BMJ Best Practice

Absence seizures

Straight to the point of care

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Summary

Typical absence seizure: behavioural arrest or staring, lasting 5 to 10 seconds, interrupting otherwise normal activity. Can be hyperventilation-induced.

Atypical absence seizures: less distinct beginning and end, not usually precipitated by hyperventilation.

Electroencephalogram (EEG) is the definitive test. Determining the exact nature of the seizure is key to the appropriate treatment and prognosis.

Most typical absence seizures are medically responsive, and childhood absence epilepsy (CAE) tends to remit by adulthood. Typical absence seizures in CAE, juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME) are treated with ethosuximide, valproate, or lamotrigine as first-line therapies.

Atypical absence seizures tend to be medically refractory and associated with intellectual disability. Atypical absence seizures in Lennox-Gastaut syndrome and epilepsy with myoclonic absences are treated with valproate or lamotrigine as first-line therapies.

Definition

An epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain".[1] Epilepsy is a disease of the brain defined by any of the following conditions:[1] (1) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy is further classified by aetiology (genetic, structural/metabolic, or unknown cause) and by epilepsy syndromes, which are defined by the conglomeration of seizure types, EEG patterns, age of onset, as well as a variety of other signs and symptoms. Classification of specific epilepsy syndromes allows for prediction of prognosis and appropriate therapy.

Absence seizures are a specific type of seizure characterised by abrupt cessation of activity and responsiveness with minimal, if any, associated movements. Absence seizures are further subdivided into typical, atypical, and absence with special features.

Typical absence seizures are approximately 5 to 10 seconds in duration, have minimal, if any, postictal confusion, and are usually precipitated by hyperventilation and sometimes by photic stimulation. They have a classic ictal EEG pattern of bilateral symmetric 3 Hz spike-and-wave with normal interictal background. Epilepsy syndromes with typical absence seizures include childhood absence epilepsy (CAE; characterised by brief absence seizures, usually without convulsions), juvenile absence epilepsy (JAE; characterised by absence seizures with tonic-clonic and, less commonly, myoclonic seizures), and juvenile myoclonic epilepsy (JME; generalised syndrome characterised by myoclonic jerks, generalised tonic-clonic seizures, and, less commonly, absence seizures; strong association with photosensitivity).

Atypical absence seizures have a less distinct beginning and end and are not usually precipitated by hyperventilation or photic stimulation, and the EEG shows generalised slow (<2.5 Hz) spike-and-wave with a diffusely slow background.[2] The classic epilepsy syndrome with atypical absence seizures is Lennox-Gastaut syndrome, characterised by multiple seizure types (severe tonic seizures, myoclonic-atonic seizures, and absence seizures), intellectual disability, and slow spike-and-wave on EEG.

OVERVIEW

Absence seizures with special features include myoclonic absence and eyelid myoclonia, characteristic of Jeavons syndrome.

Epidemiology

Epidemiological data for various forms of epilepsy can be quite difficult to ascertain due to variability in epilepsy classification and the age range of the population studied. It has been estimated, based on prior epidemiological studies, that 4000 children (younger than 18 years) are diagnosed with absence epilepsy and 1500 children with juvenile myoclonic epilepsy (JME) annually in the US.[9]

Subsequent studies based on the newer classification of epilepsy syndromes find the following:

Childhood absence epilepsy (CAE):[2] [10] [11] [12] [13] [14]

- Incidence reported varies from of 0.7 to 8 per 100,000 in the general population
- Prevalence of 0.1 to 0.7 per 1000 persons
- Age: the highest prevalence is in patients aged 2 to 9 years
- Sex: in general the male-to-female ratio for CAE averages 1:2 to 1:5.

Juvenile absence epilepsy (JAE):[2] [12]

- Fewer data on JAE available
- Estimated prevalence of 0.1 per 100,000 persons in the general population
- Age: onset averages at 10 to 17 years.

Juvenile myoclonic epilepsy (JME):[10] [12] [15] [16] [17] [18]

- Incidence is approximately 1 per 100,000
- Prevalence ranges from 0.1 to 0.2 per 1000
- Age: onset peaks between ages 12 to 18 years
- Sex: a female predominance in JME has been reported
- JME appears to be less frequent in developing countries.

Lennox-Gastaut syndrome:[8] [19] [20]

- Incidence in children younger than 15 years has been estimated at 1.93 per 100,000
- Lifetime prevalence at age 10 years has been estimated at 0.26 per 1000
- Sex: a slightly higher frequency in males over females has been reported.

Epilepsy with myoclonic absences:[8] [21]

- Minimal data are available on the incidence
- Epilepsy with absences accounted for 0.5% to 1% of all epilepsies observed at Centre Saint-Paul in Marseille, France, with a 70% male preponderance
- Incidence of epilepsy with myoclonic absences was reported to be 2.6% in a selected population of children (aged <15 years) with newly diagnosed epilepsy in Navarre, Spain.

Aetiology

The most likely aetiology for absence epilepsy syndromes is genetic, with complex, multifactorial inheritance.[22] A study published in 1991 evaluated 671 first-degree relatives of 151 patients with either childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE). Of those, 4.9% had some form of epilepsy, with one third of the affected relatives having an absence seizure. Of note, this does not correspond with the 25% expected chance of inheriting an autosomal recessive disorder.[23]

Epilepsies with atypical absence seizures, such as Lennox-Gastaut syndrome, may be secondary to a variety of congenital or acquired brain disorders, such as hypoxia-ischaemia, trauma, central nervous system infection, cortical malformations, or inborn errors of metabolism.

Pathophysiology

The current understanding of the pathogenesis of absence seizures is based on animal models that generate generalised spike-and-wave discharges on EEG. A reverberating circuit between the thalamus and cortex is the basis for this model, with the hypothesis being that aberrant rhythmic oscillations are generated in the circuit, analogous to a mechanism that generates normal sleep spindles. The reticulothalamic nucleus of the thalamus has been particularly implicated and contains a predominance of inhibitory GABA-containing interneurons. In this case, GABA-mediated activity may trigger absence seizures by inducing prolonged hyperpolarisation and activating low-threshold Ca^2+ currents.[24] [25] The concept of 't-type' or 'low-threshold' calcium channels playing a role in absence seizures is supported by the responsiveness of typical absence seizures to medicines such as ethosuximide, which is known to block these channels.

Multiple studies have been conducted in an attempt to identify a single gene locus for childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), or generalised epilepsies (GE). Most identified genes associated with GE involving absence seizures are for different types of ion channels (channelopathies). A gene for a component of GABA^A receptor has been implicated in a large family with JME with autosomal dominant inheritance.[26] To date, CAE has been associated with defects in GABA^A receptor gamma2 subunit and voltage-gated Ca^2+ channel alpha-1A subunit (CACNA1A), among others.[25] [27] Mutations in a gene that encodes voltage-gated chloride channel CLC-2 has been associated with CAE, juvenile absence epilepsy (JAE), and JME.[28] Studies have demonstrated that a loci on chromosome 6p and chromosome 15q may predispose to JME; 15q maps to the alpha-7 subunit of the neuronal nicotinic acetylcholine receptor (CHRNA7).[27] Some cases of early-onset absence epilepsy have been attributed to mutations in the GLUT1 glucose transporter.[29]

Classification

International League Against Epilepsy (ILAE) classification of seizures[3] [4]

1. Generalised onset seizures
    - Motor
        - Tonic-clonic
        - Clonic
        - Tonic
        - Myoclonic
        - Myoclonic-tonic-clonic
        - Myoclonic-atonic
        - Atonic
        - Epileptic spasms
    - Non-motor (absence)
        - Typical

- Atypical
- Myoclonic absence
- Eyelid myoclonia

2. Focal onset seizures
3. Unknown onset seizures

Electroclinical syndromes and other epilepsies[5]

Electroclinical syndromes arranged by age at onset

- Neonatal period
  - Benign familial neonatal seizures (BFNS)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in non-progressive disorders
- Childhood
  - Febrile seizures plus (FS+)
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal-dominant nocturnal frontal lone epilepsy (ADNFLE)
  - Late-onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
  - Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)
- Adolescence
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalised tonic-clonic seizures alone
  - Progressive myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies

Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen's syndrome
- Gelastic seizure with hypothalamic hamartoma
- Hemiconvulsion-hemiplegia-epilepsy

Epilepsies attributed to and organised by structural-metabolic causes

- Malformations of cortical development
- Neurocutaneous syndromes
- Tumour
- Infection
- Trauma

Angioma

- Perinatal insults
- Stroke

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se

- Benign neonatal seizures (BNS)
- Febrile seizures (FS)

International League Against Epilepsy (ILAE) Commission 1989: inclusion criteria for childhood absence epilepsy[6]

Inclusion criteria:

1. Children of school age (peak manifestations 6 to 7 years)
2. Very frequent (several to many per day) absences
3. EEG with bilateral, synchronous, and symmetrical spike-waves, usually at 3 Hz
4. Development of generalised tonic-clonic seizures often occurs during adolescence.

