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# Treatment Strategies for Paediatric Epilepsy: A Narrative Review

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**ABSTRACT:**

Epilepsy, a prevalent chronic neurological disorder in children, is characterized by recurrent, unprovoked seizures resulting from abnormal neuronal activity in the brain. Early and accurate diagnosis, coupled with tailored treatment strategies, is vital for enhancing the prognosis and quality of life for affected children and their families. The incidence of epilepsy is highest in the first year of life and decreases with age, with various causes such as genetic, structural, metabolic, immune, infectious, and unknown etiologies.

Diagnostic approaches include electroencephalography (EEG), neuroimaging, and genetic testing, which help identify the type and cause of epilepsy. Treatment primarily involves antiepileptic drugs (AEDs), classified into first-, second-, and third-generation, each with specific mechanisms, indications, and side effects. For drug-resistant epilepsy (DRE), surgical interventions such as resective surgeries and neurostimulation techniques offer alternative solutions. Emerging therapies, including gene therapy, cannabinoids, and the ketogenic diet, show potential in managing DRE and improving seizure control.

Additionally, the review explores the role of biomarkers and advanced neuroimaging techniques in predicting seizure recurrence and localizing epileptogenic zones, crucial for treatment planning. Despite significant advancements, predicting seizure recurrence remains a challenge, underscoring the need for further research. Integrating these diagnostic and therapeutic advancements into clinical practice is essential for optimizing care and improving long-term outcomes for pediatric epilepsy patients. This comprehensive approach aims to ensure better management and a higher quality of life for children with epilepsy and their families.

Keywords: Antiepileptic drugs, neurostimulation, pediatric

## Introduction

Seizures are transient symptoms caused by abnormal neuronal activity in the brain, while epilepsy is a chronic condition characterized by a predisposition to unprovoked seizures affecting the nervous system, cognition, and behaviour. Epilepsy is diagnosed after at least two unprovoked seizures more than 24 hours apart. Recurrent seizure risk may be indicated by epileptiform EEG activity or brain abnormalities. [1]

Seizures are common in children, with epilepsy being the most frequent chronic neurological disorder in this age group. A 2012 study found an epilepsy incidence of 144 per 100,000 in the first year of life, decreasing to 58 per 100,000 by age 10. The cumulative incidence by age five and ten is 0.45% and 0.66%, respectively. In 2005, the lifetime prevalence of epilepsy in children under ten was 0.6%, with 5% experiencing febrile seizures by age five. The neonatal stage carries the highest seizure risk due to brain characteristics promoting excitability. [2]

According to population-based research, almost half of all patients are able to wean off antiseizure medication, and nearly two-thirds of children with epilepsy attain epileptic independence for longer than three to five years. Regretfully, about 25% of patients experience drug-resistant epilepsy, which is characterised by the inability to control seizures after two or more adequate trials of antiseizure therapy. Such children run the danger of developing medical issues like osteoporosis, damage from seizures, and sudden unexpected death from epilepsy, in addition to cognitive, behavioural, and mental comorbidities. [3]

Early diagnosis improves prognosis and treatment, enhancing the quality of life for children and their families. Diagnosis involves identifying the epilepsy type (focal, generalized, or unknown), the seizure type, and potential syndromes. EEG is crucial for diagnosing generalized epilepsy, which includes various seizure types. Focal epilepsies are diagnosed based on clinical symptoms and EEG results, differentiating between focal and generalized epilepsy through careful examination. Epileptic syndromes are defined by clinical and EEG characteristics, often with specific etiological findings. Most childhood-onset generalized epilepsies are genetic, warranting genetic testing if single medication treatment fails. Diagnostic tests include microarrays, next-generation sequencing, and traditional Sanger sequencing. For metabolic epilepsy, biochemical tests, tissue biopsies, and

genetic testing are needed if the diagnosis is unclear. Immune-mediated epilepsy is diagnosed through antibody testing for conditions like LGI1 and NMDA receptor encephalitis.

