317-22. Full text (https://www.thelancet.com/journals/laneur/article/PIIS1474-4422%2806%2970383-0/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16545748?tool=bestpractice.bmj.com)

74. Koch MW, Polman SK. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006453. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006453.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19821367?tool=bestpractice.bmj.com)

75. Brodie MJ, Perucca E, Ryvlin P, et al; Levetiracetam Monotherapy Study Group. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology. 2007 Feb 6;68(6):402-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17283312?tool=bestpractice.bmj.com)

76. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr. 2018 Jul-Aug;18(4):260-8. Full text (https://journals.sagepub.com/doi/10.5698/1535-7597.18.4.260) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30254527?tool=bestpractice.bmj.com)

REFERENCES

77. Lattanzi S, Zaccara G, Giovannelli F, et al. Antiepileptic monotherapy in newly diagnosed focal epilepsy. A network meta-analysis. Acta Neurol Scand. 2019 Jan;139(1):33-41. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30194755?tool=bestpractice.bmj.com)

78. Nevitt SJ, Tudur Smith C, Weston J, et al. Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review. Cochrane Database Syst Rev. 2018 Jun 28;(6):CD001031. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001031.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29952431?tool=bestpractice.bmj.com)

79. Nevitt SJ, Tudur Smith C, Marson AG. Oxcarbazepine versus phenytoin monotherapy for epilepsy: an individual participant data review. Cochrane Database Syst Rev. 2018 Oct 23;(10):CD003615. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003615.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30350354?tool=bestpractice.bmj.com)

80. Marson A, Burnside G, Appleton R, et al; SANAD II Collaborators. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet. 2021 Apr 10;397(10282):1363-74. Full text (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00247-6/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33838757?tool=bestpractice.bmj.com)

81. Reimers A, Ljung H. An evaluation of zonisamide, including its long-term efficacy, for the treatment of focal epilepsy. Expert Opin Pharmacother. 2019 Jun;20(8):909-15. Full text (https://www.tandfonline.com/doi/full/10.1080/14656566.2019.1595584) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30908087?tool=bestpractice.bmj.com)

82. Nevitt SJ, Sudell M, Tudur Smith C, et al. Topiramate versus carbamazepine monotherapy for epilepsy: an individual participant data review. Cochrane Database Syst Rev. 2019 Jun 24;(6):CD012065. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012065.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31233229?tool=bestpractice.bmj.com)

83. Arnold S, Badalamenti V, Diaz A, et al. Conversion to brivaracetam monotherapy for the treatment of patients with focal seizures: two double-blind, randomized, multicenter, historical control, phase III studies. Epilepsy Res. 2018 Mar;141:73-82. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29486396?tool=bestpractice.bmj.com)

84. Milovanović JR, Janković SM, Pejčić A, et al. Evaluation of brivaracetam: a new drug to treat epilepsy. Expert Opin Pharmacother. 2017 Sep;18(13):1381-9. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28737479?tool=bestpractice.bmj.com)

85. Menzler K, Mross PM, Rosenow F, et al. First clinical postmarketing experiences in the treatment of epilepsies with brivaracetam: a retrospective observational multicentre study. BMJ Open. 2019 Nov 4;9(11):e030746. Full text (https://bmjopen.bmj.com/content/9/11/e030746.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31690606?tool=bestpractice.bmj.com)

86. Feyissa AM. Brivaracetam in the treatment of epilepsy: a review of clinical trial data. Neuropsychiatr Dis Treat. 2019 Sep 9;15:2587-600. Full text (https://www.dovepress.com/brivaracetam-in-the-

treatment-of-epilepsy-a-review-of-clinical-trial-d-peer-reviewed-fulltext-article-NDT) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31571877?tool=bestpractice.bmj.com)

87. Simoens S. Lacosamide as adjunctive therapy for partial-onset epileptic seizures: a review of the clinical and economic literature. Curr Med Res Opin. 2011 Jul;27(7):1329-38. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21561394?tool=bestpractice.bmj.com)

