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Severe Epilepsy Syndromes in Childhood: A Comprehensive Review of Clinical Features, Etiologies, and Advancing Therapeutic Landscapes

Stefan Bittmann [a*], Elisabeth Luchter [a] and Elena Moschüring-Alieva [a]

[a] Department of Pediatrics, Ped Mind Institute, Hindenburgring 4, 48599 Gronau, Germany.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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Abstract

Severe childhood epilepsy syndromes, encompassing the developmental and epileptic encephalopathies together with related drug-resistant electroclinical constellations, remain among the most challenging conditions in paediatric neurology. They combine frequent, treatment-resistant seizures with developmental impairment, substantial comorbidity, and elevated premature mortality. The past two decades have transformed the field: a revised syndrome classification, an expanding catalogue of monogenic causes, and a succession of syndrome-specific and mechanism-based therapies have altered both diagnosis and management. This critical narrative review synthesises evidence on the clinical features, aetiologies, and therapeutic options for these syndromes, and evaluates the strength, consistency, and limitations of that evidence rather than cataloguing individual studies. Literature was selected from bibliographic searching, citation chaining, and appraisal of consensus statements and clinical guidelines, with every cited reference and its digital object identifier independently verified. Several themes emerge. Aetiological diagnosis, particularly through broad genetic testing, now carries direct management consequences, yet a diagnostic gap persists and genotype does not map cleanly onto phenotype or treatment response. Syndrome-specific pharmacotherapy is

**Corresponding author: Email: stefanbittmann@gmx.de;*

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supported by robust randomised evidence for a small number of agents in Dravet syndrome, Lennox-Gastaut syndrome, and CDKL5 deficiency disorder, but head-to-head comparisons, long-term developmental outcomes, and effects on the encephalopathy itself remain poorly characterised. Mechanism-based and disease-modifying strategies, including mammalian target of rapamycin inhibition, pre-emptive treatment, and antisense oligonucleotides, represent a conceptual shift from seizure suppression toward disease modification, though the durability and developmental impact of these approaches are not yet established. Sudden unexpected death in epilepsy and other causes of early mortality remain insufficiently mitigated. The available evidence supports cautious optimism: outcomes are improving, but confidence in many conclusions is constrained by small samples, heterogeneous endpoints, short follow-up, and reliance on seizure count as the dominant outcome. Priorities include earlier aetiological diagnosis, developmentally meaningful outcome measures, and trials designed to test disease modification rather than seizure frequency alone.

Keywords: Developmental and epileptic encephalopathy; Dravet syndrome; Lennox-Gastaut syndrome; infantile epileptic spasms; drug-resistant epilepsy; precision medicine; antiseizure medication; sudden unexpected death in epilepsy.

1. Introduction

Epilepsy is among the commonest serious neurological disorders of early life, and a substantial minority of affected children have conditions that are severe, treatment-resistant, and associated with impaired development. These conditions are now grouped conceptually under the developmental and epileptic encephalopathies (DEEs) and a small number of related electroclinical constellations in which frequent seizures, abundant epileptiform activity, and developmental slowing or regression coincide (Guerrini et al., 2023; Scheffer et al., 2017). The clinical importance of this group is disproportionate to its prevalence. Although each individual syndrome is rare, collectively the severe early-onset epilepsies account for a large share of childhood epilepsy-related disability, healthcare use, and mortality, and they impose a sustained burden on families and services (Symonds et al., 2019).

Reliable population-level data on these disorders have historically been scarce, but prospective cohorts have begun to quantify their frequency and to establish that a considerable proportion have an identifiable genetic basis (Symonds et al., 2019). Collectively the severe early-onset epilepsies represent a small fraction of all childhood epilepsy yet account for a disproportionate share of its long-term disability, healthcare expenditure, and mortality. Their chronicity, the frequent coexistence of intellectual disability and other comorbidities, and the limited effectiveness of conventional treatment combine to produce a burden that persists across the lifespan and extends well beyond the affected child. This disproportion between rarity and impact is a defining feature of the group and a principal justification for the sustained research effort directed at it (Guerrini et al., 2023). Recent large-scale clinical sequencing data have further demonstrated the heterogeneous molecular architecture of paediatric epilepsy and the continuing value of genome-scale testing and periodic reanalysis in unresolved cases (Henry et al., 2025).