Currently, no reliable tool predicts second epileptic seizures, emphasizing the need for more research. Abnormal neuroimaging findings, particularly in focal seizures, indicate recurrence risk. Neuroimaging techniques like PET, SPECT, and MEG are vital for assessing seizure risk and localizing epileptogenic zones, especially in drug-resistant cases. Research into microRNA and BDNF as biomarkers for epilepsy is ongoing, with BDNF showing promise for monitoring treatment responses rather than predicting onset. [4]

## Pathophysiology

The neonatal stage has the highest lifelong risk of seizures. Age-dependent brain physiologic characteristics that result in higher excitation (via the glutamatergic system) and lower inhibition (by gamma-amino-butyric acid, GABA) are linked to the neonatal brain's unique sensitivity to seizures.GABA is the main inhibitory neurotransmitter in the mature brain. Activation of the GABAA receptor causes an inflow of chloride, which causes the membranes of the neurons to become hyperpolarized and prevents action potentials from firing. On the other hand, in immature neurons, activation of the GABAA receptor causes a net efflux of chloride, which causes membrane depolarization and enhanced firing of action potentials. Through the use of ion transporters (NKCC1 and KCC2), a developmental shift in the neuronal chloride gradient mediates this modification in the GABAA action. Therefore, one may assume that GABAergic drugs (benzodiazepines and barbiturates) might exacerbate infant seizures. Still, about 50% of newborns react to phenobarbital's first doses. This implies that certain populations of the newborn's neurons are inhibitory to GABAergic drugs, which results in their antiseizure actions. Additionally, glutamate receptors change during development in ways that promote excitability in the developing brain. The growing brain contains a greater number of N-methyl-D-aspartate (NMDA) receptors than mature neurons do, in addition to having more NR2B, NR2D, and NR3A subunits. This combination of subunits is thought to be required for synaptogenesis in the developing brain, but it also increases the risk of seizures by increasing the amount of NMDA receptor-mediated calcium influx. Additionally favouring calcium influx and longer current durations is the design of AMPA receptors in newborns, which have greater GluR1 and decreased GluR2 subunits compared to mature brains. [5]

## Etiology

Epilepsy can be categorized into six subgroups based on its underlying causes: genetic, structural, metabolic, immune, infectious, and unknown. In some cases, epilepsy can involve a combination of these subgroups, such as tuberous sclerosis (genetic-structural) or Leigh syndrome (genetic-metabolic).

A genetic etiology is characterized by epilepsy resulting directly from a known or presumed genetic defect, with seizures as the primary symptom. This category includes generalized genetic epilepsy syndromes (idiopathic generalized epilepsies) like childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with tonic-clonic seizures alone. Other genetic causes associated with intellectual disability and poorer seizure control include CDKL5, ARX mutations, Dravet syndrome, protocadherin 19 female limited epilepsies, and Down syndrome. Genetic testing is highly effective for early-onset epilepsies, regardless of whether there are cortical developmental malformations.

Structural etiologies may be congenital (e.g., cortical dysplasia) or acquired (e.g., stroke, trauma). Specific structural causes like unilateral mesial temporal sclerosis often necessitate surgical intervention for better seizure outcomes despite resistance to medications.

A metabolic etiology is defined by epilepsy occurring in the context of a documented metabolic condition that significantly increases the risk of seizures. Examples include glucose transporter deficiency, creatine deficiency syndromes, and mitochondrial cytopathies. Many of these conditions are inherited genetically, and some, like glucose transporter deficiency, respond well to therapeutic approaches such as ketogenic diets.

Immune etiologies involve seizures as a core symptom of an immune disorder, typically accompanied by inflammatory changes in cerebrospinal fluid or specific autoantibodies found in serum or CSF. Conditions like anti-NMDA receptor encephalitis, mGluR5-associated limbic encephalitis, and Rasmussen syndrome fall into this category and often respond positively to immunomodulatory therapies.

Infectious etiologies indicate epilepsy resulting directly from a known infection, where seizures are a prominent feature of the disease. Examples include neurocysticercosis, tuberculosis, HIV, cerebral malaria, cerebral toxoplasmosis, and congenital infections such as Zika virus and cytomegalovirus. Identifying the specific infectious cause can guide appropriate therapeutic strategies.