A more stringent set of inclusion and exclusion criteria has been proposed but not widely accepted.[7] There is also debate about its distinction from juvenile absence epilepsy (JAE).

Case history

Case history #1

A 6-year-old female without a significant past medical history presents for evaluation of frequent unusual episodes for the past 3 months. The episodes consist of sudden activity arrest with staring and minimal eyelid flutter for 10 to 20 seconds occurring 5 to 10 times per day. The patient is unresponsive to voice or tactile stimulation during the episodes. She is able to immediately resume activities without any recollection of the event once the episode finishes. Her teachers have noted that she stares off in class repeatedly and does not seem to be remembering instructions and classroom material. The diagnosis of attention-deficit/hyperactivity disorder had been suggested. One such unusual episode is induced in front of medical staff with hyperventilation.

Other presentations

The most familiar absence epilepsy syndrome is childhood absence epilepsy (CAE), presenting with numerous typical absence seizures a day starting at early school age in children who are developing normally. Juvenile absence epilepsy (JAE) typically begins around puberty, absence seizures are considerably less frequent than in CAE, and many patients will have generalised tonic-clonic seizures. Juvenile myoclonic epilepsy (JME) also begins around puberty but with frequent myoclonic jerks, particularly around awakening. People with JME have generalised tonic-clonic seizures, and up to one third have rare typical absence seizures. Lennox-Gastaut syndrome begins in early childhood with multiple seizure types, including atypical absence seizures. Lennox-Gastaut syndrome patients almost universally are neurologically impaired. Patients with epilepsy with myoclonic absences also present in early childhood with atypical absence seizures. They rapidly develop other seizure types. Around 50% are neurologically impaired at baseline.[8]

Approach

The critical components to the diagnosis of an absence epilepsy syndrome are a detailed description of the patient's unusual episodes and the EEG characteristics.

History

Essential to the history is a detailed description of the unusual episode, including:

- Patient's activity at onset: behavioural arrest or staring; interrupting otherwise normal activity
- Simple or complex automatisms: any associated movements of eyes, face, and hands[32]
- The duration of an event: typically lasting 5 to 10 seconds
- The frequency of events: several per day
- No aura and minimal to no postictal state should occur
- Age of onset
- Birth and developmental history, including specifically any history of learning disabilities or problems such as attention deficit hyperactivity disorder (ADHD), as well as any prior history of seizures of any type, which is also significant in considering the specific classification of the electroclinical syndrome.

Physical Examination

For childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME), a patient should typically have an entirely normal physical examination. However, hyperventilation is an easily performed manoeuvre that often will trigger absence seizures and can be diagnostic on clinical grounds.

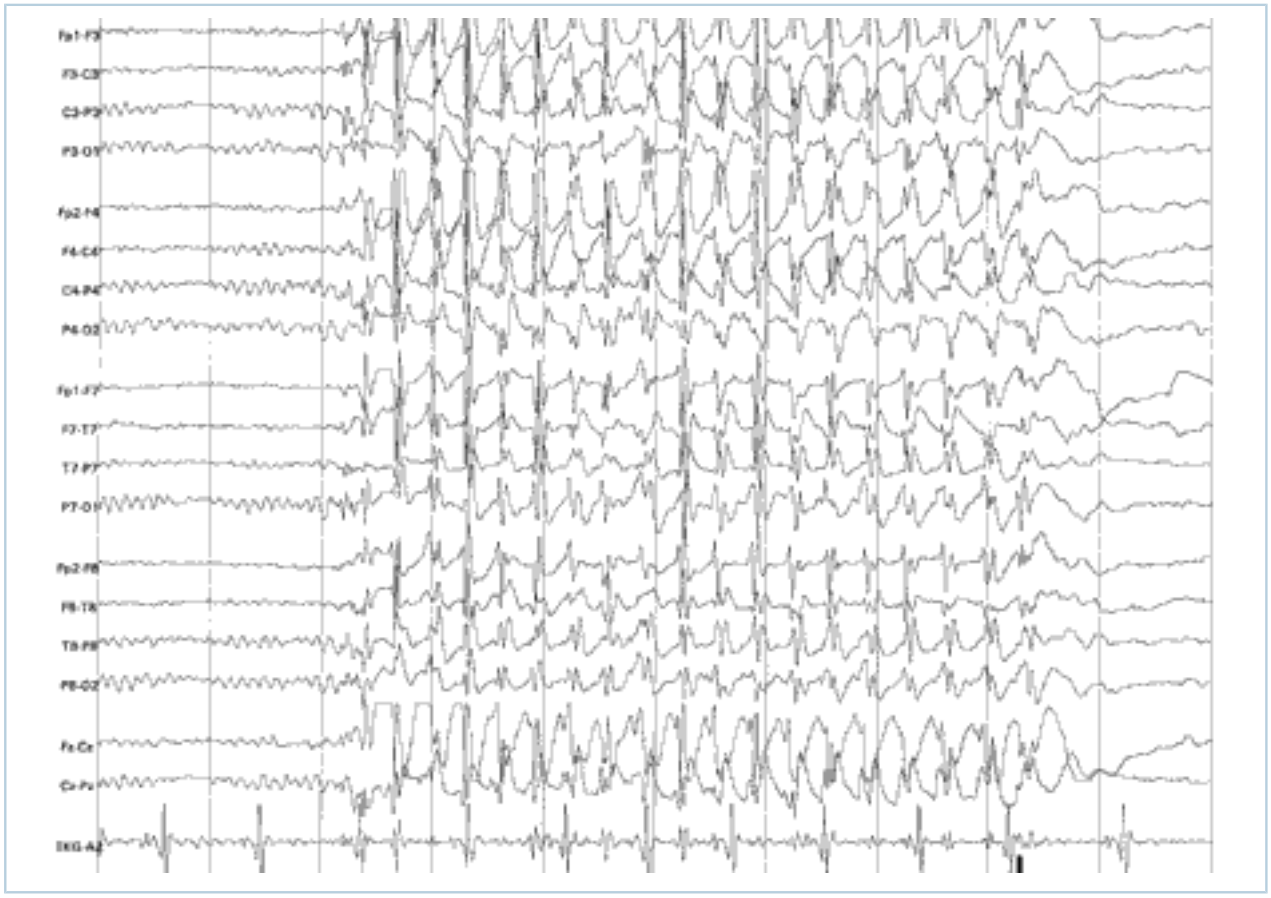
If the patient has evidence of cognitive impairment or abnormalities in muscle tone or tendon reflexes, an epilepsy syndrome that is more likely to be symptomatic (due to an identified structural brain lesion), such as Lennox-Gastaut, is probable. Abnormal physical or cognitive findings indicate the need for further diagnostic work-up, such as MRI or metabolic and genetic testing.

EEG

An EEG should be ordered in the initial assessment of all patients. The EEG should be conducted when the patient is sleep deprived, to include those periods of time when the patient is alternately awake and asleep. It is essential to ask the patient to hyperventilate in order to induce an absence seizure, a classic finding.

The EEG may be repeated to assess treatment response in CAE. There is some suggestion that normalisation of EEG correlates with greater likelihood of resolution of CAE.