88. Gidal BE, Laurenza A, Hussein Z, et al. Perampanel efficacy and tolerability with enzyme-inducing AEDs in patients with epilepsy. Neurology. 2015 May 12;84(19):1972-80. Full text (https://n.neurology.org/content/84/19/1972) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25878177?tool=bestpractice.bmj.com)

89. Li-Na Z, Deng C, Hai-Jiao W, et al. Indirect comparison of third-generation antiepileptic drugs as adjunctive treatment for uncontrolled focal epilepsy. Epilepsy Res. 2018 Jan;139:60-72. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29197667?tool=bestpractice.bmj.com)

90. Brigo F, Lattanzi S, Igwe SC, et al. Zonisamide add-on therapy for focal epilepsy. Cochrane Database Syst Rev. 2020 Jul 24;(7):CD001416. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001416.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32715463?tool=bestpractice.bmj.com)

91. Bresnahan R, Panebianco M, Marson AG. Brivaracetam add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev. 2022 Mar 14;3:CD011501. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011501.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35285519?tool=bestpractice.bmj.com)

92. Bresnahan R, Hounsome J, Jette N, et al. Topiramate add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2019 Oct 23;(10):CD001417. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001417.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31642054?tool=bestpractice.bmj.com)

93. Panebianco M, Bresnahan R, Ramaratnam S, et al. Lamotrigine add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2020 Mar 20;(3):CD001909. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001909.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32196639?tool=bestpractice.bmj.com)

94. Bresnahan R, Martin-McGill KJ, Williamson J, et al. Clobazam add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev. 2019 Oct 22;(10):CD004154. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004154.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31638272?tool=bestpractice.bmj.com)

95. Potschka H, Trinka E. Perampanel: does it have broad-spectrum potential? Epilepsia. 2019 Mar;60 (suppl 1):22-36. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.14456) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29953584?tool=bestpractice.bmj.com)

96. Panebianco M, Al-Bachari S, Hutton JL, et al. Gabapentin add-on treatment for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2021 Jan 12;(1):CD001415. Full text (https://

www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001415.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33434292?tool=bestpractice.bmj.com)

97. Bresnahan R, Atim-Oluk M, Marson AG. Oxcarbazepine add-on for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2020 Mar 4;(3):CD012433. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012433.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32129501?tool=bestpractice.bmj.com)

98. Mbizvo GK, Chandrasekar B, Nevitt SJ, et al. Levetiracetam add-on for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2020 Jun 30;(6):CD001901. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001901.pub3/full)

99. Babar RK, Bresnahan R, Gillespie CS, et al. Lacosamide add-on therapy for focal epilepsy. Cochrane Database Syst Rev. 2021 May 17;(5):CD008841. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008841.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33998660?tool=bestpractice.bmj.com)

100. Chang XC, Yuan H, Wang Y, et al. Eslicarbazepine acetate add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2021 Jun 22;(6):CD008907. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008907.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34155624?tool=bestpractice.bmj.com)

101. Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020 Jan;19(1):38-48. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31734103?tool=bestpractice.bmj.com)

102. Sperling MR, Abou-Khalil B, Aboumatar S, et al. Efficacy of cenobamate for uncontrolled focal seizures: post hoc analysis of a phase 3, multicenter, open-label study. Epilepsia. 2021 Dec;62(12):3005-15. Full text (https://onlinelibrary.wiley.com/doi/10.1111/epi.17091) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34633084?tool=bestpractice.bmj.com)

103. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Curr. 2018 Jul-Aug;18(4):269-78. Full text (https://journals.sagepub.com/doi/10.5698/1535-7597.18.4.269) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30254528?tool=bestpractice.bmj.com)

104. Bresnahan R, Gianatsi M, Maguire MJ, et al. Vigabatrin add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2020 Jul 30;(7):CD007302. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007302.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32730657?tool=bestpractice.bmj.com)