The unknown etiology category includes cases where the underlying cause of epilepsy remains unidentified despite normal imaging and no documented genetic, metabolic, immune, or infectious etiology.Understanding these distinct categories helps in diagnosing epilepsy accurately and tailoring treatment strategies to improve patient outcomes based on the underlying cause when identifiable. [3]

## Diagnosis

The first step in assessing a child with suspected seizures is confirming whether the episodes are indeed seizures or another condition that mimics them, such as syncope, migraines, tics, sleep disorders, or behavioral events. Accurate diagnosis prevents unnecessary and potentially risky tests and treatments, reduces anxiety and stress for patients and families, and ensures appropriate management. Typically, a comprehensive history is sufficient

to distinguish epileptic seizures from non-epileptic events in children. The constellation of symptoms throughout the episode aids in confirming or ruling out a seizure diagnosis. While sudden symptom onset may occur in both epileptic seizures and syncope, seizure auras (e.g., unusual tastes, smells, déjà vu, or abdominal discomfort) typically differ from syncope symptoms, which include light-headedness, dizziness, and visual disturbances resembling a curtain descending. In epileptic seizures, uncontrollable motor activity during the episode is more indicative, while non-epileptic seizures may be influenced by intervention. Post-ictal symptoms like drowsiness or memory loss are also suggestive of epileptic seizures. Generally, a complex, repetitive clinical pattern with distinctive features and progression strongly suggests epileptic seizures. Although many childhood epilepsies follow a specific clinical pattern, severe forms may manifest with multiple seizure types. Additionally, brief seizures may not exhibit the full pattern seen in longer seizures. In cases where spells are infrequent, inpatient video-EEG monitoring can aid in characterizing episodes and distinguishing between suspected non-epileptic events and epileptic seizures. Ambulatory EEG monitoring is also useful when spells are less frequent in differentiating between seizure disorders and non-epileptic events. [6]

## Treatment

### Indications for Treatment

Following a first unprovoked seizure, the risk of experiencing a second seizure ranges from 3% to 55% over the next 2–5 years. This risk is higher in children who have a known cause for the seizure, abnormal examination or brain MRI, seizures during sleep, and an abnormal EEG with epileptiform discharges. Treating the first unprovoked seizure can reduce the risk of recurrence but does not affect the long-term prognosis. As such, AED (antiepileptic drug) therapy is typically not initiated after the first unprovoked seizure unless the risk of seizure-related injury is very high.

After a second seizure, the risk of further seizures rises significantly, ranging from 80% to 90% within two years without treatment. Therefore, most clinicians will recommend starting treatment after the second seizure, or even after the first seizure if the risk of recurrent seizures is deemed high. The frequency and severity of seizures also play a crucial role in selecting the most appropriate AED. Drugs that can be rapidly titrated to therapeutic doses are often preferred, especially when a child presents with frequent prolonged generalized tonic-clonic seizures. Additionally, the age at onset and the duration of the epileptic disorder may provide valuable insights for selecting targeted AED treatment options. [6]

Most children with new-onset epilepsy, particularly those with idiopathic generalized epilepsies, achieve seizure freedom with appropriate AEDs. Approximately 20% of children with epilepsy will experience only a few seizures within the context of an idiopathic focal syndrome before spontaneous remission of epilepsy. However, nearly 20% of the pediatric epilepsy population will continue to have seizures despite treatment with AEDs, whether used as monotherapy or in combination. [7]

## First-Generation Antiepileptic Drugs

### 1. Carbamazepine (CBZ)

Children's maintenance dose: 20–30 mg/kg/day

ADR: Fatigue, light-headedness, unsteadiness, ataxia, impaired vision, diplopia, hyponatremia, lowered bone mineral density, and anomalies in cardiac conduction

Indication: Generalised tonic-clonic seizures; mixed seizure patterns incorporating the above; complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation [8]

MOA: Carbamazepine blocks potential-dependent sodium channels, leading to a secondary reduction in glutamate release and catecholamine metabolism in the central nervous system. This results in the stabilization of over-excited nerve fibers' membranes, inhibition of repetitive neuronal discharges, and a reduction in the synaptic transmission of excitatory stimuli.

### 2. Clobazam (CLB)

Maintenance dose: 40 mg/kg/day

ADR: sedation, drowsiness, headache, pyrexia, lethargy, constipation, dry mouth, blurred vision [9]

MOA: Clobazam acts as a partial agonist at GABA-A receptors, in contrast to typical BZDs, which are full agonists. By enhancing the GABA-activated chloride channel, clobazam increases chloride conduction, leading to hyperpolarization of the neuronal membrane potential. This inhibits action potential generation and decreases neuronal hyperexcitability. [10]

Indication: Adjunctive treatment of Lennox-Gastaut syndrome (LGS) in patients aged 2 years or older. [7]

### 3. Clonazepam (CZP)

Maintenance dose: 1.5 mg/day [11]