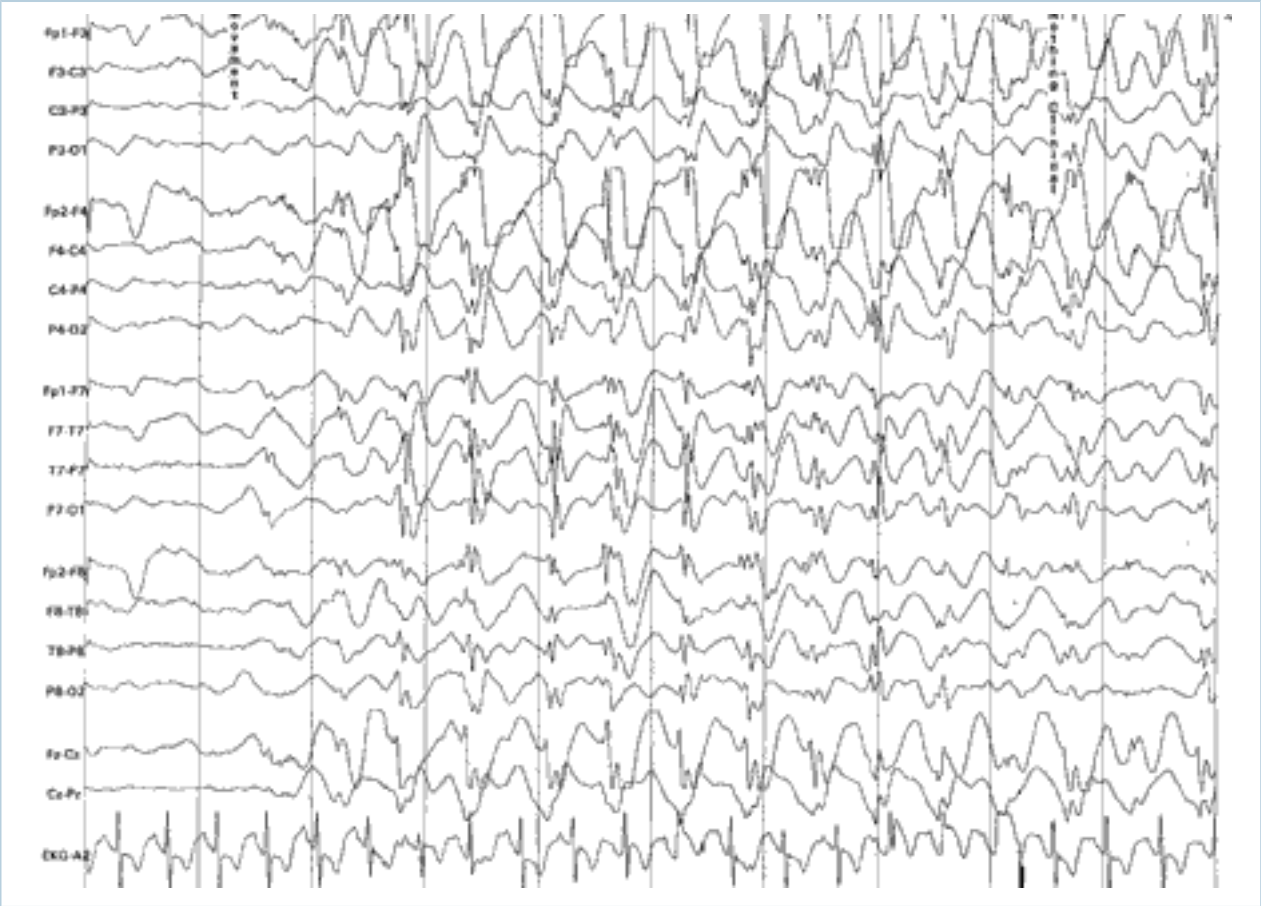
For typical absence seizures, a classic 3 Hz generalised spike-and-wave pattern, often activated by hyperventilation, is considered the most specific and sensitive test confirming a diagnosis of absence seizures.



3 Hz generalised spike-and-wave pattern on EEG pathognomonic for typical absence seizures and childhood absence epilepsy

From the personal collection of Dr M. Wong; used with permission

For atypical absence seizures a slow (<2.5 Hz) generalised spike-wave pattern is characteristic.



Slow (<2.5 Hz) generalised spike-and-wave on EEG associated with atypical absence seizures and Lennox-Gastaut syndrome

From the personal collection of Dr M. Wong; used with permission

MRI

An MRI is required only in settings where the history, clinical course, physical examination, or EEG findings do not fit with typical absence seizures or generalised epilepsy syndromes.

Metabolic testing

Metabolic tests are generally indicated when the clinical and EEG findings do not fit with typical absence seizures or typical epilepsy syndrome but suggest a symptomatic aetiology. There is a broad variety of metabolic tests that can be performed and these need to be tailored to the individual. Possible metabolic disorders causing atypical absence seizures include aminoacidurias, organic acidurias, mitochondrial disorders, and lysosomal storage diseases. Testing of cerebrospinal fluid and serum glucose should be considered for patients under age 4 years or with intractable absence epilepsy to evaluate for glucose transporter 1 (GLUT1) deficiency.[29] [33]

Genetic testing

In rare instances with a characteristic family history of other generalised epilepsies (generalised epilepsy with febrile seizures plus [GEFS+]), commercial testing for SCN1A gene mutations may be indicated. As more genes are identified for these syndromes, this may become more common. For epilepsies involving atypical absence seizures, karyotype and more detailed chromosomal analysis may be indicated.

For patients under age 4 years or with intractable absence epilepsy, genetic testing of the SLC2A1 gene for GLUT1 deficiency should be considered.[29] [33] [34] [35]

History and exam

Key diagnostic factors

family history of childhood seizures (common)

- Key risk factors include family history of childhood absence epilepsy or juvenile myoclonic epilepsy.

staring episode, lasting 5 to 10 seconds; several times per day with no aura/postictal state (common)

- A description of the event consisting of behavioural arrest or staring, typically lasting 5 to 10 seconds and interrupting otherwise normal activity. No aura and minimal to no postictal state should occur. One small study demonstrated that three historical features most likely to be inconsistent with an absence seizure were preserved responsiveness to tactile stimulation, lack of cessation of playing, and initial concern by a teacher or health professional rather than a parent.[36]

childhood onset (common)

- Age of onset is pathognomonic. Juvenile myoclonic epilepsy is most likely to have delayed diagnosis, as the myoclonus is often ignored and only comes to attention when the patient has a generalised tonic-clonic seizure.

normal physical examination (common)

- Patients with typical absence seizures should have a normal neurological examination.

hyperventilation-induced seizure (common)

- The hallmark of typical absence seizures is induction by hyperventilation. The patient should be encouraged to hyperventilate for up to 3 minutes in the office. Telling the patient a word during a seizure can help differentiate a seizure from a non-epileptic event.

Other diagnostic factors

simple automatisms (common)

- A description by the observer of eyelid blinking, upward eye deviation, or lip smacking is often obtained.

recent decline in school performance (common)

- With the onset of frequent absence seizures, childhood absence epilepsy (CAE) patients may have a decline in school performance, particularly if there is a lag in diagnosis. This is likely due to missed instruction time, as most children seem to resume typical academic performance subsequently.

complex automatisms (uncommon)

- Less commonly stereotypical/repetitive hand movements, walking/circling behaviour is obtained. These are more likely to occur with atypical absence seizures.

early onset (before age 4 years) (uncommon)

- One in 10 patients with early onset absence seizures may have GLUT1 deficiency.[29] [37]
- For patients under age 4 years or with intractable absence epilepsy, genetic testing of the SLC2A1 gene for GLUT1 deficiency should be considered.[29] [33] [34] [35]

Risk factors

Strong

family/genetic history of childhood absence epilepsy or juvenile myoclonic epilepsy

- Childhood absence epilepsy has a 16% to 45% positive family history.[25] Concordance of 70% to 85% in monozygotic twins, and 33% in first-degree relatives, has been reported.[23] [25] One third to one half of juvenile myoclonic epilepsy patients have a family history of epilepsy.