The intellectual boundaries of this field have shifted considerably. Historically, severe childhood epilepsies were delineated as electroclinical syndromes defined by seizure semiology, age at onset, and characteristic electroencephalographic patterns, exemplified by the descriptions of West syndrome, severe myoclonic epilepsy of infancy, and Lennox-Gastaut syndrome. The identification of de novo pathogenic variants in the sodium-channel gene *SCN1A* as the predominant cause of what is now termed Dravet syndrome marked a decisive turn toward molecular aetiology (Claes et al., 2001). Subsequent gene-discovery efforts revealed that many severe encephalopathies are monogenic, that a single gene may produce several electroclinical pictures, and that a single syndrome may arise from several genes (McTague et al., 2016). The 2017 framework of the International League Against Epilepsy (ILAE) formalised aetiology as a parallel axis to seizure type and epilepsy type, and the 2022 syndrome papers introduced aetiology-specific syndromes alongside the classical electroclinical entities (Riney et al., 2022; Scheffer et al., 2017; Specchio et al., 2022; Zuberi et al., 2022). A recent comprehensive synthesis further emphasises that developmental and epileptic encephalopathies comprise clinically and molecularly heterogeneous disorders in which electroclinical recognition and aetiological diagnosis must be considered together (Scheffer et al., 2024).

Alongside this diagnostic transformation, the therapeutic repertoire has expanded from a small set of broad-spectrum antiseizure medications to include syndrome-specific agents supported by randomised evidence, dietary and surgical interventions, and mechanism-based treatments that target the underlying molecular defect. Regulatory approvals of stiripentol, cannabidiol, and fenfluramine for Dravet syndrome, of cannabidiol and fenfluramine for Lennox-Gastaut syndrome, and of ganaxolone for CDKL5 deficiency disorder illustrate a move toward precision-informed pharmacotherapy (Devinsky et al., 2017; Knupp et al., 2022; Lagae et al., 2019; Pestana Knight et al., 2022; Thiele et al., 2018). More radical still are strategies that seek to modify disease course, including inhibition of the mammalian target of rapamycin (mTOR) pathway in tuberous sclerosis complex, pre-emptive treatment before seizure onset, and antisense oligonucleotide therapy designed to restore deficient protein expression (French et al., 2016; Kotulska et al., 2021; Laux et al., 2026). Recent randomised evidence in Lennox-Gastaut syndrome has continued to broaden the range of evaluated adjunctive therapies, although limited sample size and variation in endpoint definitions constrain firm comparative conclusions (Vossler et al., 2025).

This progress has not resolved the central difficulties of the field, and in several respects the literature is inconsistent or incomplete. Genotype-phenotype relationships are frequently imperfect, so that identical variants may produce divergent severity, and the same clinical syndrome may reflect heterogeneous molecular mechanisms. The evidence base for individual therapies is uneven: a few agents rest on well-conducted randomised trials, whereas many treatments in routine use are supported only by observational data or expert consensus. Trials have almost universally used short-term seizure frequency as the primary endpoint, leaving the effects of treatment on cognition, behaviour, adaptive function, and survival poorly quantified, even though these outcomes matter most to families. Sudden unexpected death in epilepsy (SUDEP) and other causes of early death remain incompletely understood and

inadequately prevented (Harden et al., 2017; Sakauchi et al., 2011; Whitney et al., 2023). Longitudinal observations further indicate that cognitive and electroencephalographic trajectories may deteriorate over time in genetic developmental and epileptic encephalopathies, reinforcing the need for outcomes that extend beyond short-term seizure counts (Surdi et al., 2024).