ADR: lethargy, fatigue, sedation, drowsiness, and motor impairment (impaired coordination, impaired balance, dizziness) [12]

MOA: Benzodiazepines facilitate GABA-A action by increasing the frequency of chloride channel opening resulting in reduced neurons firing, thus producing calming effects on the brain. [13]

Indication: Second- and third-line treatments for focal seizures (FS) and generalized seizures (GTCS). When first-line medications are ineffective or poorly tolerated, the NICE guidelines recommend using CZP in patients with absences and myoclonic seizures. [7]

**4. Ethosuximide (ETS)**

Maintenance dose:20-30mg/kg/day

ADR: Nausea, abdominal discomfort, vomiting, diarrhoea, drowsiness, psychosis

Indication: First-line and adjunctive therapy for treatment of generalized absence seizures; Drug of choice for childhood absence epilepsy without GTCS. [7]

MOA: The electroencephalographic signatures of absence seizures, known as pulse-wave discharges, are produced by thalamocortical rhythms. Low-threshold T-type calcium currents in the thalamus are involved in the spontaneous activity of thalamocortical circuits; ethosuximide is considered to decrease these low-threshold currents in thalamic neurons.[4]

**5. Phenobarbital (PB)**

Maintenance dose: 60 - 200 mg /day

ADR: Agitation, somnolence, confusion, CNS depression, hyperkinesia, ataxia, nervousness, nightmares [14]

Indication: First-line and adjunctive treatment for FS and generalised seizures, including myoclonus but not absences. [7]

MOA: PB binds to GABA-A receptor subunits allowing the chloride ion gates to open and stay open, allowing a steady influx of chloride ions into neuronal cells. [2] This action hyperpolarizes the cell membrane, raising the action potential threshold, making the drug effective in treating seizures. [14]

**6. Phenytoin (PHT)**

Maintenance dose :4-10 mg/kg/day

ADR: Nystagmus, dizziness, unsteadiness, ataxia, blurred vision, diplopia, hirsutism

Indication: First-line and adjunctive therapy for the treatment of FS and GTCS. [7]

MOA: Inhibition of intracellular sodium currents. Reduces the influx of calcium ions into the cell. Inhibition of motor cortex and subcortical centres responsible for the tonic phase of convulsions. [4]

**7. Valproic Acid (VPA)**

Maintenance dose:15-40mg/kg/day

ADR: Tremor, nausea, abdominal discomfort, hyperammonaemia, hepatotoxicity, pancreatitis

Indication: Management of primary generalised epilepsy, including focal or partial epilepsies, either alone or as adjuvant therapy, petit mal absences, different types of myoclonic epilepsies, and tonic-clonic grand mal seizures.[8]

MOA: Selective activation of the enzymes responsible for the production of GABA and inhibition of the enzymes that break down GABA. cell membrane stabilisation through the manipulation of voltage-dependent sodium channels.[4]

## Second-Generation AEDs

**1. Felbamate (FBM)**

Maintenance dose: 3.6g/day. [15]

ADR: drowsiness, insomnia, anorexia, nausea, dizziness, and headache [16]

MOA: It is believed that the main antiepileptic action involves modulating the N-Methyl-aspartate (NMDA) receptor, which in turn reduces glutamatergic transmission [5] Additional activities include modest inhibition of voltage-gated sodium and calcium channels, as well as weak inhibition of GABA receptor binding.[17]

Indication: FBM was initially approved by the FDA as add-on treatment of Lennox-Gastaut syndrome and focal and secondary generalized seizures in patients refractory to other drugs. [7]

**2. Gabapentin (GPT)**

Maintenance dose: 900 -3600 mg / day

ADR: ataxia, dizziness, fatigue, somnolence, fever, nystagmus, peripheral edema, hostility, hyperkinesia (in pediatric patients), tremor, asthenia, diplopia, xerostomia, infection, amblyopia. [18]

MOA: Inhibits voltage-gated calcium channels. Gabapentin is used as monotherapy or as adjunctive therapy in focal seizures. [4]

Indication: Adjunctive therapy in the treatment of FS, with or without secondary generalization, in adults and pediatric patients 3 years and older. [7]

**3. Lamotrigine (LTG)**

Maintenance dose: 2-10mg/kg/day

ADRS: Dizziness, ataxia, blurred vision, diplopia, insomnia, hypersensitivity reactions

Indication: Treatment of partial and generalized seizures in adults and children. Initial monotherapy treatment in newly diagnosed pediatric patients is not recommended [9].