Weak

acquired brain injury: for example, hypoxia-ischaemia, trauma, infection

- Patients with a history of hypoxia-ischaemia, trauma, or infection are more likely to have atypical absence seizures and are at increased risk for a medically refractory epilepsy syndrome such as Lennox-Gastaut. A small study identified 3 out of 25 patients with Lennox-Gastaut syndrome to have a history of stroke or central nervous system infection.[19]

other congenital inborn errors of metabolism, structural defects, chromosomal abnormalities

- Patients with a history of congenital inborn errors of metabolism, structural defects, or chromosomal abnormalities are more likely to have atypical absence seizures and are at increased risk for a medically refractory epilepsy syndrome such as Lennox-Gastaut. A small study identified 5 out of 25 patients with Lennox-Gastaut syndrome to have a history of chromosomal abnormality or brain malformation.[19] A study of 14 patients with epilepsy with myoclonic absences identified 7 out of 14 patients with a chromosome abnormality.[30]

developmental delay or intellectual disability

- Fifty percent (50%) of patients with epilepsy with myoclonic absences have abnormal cognition at onset of their epilepsy.[8]

female sex

- Childhood absence epilepsy and possibly juvenile myoclonic epilepsy have female predominance.[14] [17] Studies have shown a female prevalence for generalised epilepsy.[31]

Investigations

1st test to order

Test	Result
EEG • Order in the initial assessment of all patients; a sleep-deprived routine EEG including awake and asleep. Hyperventilation is essential. • The EEG may be repeated to assess treatment response in childhood absence epilepsy (CAE). There is some suggestion that normalisation of EEG correlates with greater likelihood of resolution of CAE. Patients with longer seizures at baseline may have more favourable initial treatment response, but are at greater risk for inattention.[38]	**generalised 3 Hz spike-and-wave in typical absence; generalised 1.5 to 2.5 Hz spike-and-wave in atypical absence; generalised 4 to 6 Hz spike-and-wave in juvenile myoclonic epilepsy (JME)**

Other tests to consider

Test	Result
MRI brain • Required only in settings where the history, clinical course, physical examination, or EEG findings do not fit with typical absence seizures or generalised epilepsy syndromes or if clinical course is not typical (e.g., a patient with suspected CAE has not responded to first 2 treatment modalities).	**usually normal in childhood absence epilepsy (CAE); variety of findings ranging from focal encephalomalacia or cortical dysplasia to diffuse cortical malformations may be found in epilepsies such as Lennox-Gastaut**
testing for metabolic disorders (e.g., serum amino acids, urine organic acids, lactate pyruvate or specific enzymatic tests) • Metabolic tests are generally indicated when the clinical and EEG findings do not fit with typical absence seizures or an epilepsy syndrome but suggest a symptomatic aetiology. There is a broad variety of metabolic tests that can be performed and these need to be tailored to the individual. Possible metabolic disorders causing atypical absence seizures include aminoacidurias, organic acidurias, mitochondrial disorders, and lysosomal storage diseases.[39]	**variable, depending on specific test**
cerebrospinal fluid and serum glucose • Consider if the patient has typical absence seizures that began before 4 years of age. • May also be indicated in patients with refractory absence seizures.	**cerebrospinal fluid glucose low; serum glucose normal**

Emerging tests

Test	Result
gene testing • In rare instances with a characteristic family history of other generalised epilepsies (generalised epilepsy with febrile seizures plus [GEFS+]), commercial testing for SCNA gene mutations may be indicated. As more genes are identified for these syndromes, this may become more common. For patients under age 4 years or with intractable absence epilepsy, genetic testing of the SLC2A1 gene for GLUT1 deficiency should be considered.[29] [33] [34] For epilepsies involving atypical absence seizures, karyotype and more detailed chromosomal analysis may be indicated.	**may be positive**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Daydreaming	• More likely to occur only during quiet, non-stimulating activities such as watching TV. No history of activity cessation. No unusual episodes induced by hyperventilation.	• EEG will be normal.
Attention deficit hyperactivity disorder (ADHD)	• More likely to occur only during quiet, non-stimulating activities such as watching TV. No history of activity cessation. No unusual episodes induced by hyperventilation.	• EEG will be normal. A variety of neuropsychological tests can help with formalising diagnosis.
Complex partial epilepsy of frontal or temporal lobe origin	• Patients more likely to have eye deviation, facial twitching, or other localising component at onset of seizure. Seizures typically last at least 30 seconds. There may be a preceding aura and a postictal state.	• EEG will be normal, asymmetric, or show focal epileptiform abnormality.
Psychogenic unresponsiveness/non-epileptic event	• Careful history will likely elicit characteristics of the unusual episode that are atypical for any kind of seizure. In some instances a social history may reveal a stressor that is precipitating these events.	• Routine EEG will be normal. It is often necessary to do prolonged video EEG monitoring to completely characterise the event and establish that there is no ictal electrographical abnormality.

Approach

The goal of treatment for any epilepsy syndrome is complete freedom from seizures. At the same time, the risk of adverse medicine effects need to be considered. Most treatment choices are based on expert opinion, as there is minimal good evidence.[40] [41] A large randomised prospective trial comparing ethosuximide, lamotrigine, and valproate for the treatment of childhood absence epilepsy (CAE) concluded that ethosuximide might represent first-line treatment for CAE.[42] Initial treatment effect persisted at 12 month follow-up.[43]

Monotherapy is preferred, but an adjunctive medicine to first-line therapy may be required. Evidence suggests that earlier age of onset and male sex may increase the need for a second agent for seizure control.[44]

Typical absence seizures without a history of generalised tonic-clonic seizures (childhood absence epilepsy)

A syndrome with only typical absence seizures is likely to respond to ethosuximide, valproic acid, or lamotrigine as first-line treatments. Evidence suggests that ethosuximide and valproate have significantly greater efficacy than lamotrigine.[42] Ethosuximide had a small but significantly lower rate of attentional difficulties than valproate, suggesting that ethosuximide should be considered first-line treatment for CAE.[42] A Cochrane review concluded that ethosuximide is the optimal initial empirical monotherapy for children and adolescents with absence seizures.[41] Second-line agents include topiramate, zonisamide, and levetiracetam.

In the subgroup of patients with GLUT1 deficiency, a ketogenic diet is recommended. Patients are monitored and treated by an epileptologist. This is typically a high-fat, adequate-protein, low-carbohydrate diet, and should be initiated in hospital, under close medical supervision. It may take a couple of months before a clinical response is noted. Antiepileptic medication is continued initially. If a patient responds very well and has little or no seizure activity, medication is tapered slowly.

Typical absence seizures with a history of generalised tonic-clonic seizures (CAE, JAE, JME)

If there is any history of generalised tonic-clonic seizures (childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE], and juvenile myoclonic epilepsy [JME]), ethosuximide is less appropriate, and valproic acid and lamotrigine would be preferred first-line agents. Second-line agents would include topiramate, zonisamide, and levetiracetam. Typically, second-line agents are added as adjunct therapy to first-line therapy. However, second-line therapy can be substituted for the first-line therapy, with the first-line medicine being weaned.

Atypical absence seizures

Valproic acid, lamotrigine, and topiramate are all indicated for first-line treatment of atypical absence seizures, syndromes with generalised epilepsies, or multiple seizure types. Typically, zonisamide and levetiracetam are second-line agents that are added as adjunct therapy to first-line therapy. However, second-line therapy can be substituted for the first-line therapy, with the first-line medicine being weaned.

Failure of therapy

Multiple other therapies can be considered if first and second line therapies have failed (i.e., lack of seizure freedom), such as acetazolamide, felbamate, the ketogenic diet, and vagal nerve stimulation. These are beyond the scope of this review and would be initiated by an epileptologist.

GLUT1 testing should be considered before initiating the ketogenic diet.

Drugs usually more appropriate for focal seizures, such as carbamazepine and phenytoin, are generally felt to worsen generalised seizures, including absence seizures.

Medication used

Ethosuximide

- One double-blind RCT compared ethosuximide, valproic acid, and lamotrigine as first-line treatments in children with newly diagnosed childhood absence epilepsy. Ethosuximide and valproic acid had similar efficacy (53% and 58%, respectively, P = 0.35), but ethosuximide was better tolerated with fewer adverse attentional effects.[42] Initial treatment effect persisted at 12 month follow-up.[43] A Cochrane review concluded that ethosuximide is the optimal initial empirical monotherapy for children and adolescents with absence seizures.[41] Ethosuximide is considered very effective in patients with only typical absence seizures. It is generally well tolerated. A common adverse effect is gastrointestinal upset. In rare instances, it can cause aplastic anaemia, and hepatic or renal failure.

Valproic acid

- Atypical absence seizures respond well to valproic acid.[45] [46]
- Valproic acid has been reported to be equally efficacious to ethosuximide in the treatment of absence seizures.[42] [47] [48] [49] However, in a double-blind RCT of children with newly diagnosed childhood absence epilepsy, valproic acid was associated with increased risk of adverse attentional effects compared with ethosuximide.[42]
- Valproic acid is reported to be effective treatment in juvenile absence epilepsy and juvenile myoclonic epilepsy.[50] [51]
- Medicines containing valproate increase the risk of congenital malformations and developmental problems in the infant/child if taken during pregnancy (see 'Safety of anticonvulsants in pregnancy').