Existing reviews have tended either to describe individual syndromes in isolation, to focus narrowly on genetics, or to summarise pharmacological trials without integrating them with aetiology and outcome. Comprehensive treatments of the molecular biology exist, as do syndrome-specific consensus documents, but a synthesis that critically connects the clinical phenotype, the aetiological framework, and the rapidly changing therapeutic landscape, and that appraises the quality and coherence of the underlying evidence, is less well represented. The pace of change, particularly the recent emergence of disease-modifying approaches, means that syntheses even a few years old no longer capture the current position. A critical, integrative account is therefore timely.

1.1 Scope, Research Gap and Objectives

This review concerns severe, drug-resistant epilepsy syndromes with onset in the neonatal period, infancy, or childhood, in which seizures are accompanied by developmental impairment or a high risk of it. Its scope covers the developmental and epileptic encephalopathies and the closely related severe electroclinical constellations, considered together across three linked dimensions: their clinical and electrophysiological features, their aetiologies, and their treatment. The review does not attempt exhaustive coverage of every rare monogenic disorder, of the self-limited focal epilepsies of childhood, of the genetic generalised epilepsies, or of the adult epilepsies, and it does not address the primary neurosurgical or intensive-care management of acute status epilepticus except where relevant to syndrome-level treatment decisions.

The specific gap this review addresses is the absence of an up-to-date, critical synthesis that integrates phenotype, aetiology, and therapy for the severe childhood epilepsies while explicitly appraising the strength and consistency of the evidence and representing disagreement fairly. The objectives are fourfold: to define the current state of knowledge on the clinical characterisation and classification of these syndromes; to evaluate the aetiological framework and the clinical consequences of precision diagnosis; to appraise critically the evidence for the expanding range of pharmacological, dietary, surgical, and mechanism-based therapies, distinguishing well-supported conclusions from preliminary claims; and to identify defensible research priorities. The intended contribution is an evidence-calibrated overview that clinicians and researchers can use to locate the boundaries of current certainty and to direct future work. Important exclusions, and the limits of the underlying evidence, are stated explicitly in the final section.

2. Methods for Literature Selection

2.1 Review Design and Rationale

A critical narrative review was chosen in preference to a systematic review, scoping review, or meta-analysis because the question is broad, spans several disciplines, and requires integration of heterogeneous evidence types, from molecular studies and case series to randomised controlled trials and consensus guidelines. A meta-analytic approach would be inappropriate given the diversity of syndromes, interventions, and outcome measures, and the small, non-comparable samples typical of rare-disease research. A narrative synthesis permits interpretive integration across these domains while retaining the capacity to weigh methodological quality and to represent conflicting findings. This design does not remove the obligation for transparency and critical appraisal; the search approach, selection reasoning, and appraisal criteria are described below, and the interpretive and selection limitations intrinsic to narrative reviews are acknowledged in the final section (Guerrini et al., 2023).

2.2 Information Sources

The literature search drew principally on the PubMed/MEDLINE bibliographic database and on Crossref Metadata Search, supplemented by broad scholarly web searching to identify additional peer-reviewed articles, consensus statements, and guideline documents. These sources were complemented by backward and forward citation searching, by examination of the reference lists of recent authoritative reviews and consensus documents, and by targeted searches of the websites of recognised professional and clinical-trial registries where relevant. Subscription-only indexing platforms such as Web of Science, Scopus, and Embase were not directly searched; this constraint is stated among the limitations. Bibliographic metadata, including author lists, titles, journal details, and digital object identifiers, were independently verified against Crossref registration records and against publisher or PubMed records before any source was cited.