MOA: Lamotrigine inhibits sodium channels and blocks the release of excitatory amino acids (glutamic acid). [4]

**4. Levetiracetam (LEV)**

Maintenance dose:20-60mg/kg/day

ADRS: Drowsiness, fatigue, irritability, aggression, depression, psychosis

MOA: Levetiracetam selectively assembles and inhibits quickly firing neurons by binding to the synaptic vesicle protein SV2A and preventing the release of neurotransmitters (calcium ions) that are stored in the vesicle. Moreover, levetiracetam blocks N-type calcium and potassium channels.

Indication: Both Monotherapy and adjuvant therapy for localised or generalised myoclonic and tonic-clonic seizures. [4]

**5. Oxcarbazepine (OXC)**

Maintenance dose: 30-50mg/kg/day

ADRs: Dizziness, unsteadiness, ataxia, blurred vision, diplopia, nausea, hyponatraemia

Indication: Monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic eclonic seizures, in adults and children [8]

MOA: Blocks potential-dependent sodium channels. stabilises the membranes of overexcited nerve fibres. prevents recurrent neural firing. decreases the excitatory stimuli's synaptic transduction. models calcium channels that are voltage-dependent. [4]

**6. Pregabalin (PGB)**

Maintenance dose: 150- 600 mg daily.

ADR: Somnolence, dizziness, blurred vision, difficulty with concentration/attention, dry mouth, edema, and weight gain

Indication: Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older.

MOA: Binds to an auxiliary subunit (α2-δ protein) of the membrane voltage-shifted calcium channel in the central nervous system. [8]

**7. Tiagabine (TGB)**

Maintenance dose: 4-8mg/day

ADR: dizziness, asthenia, somnolence, nausea, irritability, tremor, abdominal pain, and thinking abnormal

MOA: By blocking the GAT-1 GABA transporter on presynaptic neurons and glial cells, it raises the availability of GABA at synapses. By doing this, the neural impulses that cause seizures are stopped from spreading.

Indication: Adjuvant treatment for partial seizures in patients 12 years of age and older. [19]

**8. Topiramate (TPM)**

Maintenance dose: 2-10mg/kg/day

ADRs: Cognitive impairment, concentration/attention and word finding difficulties, depression, psychosis, paraesthesia

Indications: Use in children and adults two years of age and up, In individuals with recently diagnosed epilepsy, as a monotherapy, to transition epileptic patients to monotherapy, As supplemental treatment for drop episodes linked to LGS, initial generalised tonic-clonic seizures, or partial onset seizures (with or without secondary generalisation).

MOA: Increases GABA activity, blocks membrane voltage-dependent sodium channels, and exhibits antagonistic behaviour towards the glutamic acid receptor. [4]

**9. Vigabatrin (GVG)**

Maintenance dose: 3g/day

ADR: insomnia, drowsiness, hypotonia, behavioral changes, MRI changes and visual disturbances [20]

MOA: It releases GABA in the synaptic cleft by serving as a substrate for GABA-T (γ-aminobutyric acid aminotransferase). Seizure activity is stopped when the brain's GABA content rises. Vigabatrin not only inhibits GABA-T but also stops GABA from being absorbed by neurons and promotes its release into the synapses. [21]

Indication: Monotherapy to treat infantile spasms in children between the ages of one month and two years. [7]

**10. Zonisamide (ZNS)**

Maintenance dose: 300 to 400 mg daily

ADR: Dizziness, somnolence, anorexia, ataxia, fatigue, abnormal thinking, confusion and mild to moderate weight loss [22]

MOA: T-type and voltage-dependent sodium and calcium channels are blocked by zonisamide. It may also prevent the release of glutamate. [23]

Indication: Adjuvant treatment for adult partial seizures. [24]

## Third-Generation AEDs

**1. Eslicarbazepine Acetate (ESL)**

Maintenance dose: 800 to 1600 mg/day

ADR: dizziness, impaired coordination, diarrhoea, nausea, vomiting, rash, hyponatremia

MOA: Eslicarbazepine acts by modifying the fast inactivation of voltage-gated sodium channels (VGSCs), hence decreasing the availability of VGSCs by augmentation of slow inactivation.