Lamotrigine

- In open label and crossover studies, lamotrigine appeared to be as effective as valproic acid for typical absence seizures in children, and generalised epilepsy.[52] [53] [54] [55] [56] However, in a double-blind, randomised controlled trial of children with newly diagnosed childhood absence epilepsy, ethosuximide and valproate were significantly more likely to be effective than lamotrigine.[42]
- Lamotrigine has been shown to be of benefit in juvenile myoclonic epilepsy and for some seizure types of Lennox-Gastaut syndrome.[54] [57] [58]

Topiramate

- There are good data for the use of topiramate for primary generalised tonic-clonic seizures but not for absence seizures.[54] [59]
- Topiramate has been shown to have some efficacy in Lennox-Gastaut syndrome as adjunctive therapy.[60] It can also be used as monotherapy.

Zonisamide

- Small case series and abstracts have suggested efficacy of zonisamide in reducing seizure frequency in patients with typical absence seizures, as well as refractory primary generalised epilepsy.[54] One retrospective chart review of 45 patients aged 18 years or under with absence seizures found a 51.1% rate of seizure elimination with zonisamide.[61]

Levetiracetam

- Levetiracetam is indicated as adjunctive therapy for juvenile myoclonic epilepsy (JME).[40] [54] [62] A review concluded that levetiracetam is an effective adjunct in patients with insufficiently controlled juvenile absence epilepsy (JAE) and JME.[63]
- One small, prospective study (n=21) suggested that levetiracetam monotherapy may be effective in patients with CAE and JAE.[64] However, a randomised placebo-controlled trial conducted in children with newly diagnosed CAE or JAE for 2 weeks reported a 23.7% response rate to levetiracetam monotherapy, which was not significantly higher than in the placebo arm.[65] Of note, the trial was of short duration to minimise exposure to placebo, and high levetiracetam doses could not be attained.

Safety of anticonvulsants in pregnancy

For women and girls of childbearing potential, the safety of anticonvulsants in pregnancy must be taken into account in choice of medication.

In both the US and Europe, valproate and its analogues are contraindicated during pregnancy due to the risk of congenital malformations and developmental problems in the child. If it is not possible to stop valproate, treatment may be continued with appropriate specialist care. Valproate and its analogues must not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place and certain conditions are met.[66] If the patient is taking the drug to prevent major seizures and is planning to become pregnant, the decision of continuing valproate versus changing to an alternate agent should be made on an individual basis.

A review of the safety of anticonvulsants (other than valproate) in pregnancy by the UK Medicines and Healthcare products Regulatory Agency concluded that lamotrigine and levetiracetam, at maintenance doses, are not associated with an increased risk of major congenital malformations. Available studies also 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. Data for other drugs show an increased risk of major congenital malformations associated with topiramate; and an increased risk of fetal growth restriction associated with topiramate and zonisamide.[67] A specialist should be consulted for more guidance on the use of specific drugs in pregnancy.

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.[68] Abrupt medication discontinuation is inadvisable, but, beyond this, there is little evidence to guide the speed of medication taper in adults.[69]

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.[68]

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)
typical absence seizures without a history of generalised tonic-clonic seizures (childhood absence epilepsy)		
	1st	ethosuximide or valproic acid or lamotrigine
	2nd	topiramate or zonisamide or levetiracetam
■ GLUT1 deficiency	plus	ketogenic diet
typical absence seizures with a history of generalised tonic-clonic seizures (CAE, JAE, JME)		
	1st	valproic acid or lamotrigine
	adjunct	topiramate or zonisamide or levetiracetam
atypical absence seizures		
	1st	valproic acid or lamotrigine or topiramate
	adjunct	levetiracetam or zonisamide

Ongoing		(summary)
refractory to treatment		
	1st	specialist referral

MANAGEMENT

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

typical absence seizures without a history of generalised tonic-clonic seizures (childhood absence epilepsy)

1st **ethosuximide or valproic acid or lamotrigine**

Primary options

» ethosuximide: children 3-6 years of age: 15 mg/kg/day (maximum 250 mg) orally given in 2 divided doses initially, increase every 4-7 days according to response, usual maintenance dose is 15-40 mg/kg/day, maximum 1500 mg/day; children >6 years of age, adolescents and adults: refer to consultant for guidance on dosage

Secondary options

» valproic acid: children <10 years of age: consult specialist for guidance on dose; adults and children ≥10 years of age: 15 mg/kg/day orally given in 1-3 divided doses initially, increase by 5-10 mg/kg/day increments every 7 days as tolerated and according to response

OR

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

» A patient with only typical absence seizures is likely to respond to ethosuximide, valproic acid, or lamotrigine as first-line treatments.[42] A Cochrane review concluded that ethosuximide is the optimal initial empirical monotherapy for children and adolescents with absence seizures.[41]

» In rare instances, ethosuximide can cause aplastic anaemia, and hepatic or renal failure.

» Valproic acid can cause hepatotoxicity and pancreatitis (black box warning), thrombocytopenia or pancytopenia, hyperammonaemia, fatigue, weight gain, and hair thinning. Periodic monitoring of FBCs and liver transaminases should be strongly considered. Trough drug levels can help with

Acute

assessing compliance and effectiveness of therapy.

» Valproic acid should be used with extreme caution in children aged younger than 2 years, due to increased risk of hepatotoxicity in this age group.

» When initiating lamotrigine treatment, a slow titration is necessary to avoid Stevens-Johnson syndrome (black box warning). Rare cases of hepatotoxicity or multi-organ failure have been reported. Adverse effects also include diplopia, ataxia, and insomnia.

» In both the US and Europe, valproate and its analogues are contraindicated during pregnancy due to the risk of congenital malformations and developmental problems in the child. If it is not possible to stop valproate, treatment may be continued with appropriate specialist care. Valproate and its analogues must not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place and certain conditions are met.[66] If the patient is taking the drug to prevent major seizures and is planning to become pregnant, the decision of continuing valproate versus changing to an alternate agent should be made on an individual basis.

» A review of the safety of anticonvulsants (other than valproate) in pregnancy by the UK Medicines and Healthcare products Regulatory Agency concluded that lamotrigine and levetiracetam, at maintenance doses, are not associated with an increased risk of major congenital malformations. Available studies also 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. Data for other drugs show an increased risk of major congenital malformations associated with topiramate, and an increased risk of fetal growth restriction associated with topiramate and zonisamide. Ethosumide was not studied.[67] A specialist should be consulted for more guidance on the use of specific drugs in pregnancy.

2nd **topiramate or zonisamide or levetiracetam**

Primary options

» topiramate: children 2-16 years of age: 1-3 mg/kg/day orally once daily at night for 1 week initially, increase by 1-3 mg/kg/day increments given in 2 divided doses every 1-2 weeks according to response, maximum 15

Acute

mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

OR

» zonisamide: children <16 years of age: 1-2 mg/kg/day orally given in 2 divided doses initially, increase by 0.5 to 1 mg/kg/day increments every 2 weeks according to response, maximum 8 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

OR

» levetiracetam: children 4-16 years of age: 10 mg/kg/dose orally twice daily initially, increase by 10 mg/kg/dose increments every 2 weeks, maximum 60 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

» Second-line agents include topiramate, zonisamide, and levetiracetam.

» Adverse effects of topiramate include word-finding difficulties or cognitive problems, weight loss, nephrolithiasis, and anhidrosis. Rarely, it can precipitate acute angle-closure glaucoma. Therefore, eye pain should be treated as an emergency.

» Adverse effects of zonisamide include cognitive slowing, abdominal pain, nephrolithiasis, and weight loss.

» Adverse effects of levetiracetam include agitation or aggressive behaviour, predominantly in younger children or elderly, and, rarely, psychosis or hallucinations. There are no significant drug interactions. It is renally cleared.

GLUT1 deficiency **plus** **ketogenic diet**

Treatment recommended for ALL patients in selected patient group

» In the subgroup of patients with GLUT1 deficiency, a ketogenic diet is recommended. Patients are monitored and treated by an epileptologist.

» This is typically a high-fat, adequate-protein, low-carbohydrate diet, and should be initiated in hospital, under close medical supervision. It may take a couple of months before a clinical response is noted.