105. Panebianco M, Prabhakar H, Marson AG. Rufinamide add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020 Nov 8;(11):CD011772. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011772.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33179247?tool=bestpractice.bmj.com)

106. Bresnahan R, Martin-McGill KJ, Hutton JL, et al. Tiagabine add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2019 Oct 14;(10):CD001908. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001908.pub4/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31608990?tool=bestpractice.bmj.com)

107. Shi LL, Bresnahan R, Martin-McGill KJ, et al. Felbamate add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2019 Aug 1;(8):CD008295. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008295.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31425617?tool=bestpractice.bmj.com)

108. Slater J, Chung S, Huynh L, et al. Efficacy of antiepileptic drugs in the adjunctive treatment of refractory partial-onset seizures: meta-analysis of pivotal trials. Epilepsy Res. 2018 Jul;143:120-9. Full text (https://www.sciencedirect.com/science/article/pii/S0920121117301766) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29784458?tool=bestpractice.bmj.com)

109. Glauser T, Ben-Menachem E, Bourgeois B, et al; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013 Mar;54(3):551-63. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.12074) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23350722?tool=bestpractice.bmj.com)

110. Lattanzi S, Trinka E, Del Giovane C, et al. Antiepileptic drug monotherapy for epilepsy in the elderly: a systematic review and network meta-analysis. Epilepsia. 2019 Nov;60(11):2245-54. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31608438?tool=bestpractice.bmj.com)

111. Lezaic N, Gore G, Josephson CB, et al. The medical treatment of epilepsy in the elderly: a systematic review and meta-analysis. Epilepsia. 2019 Jul;60(7):1325-40. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31185130?tool=bestpractice.bmj.com)

112. Stephen LJ, Harden C, Tomson T, et al. Management of epilepsy in women. Lancet Neurol. 2019 May;18(5):481-91. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30857949?tool=bestpractice.bmj.com)

113. Johansen-Bibby A. Prescribing for pregnancy: epilepsy. Drug Ther Bull. 2020 Jul;58(7):103-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32503804?tool=bestpractice.bmj.com)

114. Pack AM, Oskoui M, Williams Roberson S, et al. Teratogenesis, perinatal, and neurodevelopmental outcomes after in utero exposure to antiseizure medication: practice guideline from the AAN, AES, and SMFM. Neurology. 2024 Jun;102(11):e209279. Full text (https://www.neurology.org/doi/10.1212/WNL.0000000000209279) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/38748979?tool=bestpractice.bmj.com)

115. Wyszynski DF, Nambisan M, Surve T, et al; Antiepileptic Drug Pregnancy Registry. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005 Mar 22;64(6):961-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15781808?tool=bestpractice.bmj.com)

116. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol. 2004 May;61(5):673-8. Full text (https://jamanetwork.com/journals/

jamaneurology/fullarticle/785808) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15148143?tool=bestpractice.bmj.com)

117. Meador KJ, Baker GA, Browning N, et al; NEAD Study Group. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med. 2009 Apr 16;360(16):1597-605. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19369666?tool=bestpractice.bmj.com)

118. Medicines and Healthcare products Regulatory Agency. Antiepileptic drugs in pregnancy: updated advice following comprehensive safety review. Jan 2021 [internet publication]. Full text (https://www.gov.uk/drug-safety-update/antiepileptic-drugs-in-pregnancy-updated-advice-following-comprehensive-safety-review)

119. American College of Obstetricians and Gynecologists. Gynecologic management of adolescents and young women with seizure disorders: ACOG Committee Opinion, number 806. Obstet Gynecol. 2020 May;135(5):e213-20. Full text (https://journals.lww.com/greenjournal/Fulltext/2020/05000/Gynecologic_Management_of_Adolescents_and_Young.55.aspx) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32332416?tool=bestpractice.bmj.com)

120. Bjørk MH, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol. 2022 Jul 1;79(7):672-81. Full text (https://jamanetwork.com/journals/jamaneurology/fullarticle/2793003) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35639399?tool=bestpractice.bmj.com)