Indication: Monotherapy or adjunctive therapy for treating focal-onset seizures [25]

**2. Perampanel (PER)**

Maintenance dose: 8 to 12 mg / day

ADR: dizziness, somnolence, headache, irritability, fatigue, ataxia, vertigo

MOA: The postsynaptic ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor is the target of the novel non-competitive selective antagonist Perampanel. AMPA receptor antagonism may lessen overstimulation and the effects of anticonvulsants while also preventing the onset and progression of seizures. [26]

Indication: Adjuvant treatment for FS in adults and children as young as 12 years old in both the USA and Europe, with or without secondary generalisation. [7]

**3. Retigabine (RTG)**

Maintenance dose: 600-1200 mg/day

ADR: dizziness, somnolence, confusional state, vertigo, disturbance in attention, memory impairment, diplopia and blurred vision.

MOA: RTG functions as an opener of KCNQ channels KCNQ2-5, which reduces neuronal excitability.

Indication: As an adjuvant treatment for partial seizures [27]

**4. Rufinamide (RUF)**

Maintenance dose: 400-3200 mg/day

ADR: somnolence, vomiting, dizziness, nausea, and rarely, flu-like symptoms, nasopharyngitis, rash, ataxia, and diplopia

MOA: It modifies sodium channel function, namely by prolonging the inactive state. In young rat cortical neurons, rufinamide prevented the prolonged repeated firing of sodium-dependent action potentials and significantly slowed the recovery of sodium channels from inactivation after an extended prepulse. [28]

Indication: Adjuvant treatment for seizures linked to LGS in adults and children 4 years of age and older. [7]

**5. Stiripentol (STP)**

Maintenance dose: 20 to 50 mg/kg/day

ADR: loss of appetite, weight loss, drowsiness, ataxia, hypotonia, dystonia, aggressiveness, irritability, hyperexcitability, hyperkinesias

MOA: By lengthening the duration of GABA-A receptor channel opening in hippocampus slices, it has a barbiturate-like effect at clinically relevant dosages that improves central GABA neurotransmission. Additionally, through interfering with GABA's metabolism and reuptake, it has been demonstrated to raise GABA levels in brain tissues. [29]

Indication: When these treatments are insufficient for treating GTCS in children with severe myoclonic epilepsy of infancy (SMEI or Dravet syndrome), STP is added to CLB and VPA in Europe.[7]

6. **Lacosamide**

Maintenance dose: 200-400 mg/day

ADRs: Dizziness, headache, nausea, diplopia, tremor, vomiting

MOA: Enhances the voltage-gated sodium channel's gradual inactivation, which stabilises the membranes of hyperexcitable neurons.

Indications: Adjunctive treatment for people with epilepsy experiencing refractory partial onset seizures, irrespective of secondary generalisation. [8]

## Medication Non-responders

For the most part, children will react to the first AED.The strategy for picking the second AED in cases of initial failure are the same as when choosing the first AED.The possibility of negative side effects without increased efficacy is common when AEDs are introduced.24 Generally speaking, using more than three AEDs at once significantly raises the likelihood of undesirable side effects. Knowledge about AED drug–drug interactions is important, especially in enzyme-inducing and enzyme-inhibiting qualities. When a child does not respond to the first AED, the doctor should evaluate why the monotherapy didn't work in the first place. In order to inform future management, it may be helpful to confirm the diagnosis of epilepsy and assess non-epileptic seizures, nonadherence problems, and potential triggers. Nonadherence is a typical reason for non-responders. It is estimated that over 50% of children with newly diagnosed epilepsy are noncompliant over the first six months of treatment following initial diagnosis.25 Reducing treatment bias, providing access to follow-up, and educating patients about their disease could all assist reduce nonadherence. [6]

## Medication Discontinuation

The majority of clinicians will suggest an antiepileptic medication discontinuation after two years without seizures. Drugs can be weaned down gradually over the course of six weeks. It is recommended to taper off medications one at a time. Some clinicians may choose to use a routine EEG to evaluate the risk of seizure recurrence before stopping medication. When stopping medicine, the underlying aetiology of the condition should also be taken into account. For example, discontinuation could be delayed in a child with a symptomatic generalised seizure syndrome and an abnormal neurologic exam, EEG, and brain MRI. On the other hand, a child who is growing up normally and who has a normal neurologic exam, EEG, and brain MRI is more likely to gradually wean off anticonvulsants successfully and not have another seizure. [6]

## Surgical treatment of epilepsy:

Surgery is an option for patients with drug-resistant epilepsy (DRE) and has shown to improve cognitive function in pediatric patients. Surgical procedures include excision, separation, or neurostimulation, depending on the seizure cause.