2.3 Search Strategy and Search Period

Search concepts combined the principal syndromes and the umbrella construct with terms for aetiology and for treatment. Representative free-text and controlled-vocabulary strings, applied with Boolean operators and adapted to each resource, included: ("developmental and epileptic encephalopathy" OR "epileptic encephalopathy" OR "Dravet syndrome" OR "Lennox-Gastaut syndrome" OR "infantile spasms" OR "West syndrome" OR "CDKL5 deficiency") AND (child *OR infant* OR neonat *OR paediatric) AND (seizure* OR epilep*); the aetiological arm added (*SCN1A *OR* KCNQ2 *OR* STXBP1 *OR* CDKL5 *OR "exome sequencing" OR "gene panel" OR genetic OR aetiolog*); and the therapeutic arm added (cannabidiol OR fenfluramine OR stiripentol OR ganaxolone OR vigabatrin OR "ketogenic diet" OR everolimus OR "antisense oligonucleotide" OR surgery OR "randomised controlled trial"). The search considered literature published from January 1990 to 26 May 2026. Seminal earlier descriptions were considered where they were historically or conceptually necessary to explain the development of the field.

2.4 Eligibility Criteria

Sources were eligible if they addressed the clinical features, aetiology, prognosis, or treatment of severe childhood epilepsy syndromes and were published as peer-reviewed original research, high-quality reviews, consensus statements, or clinical or professional guidelines. Randomised controlled trials, prospective cohorts, well-characterised case series for rare disorders, systematic reviews, and authoritative position papers were prioritised. Publications were excluded if they concerned only adult populations without paediatric relevance, addressed self-limited or benign epilepsies outside the review scope, were available only as non-peer-reviewed material when peer-reviewed evidence existed, or could not be bibliographically verified. Only sources with retrievable full bibliographic detail and a resolvable identifier were retained. Language was restricted to publications available in English or with an English-language abstract sufficient for appraisal.

2.5 Screening, Duplicate Handling and Study Selection

Records were screened first by title and abstract for relevance to the review question, and potentially relevant items were assessed in full where the full text or a sufficiently detailed record was accessible. Duplicate records arising from indexing in more than one resource were identified by matching titles, author lists, and digital object identifiers, and were consolidated to a single entry. Where records could not be located in full or where bibliographic details could not be confirmed, the source was not cited. Because this is a narrative rather than a systematic review, no formal record-count flow diagram was produced and no quantitative screening tally is reported; selection was purposive and directed toward the most methodologically sound and conceptually important evidence for each theme, as described below.

2.6 Critical Appraisal and Evidence Synthesis

Each source was appraised for its contribution using criteria appropriate to its design, including the suitability of the study design to the question, sample size and representativeness, presence of controls, blinding and randomisation for interventional studies, validity of outcome measurement, handling of confounding, replication or independent confirmation, and external validity. Particular attention was paid to distinguishing association from causation, mechanistic plausibility from demonstrated clinical benefit, and short-term seizure outcomes from durable developmental effects. Evidence was organised thematically around conceptual foundations, electroclinical phenotype, aetiology, therapy, and outcome, rather than as a sequence of study summaries. For each theme, the strongest supporting evidence was synthesised, conflicting findings were examined, the likely reasons for disagreement were considered, and the confidence that could reasonably be placed in current conclusions was assessed. Where evidence was mixed, the disagreement was represented explicitly rather than resolved by assertion.

3. Conceptual Foundations: Terminology, Classification, and the Encephalopathy Construct

Coherent discussion of severe childhood epilepsies depends on a shared vocabulary that has itself evolved. The term epileptic encephalopathy originally captured the idea that abundant epileptiform activity could itself impair cognitive and behavioural development beyond what the underlying cause would produce. The contemporary construct of the developmental and epileptic encephalopathy separates two contributions to impairment: a developmental component attributable to the underlying aetiology and present independently of seizures, and an epileptic component in which the epileptic activity worsens the developmental trajectory (Guerrini et al., 2023; Scheffer et al., 2017). This distinction is more than terminological, because it frames a central therapeutic question, namely how far suppressing seizures and epileptiform activity can alter developmental outcome when much of the impairment is intrinsic to the cause.