121. Medicines and Healthcare products Regulatory Agency. Topiramate (Topamax): introduction of new safety measures, including a pregnancy prevention programme. Jun 2024 [internet publication]. Full text (https://www.gov.uk/drug-safety-update/topiramate-topamax-introduction-of-new-safety-measures-including-a-pregnancy-prevention-programme)

122. European Medicines Agency. PRAC recommends new measures to avoid topiramate exposure in pregnancy. Sep 2023 [internet publication]. Full text (https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-topiramate-exposure-pregnancy)

123. Dreier JW, Bjørk MH, Alvestad S, et al. Prenatal exposure to antiseizure medication and incidence of childhood- and adolescence-onset psychiatric disorders. JAMA Neurol. 2023 Jun 1;80(6):568-77. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37067807?tool=bestpractice.bmj.com)

124. Bromley R, Adab N, Bluett-Duncan M, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2023 Aug 29;8(8):CD010224. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010224.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37647086?tool=bestpractice.bmj.com)

125. Medicines and Healthcare products Regulatory Agency. Pregabalin (Lyrica): findings of safety study on risks during pregnancy. Apr 2022 [internet publication]. Full text (https://www.gov.uk/drug-safety-update/pregabalin-lyrica-findings-of-safety-study-on-risks-during-pregnancy)

126. Athar F, Ehsan M, Farooq M, et al. Adverse fetal and neonatal outcomes following in-utero exposure to oxcarbazepine: a systematic review and meta-analysis. Br J Clin Pharmacol. 2022

Aug;88(8):3600-9. Full text (https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15413) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35591806?tool=bestpractice.bmj.com)

127. Royal College of Obstetricians and Gynaecologists. Epilepsy in pregnancy (Green-top Guideline No.68). Jun 2016 (updated May 2018) [internet publication]. Full text (https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg68_epilepsy.pdf)

128. Zhu LN, Chen D, Xu D, et al. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: an indirect comparison. Seizure. 2017 Oct;51:121-32. Full text (https://www.seizure-journal.com/article/S1059-1311(17)30404-1/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28854405?tool=bestpractice.bmj.com)

129. Harden CL, Pennell PB, Koppel BS, et al; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy - focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Neurology. 2009 Jul 14;73(2):142-9. Full text (https://n.neurology.org/content/73/2/142.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19398680?tool=bestpractice.bmj.com)

130. Morrow JI, Hunt SJ, Russell AJ, et al. Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. J Neurol Neurosurg Psychiatry. 2009 May;80(5):506-11. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18977812?tool=bestpractice.bmj.com)

131. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy - focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency. Neurology. 2009 Jul 14;73(2):126-32. Full text (https://n.neurology.org/content/73/2/126.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19398682?tool=bestpractice.bmj.com)

132. Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord. 2019 Dec 1;21(6):497-517. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31782407?tool=bestpractice.bmj.com)

133. Pennell PB, Karanam A, Meador KJ, et al. Antiseizure medication concentrations during pregnancy: results from the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study. JAMA Neurol. 2022 Apr 1;79(4):370-9. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8845026) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35157004?tool=bestpractice.bmj.com)

134. New South Wales Ministry of Health. Infants and children: acute management of seizures. Feb 2016 [internet publication]. Full text (http://cedd.org.au/wordpress/wp-content/uploads/2015/04/Infants-and-Children-Acute-Management-of-Seizures.pdf)

135. Ambrosetto G, Tassinari CA. Antiepileptic drug treatment of benign childhood epilepsy with rolandic spikes: is it necessary? Epilepsia. 1990 Nov-Dec;31(6):802-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/2123157?tool=bestpractice.bmj.com)

REFERENCES

136. Nevitt SJ, Sudell M, Weston J, et al. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017 Dec 15;(12):CD011412. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011412.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29243813?tool=bestpractice.bmj.com)

137. Schubert-Bast S, Willems LM, Kurlemann G, et al. Postmarketing experience with brivaracetam in the treatment of focal epilepsy in children and adolescents. Epilepsy Behav. 2018 Dec;89:89-93. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30390435?tool=bestpractice.bmj.com)