Acute

» Antiepileptic medication is continued initially. If a patient responds very well and has little or no seizure activity, medication is tapered slowly.

typical absence seizures with a history of generalised tonic-clonic seizures (CAE, JAE, JME)

1st **valproic acid or lamotrigine**

Primary options

» valproic acid: children <10 years of age: consult specialist for guidance on dose; adults and children ≥10 years of age: 15 mg/kg/day orally given in 1-3 divided doses initially, increase by 5-10 mg/kg/day increments every 7 days as tolerated and according to response

OR

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

» If there is any history of generalised tonic-clonic seizures (childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE], and juvenile myoclonic epilepsy [JME]), ethosuximide is less appropriate, and valproic acid and lamotrigine would be preferred first-line agents.[41]

» Valproic acid can cause hepatotoxicity and pancreatitis (black box warning), thrombo/pancytopenia, hyperammonaemia, fatigue, weight gain, and hair thinning. Periodic monitoring of FBCs and liver transaminases should be strongly considered. Trough drug levels can help with assessing compliance and effectiveness of therapy.

» Valproic acid should be used with extreme caution in children aged younger than 2 years, due to increased risk of hepatotoxicity in this age group.

» When initiating lamotrigine treatment, a slow titration is necessary to avoid the serious complication of Stevens-Johnson syndrome (black box warning). Rare cases of hepatotoxicity or multi-organ failure have been reported. Adverse effects also include diplopia, ataxia, and insomnia.

» In both the US and Europe, valproate and its analogues are contraindicated during pregnancy due to the risk of congenital malformations and developmental problems in the child. If it is

Acute

not possible to stop valproate, treatment may be continued with appropriate specialist care. Valproate and its analogues must not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place and certain conditions are met.[66] If the patient is taking the drug to prevent major seizures and is planning to become pregnant, the decision of continuing valproate versus changing to an alternate agent should be made on an individual basis.

» A review of the safety of anticonvulsants (other than valproate) in pregnancy by the UK Medicines and Healthcare products Regulatory Agency concluded that lamotrigine and levetiracetam, at maintenance doses, are not associated with an increased risk of major congenital malformations. Available studies also 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. Data for other drugs show an increased risk of major congenital malformations associated with topiramate, and an increased risk of fetal growth restriction associated with topiramate and zonisamide.[67] A specialist should be consulted for more guidance on the use of specific drugs in pregnancy.

adjunct **topiramate or zonisamide or levetiracetam**

Treatment recommended for SOME patients in selected patient group

Primary options

» topiramate: children 2-16 years of age: 1-3 mg/kg/day orally once daily at night for 1 week initially, increase by 1-3 mg/kg/day increments given in 2 divided doses every 1-2 weeks according to response, maximum 15 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

OR

» levetiracetam: children 4-16 years of age: 10 mg/kg/dose orally twice daily initially, increase by 10 mg/kg/dose increments every 2 weeks, maximum 60 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

OR

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» zonisamide: children <16 years of age: 1-2 mg/kg/day orally given in 2 divided doses initially, increase by 0.5 to 1 mg/kg/day increments every 2 weeks according to response, maximum 8 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

» Second-line agents that are added as adjunct therapy to first-line therapy. Consideration may be given to weaning the first-line agent when seizures are under control.

» Adverse effects of topiramate include word-finding difficulties or cognitive problems, weight loss, nephrolithiasis, and anhidrosis. Rarely, it can precipitate acute angle-closure glaucoma. Therefore, eye pain should be treated as an emergency.

» Adverse effects of zonisamide include cognitive slowing, abdominal pain, nephrolithiasis, and weight loss.

» Adverse effects of levetiracetam include agitation or aggressive behaviour, predominantly in younger children or elderly, and, rarely, psychosis or hallucinations. There are no significant drug interactions. It is renally cleared.

atypical absence seizures

1st **valproic acid or lamotrigine or topiramate**

Primary options

» valproic acid: children <10 years of age: consult specialist for guidance on dose; adults and children ≥10 years of age: 15 mg/kg/day orally given in 1-3 divided doses initially, increase by 5-10 mg/kg/day increments every 7 days as tolerated and according to response

OR

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

OR

» topiramate: children 2-16 years of age: 1-3 mg/kg/day orally once daily at night for 1 week initially, increase by 1-3 mg/kg/day increments given in 2 divided doses every 1-2 weeks according to response, maximum 15 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

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» Valproic acid, lamotrigine, and topiramate are all indicated for first-line treatment of atypical absence seizures, syndromes with generalised epilepsies, or multiple seizure types.

» Valproic acid can cause hepatotoxicity and pancreatitis (black box warning), thrombo/pancytopenia, hyperammonaemia, fatigue, weight gain, and hair thinning. Periodic monitoring of FBCs and liver transaminases should be strongly considered. Trough drug levels can help with assessing compliance and effectiveness of therapy.

» Valproic acid should be used with extreme caution in children aged less than 2 years, due to increased risk of hepatotoxicity in this age group.

» When initiating lamotrigine treatment, a slow titration is necessary to avoid the serious complication of Stevens-Johnson syndrome (black box warning). Rare cases of hepatotoxicity or multi-organ failure have been reported. Adverse effects also include diplopia, ataxia, and insomnia.

» Adverse effects of topiramate include word-finding difficulties or cognitive problems, nephrolithiasis, and anhidrosis. Rarely, it can precipitate acute angle-closure glaucoma. Therefore, eye pain should be treated as an emergency.

» In both the US and Europe, valproate and its analogues are contraindicated during pregnancy due to the risk of congenital malformations and developmental problems in the child. If it is not possible to stop valproate, treatment may be continued with appropriate specialist care. Valproate and its analogues must not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place and certain conditions are met.[66] If the patient is taking the drug to prevent major seizures and is planning to become pregnant, the decision of continuing valproate versus changing to an alternate agent should be made on an individual basis.

» A review of the safety of anticonvulsants (other than valproate) in pregnancy by the UK Medicines and Healthcare products Regulatory Agency concluded that lamotrigine and levetiracetam, at maintenance doses, are not associated with an increased risk of major congenital malformations. Available studies also do not suggest an increased risk

Acute

of neurodevelopmental disorders or delay associated with in-utero exposure to lamotrigine or levetiracetam, but data are more limited. Data for other drugs show an increased risk of major congenital malformations associated with topiramate, and an increased risk of fetal growth restriction associated with topiramate and zonisamide.[67] A specialist should be consulted for more guidance on the use of specific drugs in pregnancy.

adjunct **levetiracetam or zonisamide**

Treatment recommended for SOME patients in selected patient group

Primary options

» levetiracetam: children 4-16 years of age: 10 mg/kg/dose orally twice daily initially, increase by 10 mg/kg/dose increments every 2 weeks, maximum 60 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

OR

» zonisamide: children <16 years of age: 1-2 mg/kg/day orally given in 2 divided doses initially, increase by 0.5 to 1 mg/kg/day increments every 2 weeks according to response, maximum 8 mg/kg/day; adolescents and adults: refer to consultant for guidance on dosage

» Typically, zonisamide and levetiracetam are second-line agents that are added as adjunct therapy to first-line therapy. Consideration may be given to weaning the first-line agent when seizures are under control.

» Adverse effects of levetiracetam include agitation or aggressive behaviour, predominantly in younger children or elderly, and, rarely, psychosis or hallucinations. There are no significant drug interactions. It is renally cleared.

» Adverse effects of zonisamide include cognitive slowing, abdominal pain, nephrolithiasis, and weight loss.

Ongoing

refractory to treatment

1st **specialist referral**

» Multiple other therapies can be considered if first and second lines have failed (i.e., lack of seizure freedom), such as acetazolamide, felbamate, the ketogenic diet, and vagal nerve stimulation. These are beyond the scope of this review and would be initiated by an epileptologist.

» GLUT1 testing should be considered before initiating the ketogenic diet.

» Drugs usually more appropriate for focal seizures, such as carbamazepine and phenytoin, are generally felt to worsen generalised seizures, including absence seizures.

Emerging

Cannabidiol

Cannabidiol oral solution has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of seizures associated with Lennox-Gastaut's syndrome or Dravet's syndrome in both children and adults. Multi-centre, randomised, placebo-controlled trials are required to investigate efficacy in other patients with severe, treatment-resistant epilepsy.[70] [71] [72]

Primary prevention

No preventive strategies have been identified.

Secondary prevention

Avoidance of precipitating factors is advised. A regular sleep schedule is encouraged, as seizures are associated with sleep deprivation. Alcohol, multiple illicit drugs, and certain prescription medicines can also provoke seizures.

Patient discussions

In the event of a generalised tonic-clonic seizure, the patient should be positioned on their side on a firm, flat surface. Nothing should be placed in the patient's mouth. If any seizure persists for longer than 5 minutes, either an abortive agent (such as rectal diazepam) should be administered or emergency personnel contacted.