The most common resective surgery for temporal lobe epilepsy is anterior temporal lobectomy (ATL), which is more effective than selective amygdalohippocampectomy. ATL targets mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia by removing parts of the limbic system, including the amygdala, hippocampus, and parahippocampal gyrus. Resective surgeries for frontal, parietal, and occipital lobes are less common. Lesionectomy targets local lesions like dysplasia and tumors, with accurate localization crucial for preparation. Less invasive neuroablation methods like radiofrequency thermocoagulation (RFTC) and Laser Interstitial Thermal Therapy (LITT) can also be used. MR-guided LITT avoids craniotomy and shortens hospital stays. [4]

While detachment techniques and neurostimulation are palliative, reducing seizure frequency and severity, resective procedures are therapeutic. For most drug-resistant patients, complete seizure cessation is unlikely, but palliative care aims to improve quality of life. Callosotomy, effective for multifocal DRE with secondary generalized seizures, prevents developmental regression and is useful for early infantile epileptic encephalopathy. [30 31 32]

## Gene therapy, Cannabinoids and Ketogenic diet:

Gene therapy, an emerging method in pharmacological treatment, involves introducing foreign genetic material into a patient’s cells, resulting in the inhibition, increase, or alteration of gene production. [4]

Cannabinoids (CBD) are a newer treatment option for drug-resistant epilepsy. In 2018, the US FDA approved CBD for treating Dravet syndrome and LGS in patients aged two years and older. While the exact mechanism is unknown, clinical trials have shown significant seizure reduction with CBD. For Dravet syndrome, CBD resulted in a 46-49% seizure reduction compared to 27% with a placebo. For LGS, CBD led to a 44% reduction compared to 20% in the control group. Side effects include drowsiness, fatigue, and diarrhea. [4]

Another promising treatment for epilepsy is the ketogenic diet, which increases GABA, adenosine, and noradrenaline while reducing glutamate in nerve synapses. It also inhibits histone deacetylases, improves mitochondrial function, and reduces oxidative stress. Studies, including a meta-analysis by Martin-McGill et al., have shown that the ketogenic diet significantly reduces seizures in children with drug-resistant epilepsy. [33]

## Vagus Nerve stimulation:

Vagus nerve stimulation (VNS) is a palliative therapy in which the vagus nerves are stimulated. Implantable neurostimulators are a complementary treatment to drug therapy for drug-resistant epilepsy (DRE) and offer an alternative for patients who are not candidates for resective surgery. The VNS was approved in the United States in 1997 and, according to the manufacturer, around 125,000 devices were in use worldwide in 2020. VNS has been used in more than 35,000 pediatric patients worldwide and is approved as a long-term treatment for DRE in children. VNS suppresses epileptic seizures, prevents emotional disturbances and improves cognitive function; it also has a parallel effect on the control of epileptic seizures.

The four components of the VNS device are as follows: (1) an electrode that is implanted spirally; (2) an implantable pulse generator; (3) a device that programmes the stimulation conditions of the generator that is subcutaneously implanted from outside the body; and (4) an external magnet that can initiate transient stimulation through a self-regulation mechanism.

Wound infection is the side effect of VNS that causes the most trouble. Reactive cough, voice changes, paresthesias, headache pain in the back, nausea, and salivation are some other adverse effects. [34]

## Conclusion

Epilepsy in children presents a significant clinical challenge, requiring early and accurate diagnosis to improve outcomes. Treatment strategies are diverse, ranging from various generations of AEDs to surgical and emerging therapies. While most children with epilepsy achieve seizure control with appropriate AEDs, a subset continues to experience seizures despite treatment. Advances in surgical techniques and innovative treatments like gene therapy and cannabinoids offer new hope for managing drug-resistant cases. Vagus nerve stimulation provides a palliative option, enhancing seizure control and quality of life. Despite these advancements, the ability to predict subsequent seizures remains limited, underscoring the necessity for continued research in epilepsy biomarkers and treatment strategies. The integration of early diagnosis, personalized treatment plans, and emerging therapies holds the potential to significantly improve the prognosis and quality of life for children with epilepsy and their families.

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