138. Arya R, Giridharan N, Anand V, et al. Clobazam monotherapy for focal or generalized seizures. Cochrane Database Syst Rev. 2018 Jul 11;(7):CD009258. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009258.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29995989?tool=bestpractice.bmj.com)

139. Cao Y, He X, Zhao L, et al. Efficacy and safety of levetiracetam as adjunctive treatment in children with focal onset seizures: a systematic review and meta-analysis. Epilepsy Res. 2019 Jul;153:40-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30965274?tool=bestpractice.bmj.com)

140. Lattanzi S, Brigo F, Grillo E, et al. Adjunctive eslicarbazepine acetate in pediatric patients with focal epilepsy: a systematic review and meta-analysis. CNS Drugs. 2018 Mar;32(3):189-96. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29508243?tool=bestpractice.bmj.com)

141. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000 Feb 3;342(5):314-9. Full text (https://www.nejm.org/doi/10.1056/NEJM200002033420503) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10660394?tool=bestpractice.bmj.com)

142. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. 2008 Jan 1;70(1):54-65. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18166707?tool=bestpractice.bmj.com)

143. Michaelis R, Tang V, Nevitt SJ, et al. Psychological treatments for people with epilepsy. Cochrane Database Syst Rev. 2020 Sep 7;(8):CD012081. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012081.pub3/full)

144. Luedke MW, Blalock DV, Goldstein KM, et al. Self-management of epilepsy: a systematic review. Ann Intern Med. 2019 Jul 16;171(2):117-26. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31261386?tool=bestpractice.bmj.com)

145. Michaelis R, Tang V, Goldstein LH, et al. Psychological treatments for adults and children with epilepsy: evidence-based recommendations by the International League Against Epilepsy Psychology Task Force. Epilepsia. 2018 Jul;59(7):1282-302. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29917225?tool=bestpractice.bmj.com)

146. Sheng J, Liu S, Qin H, et al. Drug-resistant epilepsy and surgery. Curr Neuropharmacol. 2018;16(1):17-28. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771378) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28474565?tool=bestpractice.bmj.com)

147. Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy. Neurology. 2003 Feb 25;60(4):538-47. Full text (https://

n.neurology.org/content/60/4/538.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12601090?tool=bestpractice.bmj.com)

148. West S, Nevitt SJ, Cotton J, et al. Surgery for epilepsy. Cochrane Database Syst Rev. 2019 Jun 25;(6):CD010541. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010541.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31237346?tool=bestpractice.bmj.com)

149. Kohlhase K, Zöllner JP, Tandon N, et al. Comparison of minimally invasive and traditional surgical approaches for refractory mesial temporal lobe epilepsy: a systematic review and meta-analysis of outcomes. Epilepsia. 2021 Apr;62(4):831-45. Full text (https://onlinelibrary.wiley.com/doi/10.1111/epi.16846) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33656182?tool=bestpractice.bmj.com)

150. Grewal SS, Alvi MA, Lu VM, et al. Magnetic resonance-guided laser interstitial thermal therapy versus stereotactic radiosurgery for medically intractable temporal lobe epilepsy: a systematic review and meta-analysis of seizure outcomes and complications. World Neurosurg. 2019 Feb;122:e32-47. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30244184?tool=bestpractice.bmj.com)

151. Boon P, De Cock E, Mertens A, et al. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Curr Opin Neurol. 2018 Apr;31(2):198-210. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29493559?tool=bestpractice.bmj.com)

152. Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev. 2015 Apr 3;(4):CD002896. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002896.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25835947?tool=bestpractice.bmj.com)

153. Wang HJ, Tan G, Zhu LN, et al. Predictors of seizure reduction outcome after vagus nerve stimulation in drug-resistant epilepsy. Seizure. 2019 Mar;66:53-60. Full text (https://www.seizure-journal.com/article/S1059-1311(18)30760-X/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30802843?tool=bestpractice.bmj.com)

154. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia. 2018 Feb;59(2):273-90. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13964) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29218702?tool=bestpractice.bmj.com)

155. Toffa DH, Touma L, El Meskine T, et al. Learnings from 30 years of reported efficacy and safety of vagus nerve stimulation (VNS) for epilepsy treatment: a critical review. Seizure. 2020 Dec;83:104-23. Full text (https://www.seizure-journal.com/article/S1059-1311(20)30309-5/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33120323?tool=bestpractice.bmj.com)

156. Morris GL 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013 Oct 15;81(16):1453-9. [Reaffirmed 2019.] Full text (https://n.neurology.org/content/81/16/1453.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23986299?tool=bestpractice.bmj.com)

157. US Food and Drug Administration. RNS® System - P100026. Jan 2015 [internet publication]. Full text (http://wayback.archive-it.org/7993/20170112091430/http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm376685.htm)

158. Bergey GK, Morrell MJ, Mizrahi EM, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015 Feb 24;84(8):810-7. Full text (https://n.neurology.org/content/84/8/810) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25616485?tool=bestpractice.bmj.com)

159. Heck CN, King-Stephens D, Massey AD, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. Epilepsia. 2014 Mar;55(3):432-41. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.12534) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24621228?tool=bestpractice.bmj.com)

160. Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011 Sep 27;77(13):1295-304. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21917777?tool=bestpractice.bmj.com)

161. Freeman JM, Kossoff EH, Freeman JB, et al. The ketogenic diet: a treatment for children and others with epilepsy. New York, NY: Demos Medical Publishing; 2006.

162. Martin-McGill KJ, Jackson CF, Bresnahan R, et al. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020 Jun 24;6(6):CD001903. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001903.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32588435?tool=bestpractice.bmj.com)

163. Zhang Y, Xu J, Zhang K, et al. The anticonvulsant effects of ketogenic diet on epileptic seizures and potential mechanisms. Curr Neuropharmacol. 2018;16(1):66-70. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771386) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28521671?tool=bestpractice.bmj.com)

164. Gloss D, Pargeon K, Pack A, et al. Antiseizure medication withdrawal in seizure-free patients: practice advisory update summary. Report of the AAN Guideline Subcommittee. Neurology. 2021 Dec 7;97(23):1072-81. Full text (https://n.neurology.org/content/97/23/1072) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34873018?tool=bestpractice.bmj.com)

165. Strozzi I, Nolan SJ, Sperling MR, et al. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev. 2015 Feb 11;(2):CD001902. Full text (http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD001902.pub2/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25922863?tool=bestpractice.bmj.com)

166. Hixson JD. Stopping antiepileptic drugs: when and why? Curr Treat Options Neurol. 2010 Sep;12(5):434-42. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2918788) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20730110?tool=bestpractice.bmj.com)

167. Chen H, He H, Xiao Y, et al. Losigamone add-on therapy for focal epilepsy. Cochrane Database Syst Rev. 2019 Dec 11;(12):CD009324. Full text (https://www.cochranelibrary.com/

cdsr/doi/10.1002/14651858.CD009324.pub5/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31823350?tool=bestpractice.bmj.com)

168. Sperling MR, Klein P, Tsai J. Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures. Epilepsia. 2017 Apr;58(4):558-64. Full text (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13705) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28230252?tool=bestpractice.bmj.com)

169. American Epilepsy Society. AES position statement on cannabis as a treatment for patients with epileptic seizures. Sept 2022 [internet publication]. Full text (https://www.aesnet.org/about/about-aes/position-statements/aes-position-statement-on-cannabis-as-a-treatment-for-patients-with-epileptic-seizures)

170. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2017 Apr 25;88(17):1674-80. [Reaffirmed 2020.] Full text (https://n.neurology.org/content/88/17/1674.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28438841?tool=bestpractice.bmj.com)

171. Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure. Neurology. 2003 Jan 28;60(2):166-75 (reaffirmed 2018). Full text (https://n.neurology.org/content/60/2/166.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12552027?tool=bestpractice.bmj.com)

172. Lamberink HJ, Otte WM, Blümcke I, et al. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. Lancet Neurol. 2020 Sep;19(9):748-57. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32822635?tool=bestpractice.bmj.com)

173. Sveinsson O, Andersson T, Carlsson S, et al. The incidence of SUDEP: a nationwide population-based cohort study. Neurology. 2017 Jul 11;89(2):170-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28592455?tool=bestpractice.bmj.com)

174. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. Lancet Neurol. 2016 Jan;15(1):106-15. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26549780?tool=bestpractice.bmj.com)

175. Hesdorffer DC, Ishihara L, Mynepalli L, et al. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. Ann Neurol. 2012 Aug;72(2):184-91. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22887468?tool=bestpractice.bmj.com)

176. Maguire MJ, Marson AG, Nevitt SJ. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev. 2021 Apr 16;(4):CD010682. Full text (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010682.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33860531?tool=bestpractice.bmj.com)

177. American Epilepsy Society. Substitution of different formulations of antiseizure medication for the treatment of epilepsy. Aug 2023 [internet publication]. Full text (https://www.aesnet.org/about/about-

aes/position-statements/substitution-of-different-formulations-of-antiepileptic-drugs-for-the-treatment-of-epilepsy)

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

DISCLAIMER

Contributors:

// Authors:

Ramses Ribot, MD

Assistant Professor of Clinical Neurology
Department of Neurology, Epilepsy Division, University of Miami, Miller School of Medicine, Miami, FL
DISCLOSURES: RR declares that he has no competing interests.

Andres M. Kanner, MD, FANA, FAES, FAAN

Professor of Clinical Neurology
Director, Comprehensive Epilepsy Center and Head, Section of Epilepsy, Department of Neurology, University of Miami, Miller School of Medicine, Miami, FL
DISCLOSURES: AMK has received honoraria from Eisai Laboratories for lectures given at international scientific meetings, and from the Epilepsy Foundation of America for being Co-Editor in Chief of Epilepsy.com. AMK is an author of a number of references cited in this topic.

// Acknowledgements:

Dr Ramses Ribot and Dr Andres M. Kanner would like to gratefully acknowledge Dr Vikram R. Rao, Dr John D. Hixson, and Dr Jeffrey Cohen, previous contributors to this topic.
DISCLOSURES: VRR served as a paid consultant for Neuropace, Inc., manufacturer of the Responsive Neurostimulation (RNS) System. JDH has received research funding and consultancy funds from UCB, Inc. JC declares that he has no competing interests.

// Peer Reviewers:

Edward Bromfield, MD

Chief
Epilepsy Division, Brigham and Women's Hospital, Associate Professor of Neurology, Harvard Medical School, Boston, MA
DISCLOSURES: At the time of review, EB declared that between 2004 and 2009, he received speaking honoraria from UCB Pharma, Novartis, Abbott Laboratories, GlaxoSmithKline, and Pfizer. He received consulting fees from UCB Pharma, Genzyme, and Spherics, and research funding from UCB Pharma. Unfortunately, we have since been made aware that EB is deceased.

Angus A. Wilfong, MD

Associate Professor
Pediatrics and Neurology, Baylor College of Medicine, Medical Director, Comprehensive Epilepsy Program, Texas Children's Hospital, Houston, TX
DISCLOSURES: AAW declares that he has no competing interests.

Cigdem I. Akman, MD

Assistant Professor
Division of Pediatric Neurology, Columbia University College of Physicians and Surgeons, New York, NY
DISCLOSURES: Not disclosed.

Pasquale Striano, MD, PhD

Contributors:

Consultant Neurologist
Muscular and Neurodegenerative Diseases Unit, "G Gaslini" Institute, Genova, Epilepsy Centre, Federico II University, Napoli, Italy
DISCLOSURES: PS declares that he has no competing interests.