The 2017 ILAE framework established three diagnostic levels, seizure type, epilepsy type, and epilepsy syndrome, with aetiology considered at each level across genetic, structural, metabolic, immune, infectious, and unknown categories (Scheffer et al., 2017). Building on this, the 2022 position papers organised syndromes by typical age at onset into those beginning in neonates and infants, those beginning in childhood, and those with onset at a variable age, alongside the idiopathic generalised epilepsies (Riney et al., 2022; Specchio et al., 2022; Zuberi et al., 2022). A significant conceptual innovation was the formal recognition of aetiology-specific syndromes, in which a defined molecular cause is integral to the syndrome definition, as with *KCNQ2*-related and *CDKL5*-related encephalopathies. This move reflects the reality that molecular diagnosis increasingly informs prognosis and treatment, but it also creates a hybrid taxonomy in which electroclinical and aetiological entities coexist, and the relationship between them is not always straightforward.

The diagnostic evaluation of a child with a suspected severe epilepsy syndrome integrates several strands of evidence. Careful characterisation of seizure semiology and of the electroencephalogram, including sleep and prolonged recordings, remains the foundation for syndrome recognition, since features such as hypsarrhythmia, slow spike-and-wave discharges, and burst-suppression carry strong diagnostic weight (Scheffer et al., 2017; Specchio et al., 2022). Neuroimaging, ideally with high-resolution magnetic resonance imaging, identifies structural substrates such as malformations of cortical development and the lesions of tuberous sclerosis complex, which have direct implications for surgical candidacy and for aetiology-specific therapy. Metabolic investigation retains importance because it can reveal treatable causes that would otherwise be missed. Increasingly, however, the decisive investigation is genetic, and the sequencing of the evaluation has shifted so that broad genetic testing is now recommended early rather than as a last resort (Sheidley et al., 2022; Smith et al., 2023). This reordering reflects a wider change in diagnostic philosophy, from a stepwise exclusion of causes toward a parallel and aetiology-directed workup, and it is justified chiefly by the management consequences that a molecular diagnosis now carries (Guerrini et al., 2023).

The classification carries several unresolved tensions. Age-based grouping is pragmatic but imperfect, because syndromes evolve: an infant with an early encephalopathy may progress through epileptic spasms to a Lennox-Gastaut phenotype, so that the same child satisfies different syndrome definitions at different ages (McTague et al., 2016). The introduction of mandatory and exclusionary criteria improves diagnostic consistency but risks leaving atypical presentations unclassified. The reliance on consensus methodology, rather than on prospective validation against outcome, means that the predictive value of these categories for treatment response is assumed more often than demonstrated. Table 1 summarises the principal terms and conceptual distinctions used throughout this review and highlights where their boundaries remain contested, which is relevant because much of the apparent inconsistency across the literature reflects shifting or overlapping definitions rather than genuine empirical disagreement.

Table 1. Key terminology and conceptual distinctions in the severe childhood epilepsies

Term or distinction	Working meaning and analytical significance	Supporting references
Epileptic encephalopathy	The concept that abundant epileptiform activity can itself impair development beyond the effect of the underlying cause; motivates aggressive seizure control as a means of protecting development.	Scheffer et al., 2017
Developmental and epileptic encephalopathy (DEE)	Separates a developmental component intrinsic to the aetiology from an epileptic component; clarifies that seizure control may improve, but not fully normalise, outcome.	Guerrini et al., 2023; Scheffer et al., 2017
Electroclinical syndrome	A recognisable cluster of seizure types, age at onset, and EEG features (for example West or Lennox-Gastaut syndrome); defined by phenotype rather than cause.	Specchio et al., 2022; Zuberi et al., 2022
Aetiology-specific syndrome	A syndrome whose definition incorporates a defined molecular cause (for example *CDKL5* deficiency disorder); links diagnosis directly to prognosis and precision therapy.	Riney et al., 2022; Specchio et al., 2022
Drug-resistant epilepsy	Failure of adequate trials of two appropriately chosen and tolerated antiseizure medications to achieve sustained seizure freedom; a defining feature of most severe syndromes.	Guerrini et al., 2023
Genotype-phenotype heterogeneity	The imperfect mapping between a genetic variant and clinical severity or syndrome; a major source of prognostic and therapeutic uncertainty.	McTague et al., 2016; Symonds et al., 2019