Patients with a history of seizures should not swim alone or take baths. Heights and cooking over an open flame should be avoided.

Restrictions regarding driving are mandated by state law and vary from state to state. In general, patients are not allowed to drive unless they have been seizure free for at least 6 months.

Patients should be in regular contact with their prescribing physician if they continue to have seizures.

If a generic bioequivalent anticonvulsant drug replaces a brand product, patients (and parents/carers if appropriate) should be reassured about equivalent effectiveness, and informed if there are any changes in colour or shape.[89]

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.[68]

Females of childbearing potential should be informed that they must follow a pregnancy prevention programme while on treatment with valproate medicines. For EU countries, the European Medicines Agency state that this programme should include:[66]

- An assessment of the patient’s potential for becoming pregnant
- Pregnancy tests before starting and during treatment as needed
- Counselling about the risks of valproate treatment and the need for effective contraception throughout treatment
- A review of ongoing treatment by a specialist at least annually

- A risk acknowledgement form that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.

FOLLOW UP

Monitoring

Monitoring

Traditionally, patients are followed up in clinic approximately every 6 months while on antiepileptics, but this may vary depending on seizure frequency and severity. In general, patients are monitored clinically to assess seizure control. Parental and close family member observations are heavily relied upon to determine frequency and appearance of seizures. Medicine adjustments are made according to seizure control. Periodic monitoring of drug levels and other laboratory studies (e.g., FBC, liver enzyme tests) are often warranted to check for compliance and potential adverse drug effects, depending on the medicine.

There are some data to suggest that normalisation of routine EEG indicates good treatment response and a better chance of remission. In general, repeat routine EEGs are not indicated unless there is a change in the observable manifestations of the seizures that suggest the underlying localisation and/or epilepsy syndrome, and therefore the possibility exists that a patient has an alternative epilepsy syndrome. If a patient is having persistent or frequent atypical episodes, prolonged EEG monitoring may be necessary to capture and characterise events.

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

A trial withdrawal of medicines may be considered if a patient with childhood absence epilepsy (CAE) has been seizure free for a period of 1 to 2 years.[87] One review did not find sufficient evidence to establish when to withdraw medications in children with generalised seizures.[88] The decision to withdraw medication is individualised, and may in part be made informed by patient age at presentation. For example, a child who was diagnosed at age 8 or 9 years may be a good candidate for a medicine wean after 2 years, whereas a child who presented at age 6 years might be maintained on medicine longer.

Patients with any syndrome other than CAE may require prolonged treatment. However, a trial off medicine can be considered if the patient has been seizure free for 2 years.

Complications

Complications	Timeframe	Likelihood
cognitive impairment	**long term**	**low**
Prevalence of severe cognitive impairment is >90% in Lennox-Gastaut syndrome and >50% in epilepsy with myoclonic absences. The exact mechanism of epileptic encephalopathy is poorly understood. All types of absence seizure, including childhood absence epilepsy (CAE), have been associated with learning disability, attention deficit hyperactivity disorder (ADHD), and developmental delay.[80] [81] The presence of learning disability or cognitive impairment at time of diagnosis is predictive of this complication.[82] The presence of absence seizure at time of the first recognised seizure increases risk for cognitive difficulties compared with other seizure types at epilepsy onset.[83] Results from a very small study suggest that seizure control with medication may improve cognitive function.[84] In a large cohort of patients with CAE, a high rate of attentional deficits were reported pre-treatment.[85] These deficits persisted post-treatment at 16 to 20 weeks, regardless of seizure freedom. Valproic acid was associated with more significant attentional deficits than ethosuximide or lamotrigine.[85]		
generalised tonic-clonic seizures (GTCS)	**variable**	**medium**
Approximately 50% of all patients with absence seizures also have GTC seizures.[79] This varies significantly between epilepsy syndromes, with essentially all juvenile myoclonic epilepsy patients having GTC seizures, compared with 30% or fewer patients with childhood absence epilepsy. Treatment with valproic acid, lamotrigine, topiramate, or zonisamide is indicated, with a goal of seizure elimination. In 2018, the European Medicines Agency affirmed that valproate-containing medicines must not be used during pregnancy, unless no other effective treatment is available. Women for whom there is no suitable alternative treatment to valproate are subject to specialist care, support, and counselling.[66] Standard practice in the US is to only prescribe valproate-containing medicines if other alternative medications are not acceptable or not effective. If the patient is taking the drug to prevent major seizures and is planning to become pregnant, the decision to continue valproate or to switch to an alternative agent should be made on an individual basis. In both Europe and the US, valproate and its analogues must not be used in female patients of childbearing potential unless there is a pregnancy prevention programme in place and certain conditions are met.[66]		
accidental injuries	**variable**	**low**
In general, patients with epilepsy are at increased risk for accidental injuries. One 24-month prospective case-controlled study reported a 27% risk of accident among patients with idiopathic, cryptogenic, or remote symptomatic epilepsy, compared with a 17% risk in matched controls.[76] The majority of accidents were seizure related. The most concerning injuries are submersion injuries, burns, fractures, head injuries, soft-tissue injuries, dental injuries, and motor vehicle accidents.[77] In general, these would be expected to be less frequent with absence seizures than with other types of seizures.		

FOLLOW UP

Complications	Timeframe	Likelihood
status epilepticus	**variable**	**low**
Absence (non-convulsive) status epilepticus may occur in 5.8% to 9.4% of patients with childhood absence epilepsy (CAE), 20% with juvenile absence epilepsy (JAE), and 6.7% with juvenile myoclonic epilepsy (JME).[78] Tonic-clonic status epilepticus is exceedingly rare.[78] Similar provocative factors are attributed to status epilepticus as breakthrough seizures: for example, sleep deprivation. It should be treated with benzodiazepines such as intravenous lorazepam or rectal diazepam. If unresponsive after a number of treatments, loading with a medicine such as valproate rather than phenytoin or phenobarbital should be considered, due to the risk of worsening absence status epilepticus.		
mortality	**variable**	**low**
Death occurs in the setting of status epilepticus in approximately 1% of all epilepsy patients. Sudden unexpected death in epilepsy (SUDEP) has been reported as a cause of death in 1 in 4500 children. The major risk factor for SUDEP is the occurrence of generalised tonic-clonic seizures.[86]		

Prognosis

Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME) syndromes tend to be quite responsive to medicine. Although the majority of CAE patients remit by adulthood, JME and JAE are likely to require lifelong treatment.

Epilepsy syndromes with atypical absence seizures, such as Lennox-Gastaut syndrome and epilepsy with myoclonic absences, are medically refractory and associated with severe intellectual disability.

Childhood absence epilepsy (CAE)

Remission has been estimated at about 65% by adolescence.[73] However, this is greatly affected by the diagnostic criteria. One study found a rate of remission as high as 82% using diagnostic criteria that allowed for the definition of a homogeneous group of patients.[74]

Juvenile absence epilepsy (JAE)

There are limited data due to this being a more recently described syndrome. Seizure control is attained in the majority of cases, estimated at up to 80% with valproic acid,[2] but remission may not be as high as in CAE. Treatment may be necessary for long periods of time.[75]

Juvenile myoclonic epilepsy (JME)

Although full remission is unlikely and most patients require lifelong treatment, the prognosis for seizure control is very good. Most patients remain neurologically normal.[75]

Epilepsy with myoclonic absences

Of the patients who are neurologically normal at presentation, approximately one half will develop cognitive problems. Absence seizures resolve after approximately 5 years, but other seizure types persist.[75]

Lennox-Gastaut syndrome

Seizures are generally medically refractory, despite the use of multiple medicines.[19] Patients are also severely neurologically impaired regardless of aetiology.[19]

Diagnostic guidelines

United Kingdom

Epilepsies in children, young people and adults (https://www.nice.org.uk/guidance/ng217)

Published by: National Institute for Health and Care Excellence **Last published:** 2025

International

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

Published by: International League Against Epilepsy **Last published:** 2009

North America

Reassessment: neuroimaging in the emergency patient presenting with seizure (an evidence-based review) (https://www.aan.com/policy-and-guidelines/guidelines)

Published by: American Academy of Neurology **Last published:** 2007 (reaffirmed in 2019)

Practice parameter: evaluating a first nonfebrile seizure in children (https://www.aan.com/policy-and-guidelines/guidelines)