As Table 1 indicates, several of the field's central disputes are partly semantic. The evolution from the seizure-centred notion of the epileptic encephalopathy to the two-component developmental and epileptic encephalopathy construct reframes the goals of treatment and the interpretation of trials, because an intervention that reduces seizures without altering the developmental component may nonetheless be judged a success on a seizure endpoint while leaving the outcome that matters most largely unchanged.

4. Electroclinical Phenotypes of the Principal Severe Syndromes

The severe childhood epilepsies present as a small number of recognisable electroclinical pictures that recur across many aetiologies. Familiarity with these phenotypes remains clinically essential, because they guide the initial choice of investigation and treatment before, and often independently of, a molecular diagnosis. The principal syndromes are considered below and compared in Table 2.

4.1 Neonatal- and Early-infantile-onset Encephalopathies

The earliest-onset severe encephalopathies present within the first weeks to months of life with frequent seizures, a markedly abnormal interictal electroencephalogram, and early developmental arrest. Historically distinguished as early infantile epileptic encephalopathy with a burst-suppression pattern and early myoclonic encephalopathy, these presentations are now more often framed as early-infantile developmental and epileptic encephalopathy, reflecting the recognition that the burst-suppression electroencephalogram and the associated seizure types are aetiologically non-specific (Zuberi et al., 2022). A large proportion of cases are monogenic, with variants in genes such as *KCNQ2*, *STXBP1*, *SCN2A*, and *KCNT1* recurrently implicated, and many infants evolve toward later syndromes including epileptic spasms and Lennox-Gastaut syndrome (McTague et al., 2016). The prognosis is generally poor, but the identification of specific causes has begun to inform treatment, for example the preferential response of some *KCNQ2*-related and *SCN2A*-related presentations to sodium-channel-blocking medication, which illustrates the clinical value of early aetiological diagnosis even when the overall outlook remains guarded.

4.2 Infantile Epileptic Spasms Syndrome

Infantile epileptic spasms syndrome, historically West syndrome, typically presents between three and twelve months of age with clusters of epileptic spasms, developmental stagnation or regression, and the characteristic high-amplitude, disorganised interictal electroencephalogram termed hypsarrhythmia. It is a paradigmatic developmental and epileptic encephalopathy, in that the interictal abnormality is thought to contribute to developmental deterioration, and in which the speed of effective treatment appears to influence outcome (Specchio et al., 2022). The aetiology is heterogeneous, including structural lesions, tuberous sclerosis complex,

chromosomal and single-gene disorders, and metabolic causes, with a minority remaining of unknown cause. The syndrome may evolve into Lennox-Gastaut syndrome or other refractory epilepsies. The recognition that lead time to treatment matters has driven efforts to shorten diagnostic delay and to treat promptly, a theme returned to in the discussion of hormonal therapy and vigabatrin.

4.3 Dravet Syndrome

Dravet syndrome, formerly severe myoclonic epilepsy of infancy, is among the best-characterised of the severe childhood epilepsies and serves as a model for aetiology-informed care. It presents in a previously healthy infant, typically in the first year of life, with prolonged, often hemiclonic, febrile and afebrile seizures, followed by the emergence of multiple seizure types, developmental slowing from the second year, and marked pharmacoresistance (Wirrell et al., 2017). Pathogenic variants in *SCN1A*, most commonly de novo and frequently truncating, are identified in the substantial majority of cases, providing a molecular anchor for diagnosis and a clear illustration of how a channelopathy produces a stereotyped clinical course (Claes et al., 2001). The mechanistic understanding that *SCN1A* haploinsufficiency preferentially impairs inhibitory interneuron function explains the paradoxical worsening of seizures by sodium-channel-blocking medication and underpins syndrome-specific treatment recommendations (Wirrell et al., 2022). International consensus now supports early genetic testing when the characteristic presentation is recognised, precisely because diagnosis alters both drug selection and anticipatory management (Cardenal-Muñoz et al., 2022; Wirrell et al., 2022).

The natural history of Dravet syndrome extends well beyond seizures. After the second year of life, developmental slowing becomes apparent, and most affected individuals develop intellectual disability together with motor, behavioural, and communication difficulties and a characteristic gait disorder in later childhood (Cardenal-Muñoz et al., 2022). Seizures typically remain refractory throughout life, although their frequency may lessen with age, and status epilepticus, particularly when precipitated by fever, is a recurrent hazard. Mortality is elevated relative to the general epilepsy population, with sudden unexpected death in epilepsy and status epilepticus recognised as the principal mechanisms of early death (Sakauchi et al., 2011). This combination of refractory seizures, progressive developmental impairment, and premature mortality explains why the syndrome has become a focus of intensive therapeutic development, and why the goals of treatment now extend beyond seizure reduction toward the protection of development and the reduction of mortality (Wirrell et al., 2022). The syndrome therefore functions as a template for the broader ambition of the field, in which aetiological understanding is translated into syndrome-specific and, increasingly, disease-modifying care.

4.4 Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a childhood-onset developmental and epileptic encephalopathy defined by the triad of multiple seizure types, including tonic seizures that are considered a hallmark, together with atonic and atypical absence seizures; a characteristic electroencephalogram showing generalised slow spike-and-wave discharges in wakefulness and paroxysmal fast activity in sleep; and cognitive impairment with behavioural difficulty (Specchio et al., 2022; Strzelczyk & Schubert-Bast, 2021). Unlike Dravet syndrome, it has no single unifying cause; it arises from structural, acquired, metabolic, and genetic aetiologies, and may evolve from earlier syndromes such as infantile epileptic spasms syndrome. Drop attacks arising from tonic and atonic seizures are a major source of injury and disability, and their reduction has become a common trial endpoint. The syndrome is characteristically refractory, and no single medication has been shown to be uniformly superior, which has motivated a succession of adjunctive treatments evaluated primarily against drop-seizure frequency (Strzelczyk & Schubert-Bast, 2021).

Lennox-Gastaut syndrome typically follows a chronic course, persisting into adolescence and adulthood, and its cognitive and behavioural consequences frequently overshadow the seizures themselves. Because it can evolve from earlier encephalopathies and shares features with other generalised epilepsies, its boundaries are not always clear-cut, and the diagnosis may be applied inconsistently across centres, which complicates comparison across studies and trials (Specchio et al., 2022). The heterogeneity of underlying causes, spanning structural, acquired, and genetic aetiologies, means that no single mechanism unifies the syndrome, and this diversity has hampered the search for broadly effective treatments. The practical consequence is that management remains largely empirical and directed at the most disabling seizure types, particularly the drop attacks that cause injury, with a succession of adjunctive agents evaluated against that endpoint (Strzelczyk & Schubert-Bast, 2021). The syndrome thus illustrates a recurring difficulty in the field, namely that a recognisable clinical picture may conceal profound aetiological heterogeneity, limiting both prognostic precision and therapeutic rationalisation.

4.5 Aetiology-specific Developmental and Epileptic Encephalopathies

Beyond the classical electroclinical syndromes, a growing number of disorders are defined by their molecular cause and a recognisable, though variable, phenotype. CDKL5 deficiency disorder, an X-linked encephalopathy presenting with early, refractory seizures and severe global impairment, exemplifies this category and has become a focus of targeted drug development (Pestana Knight et al., 2022). Others include *KCNQ2*-related, *SCN2A*-related, *SCN8A*-related, *STXBP1*-related, and *PCDH19*-related encephalopathies, each with distinctive but overlapping features. The clinical importance of these entities lies in the coupling of diagnosis to management: some are associated with a preferential response to particular medications, others with specific comorbidity profiles or prognostic expectations (Guerrini et al., 2023; McTague et al., 2016). The proliferation of such entities also complicates the taxonomy, because the same gene can produce phenotypes ranging from self-limited epilepsy to severe encephalopathy, so that the aetiology-specific label captures a spectrum rather than a single clinical picture. Table 2 compares the principal syndromes and highlights both their distinguishing features and the substantial overlap that complicates diagnosis.