Published by: American Academy of Neurology **Last published:** 2000 (re-affirmed in 2023)

Treatment guidelines

United Kingdom

Epilepsies in children, young people and adults (https://www.nice.org.uk/guidance/ng217)

Published by: National Institute for Health and Care Excellence **Last published:** 2025

International

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (https://www.ilae.org/guidelines/guidelines-and-reports)

Published by: International League Against Epilepsy **Last published:** 2013

North America

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

Published by: American Academy of Neurology **Last published:** 2021

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

Published by: American Academy of Neurology **Last published:** 2018

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

Published by: American Academy of Neurology **Last published:** 2018

Practice guideline summary:#sudden unexpected death in epilepsy incidence rates and risk factors (https://n.neurology.org/content/88/17/1674.long)

Published by: American Academy of Neurology **Last published:** 2017 (reaffirmed 2023)

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Images

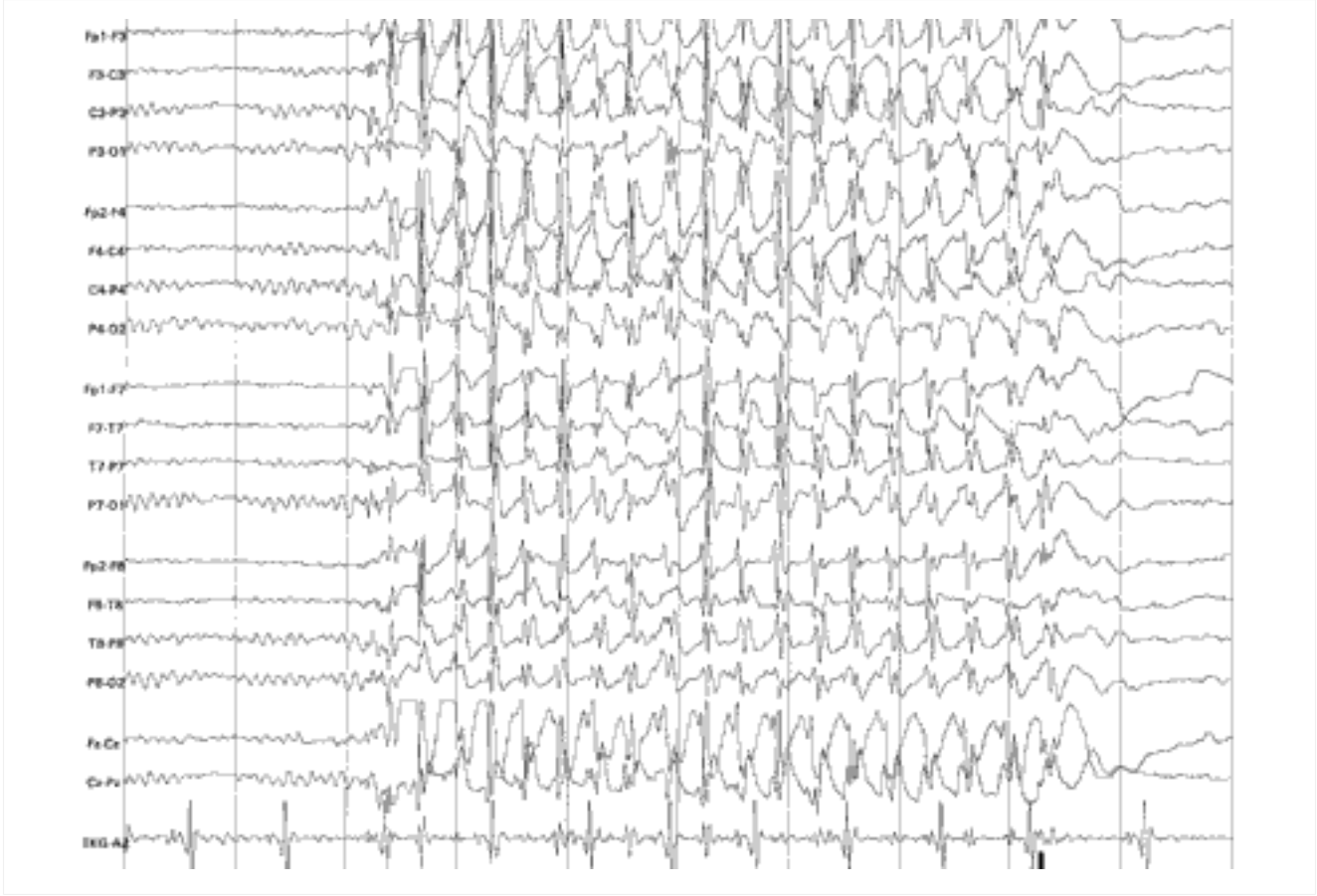

Figure 1: 3 Hz generalised spike-and-wave pattern on EEG pathognomonic for typical absence seizures and childhood absence epilepsy

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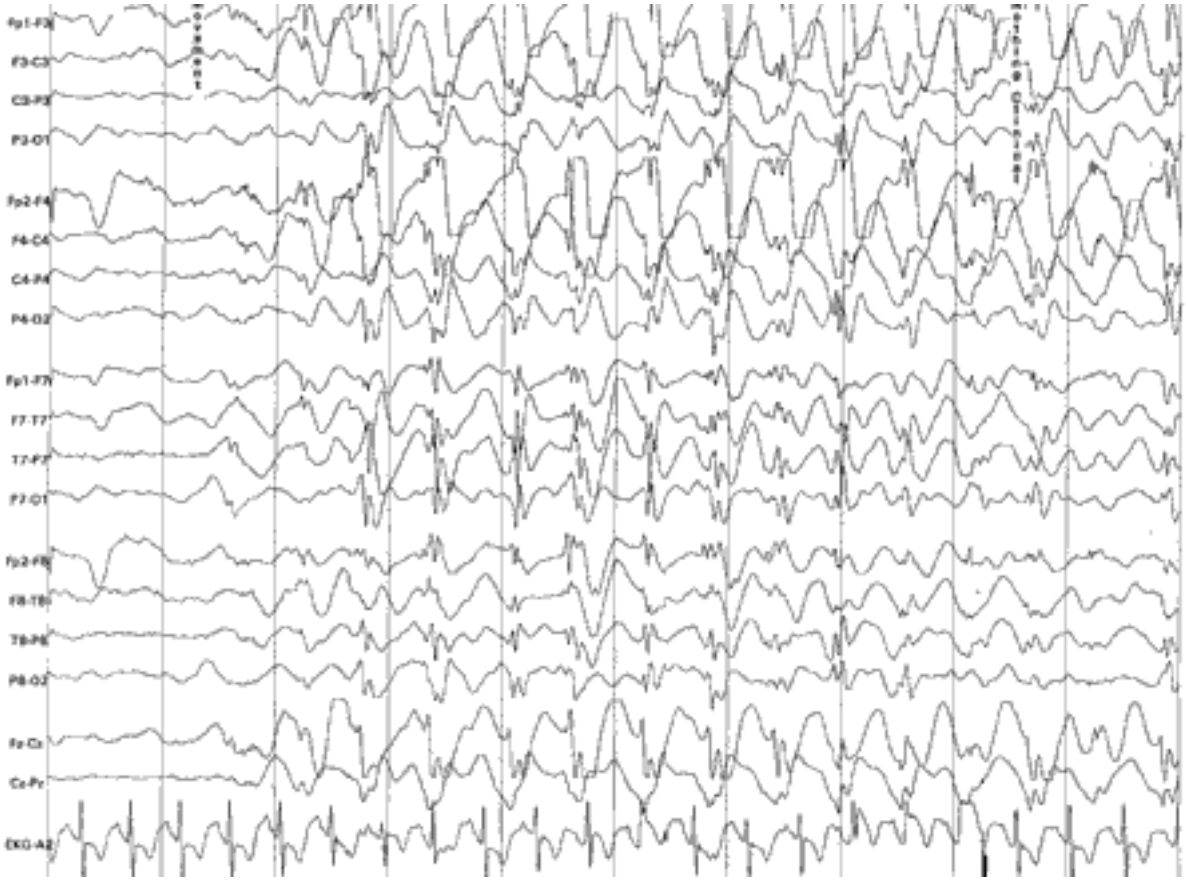

Figure 2: Slow (<2.5 Hz) generalised spike-and-wave on EEG associated with atypical absence seizures and Lennox-Gastaut syndrome

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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

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