Table 2. Comparison of the principal severe childhood epilepsy syndromes

Syndrome	Typical onset	Core seizure types and EEG	Representative aetiology and prognosis	Supporting references
Early-infantile DEE (including former Ohtahara and early myoclonic encephalopathy)	First weeks to months	Tonic spasms and myoclonus; interictal burst-suppression	Frequently monogenic (*KCNQ2*, *STXBP1*, *SCN2A*, *KCNT1*); poor prognosis, frequent evolution to later syndromes	McTague et al., 2016; Zuberi et al., 2022
Infantile epileptic spasms syndrome (West)	3-12 months	Epileptic spasms in clusters; hypsarrhythmia	Structural, genetic, metabolic, or tuberous sclerosis; outcome influenced by cause and treatment lead time	Specchio et al., 2022
Dravet syndrome	First year of life	Prolonged febrile hemiclonic seizures, then multiple types; often normal early EEG	Pathogenic *SCN1A* variants in most cases; drug-resistant, elevated mortality including SUDEP	Claes et al., 2001; Wirrell et al., 2022
Lennox-Gastaut syndrome	Childhood (commonly 3-7 years)	Tonic, atonic, atypical absence; slow spike-and-wave and paroxysmal fast activity	Heterogeneous (structural, acquired, genetic); refractory, may evolve from West syndrome	Specchio et al., 2022; Strzelczyk & Schubert-Bast, 2021
Aetiology-specific DEEs (for example *CDKL5* deficiency disorder)	Infancy onward	Variable; early refractory seizures with global impairment	Defined single-gene cause; phenotype spans a spectrum; diagnosis guides targeted therapy	McTague et al., 2016; Pestana Knight et al., 2022

Table 2 makes clear that although these syndromes are individually recognisable, they share substantial phenotypic overlap and, importantly, that several can arise from the same gene while a single syndrome can arise from many. The practical consequence is that electroclinical recognition and aetiological diagnosis are complementary rather than alternative, and that the value of syndromic labels lies chiefly in guiding immediate investigation and treatment while molecular confirmation is pursued.

5. Aetiological Architecture and the Transition to Precision Diagnosis

The aetiological understanding of severe childhood epilepsies has been reshaped by high-throughput sequencing. Population-based data indicate that a substantial proportion of early-onset epilepsies have an identifiable genetic cause, with de novo variants prominent among the most severe encephalopathies (Symonds et al., 2019). A prospective national cohort estimated that roughly a quarter of children presenting with epilepsy under three years of age had a determinable genetic aetiology, and reported that the majority of these genetic diagnoses carried potential implications for treatment, a finding that reframes genetic testing from a purely diagnostic exercise into a management tool (Symonds et al., 2019). The catalogue of implicated genes is large and functionally diverse, spanning ion channels, synaptic and vesicle-cycling proteins, and regulators of neuronal development, which helps explain both the phenotypic breadth and the difficulty of devising unifying therapeutic strategies (Guerrini et al., 2023; McTague et al., 2016).

The clinical case for broad genetic testing now rests on more than diagnostic yield. Systematic appraisal of the evidence has supported the diagnostic performance of exome and genome sequencing and of large multi-gene panels, and evidence-based guidance recommends genetic testing for individuals with unexplained epilepsy, with genome or exome sequencing or a large panel as first-tier testing (Sheidley et al., 2022; Smith et al., 2023). Crucially, a molecular diagnosis frequently changes management, whether by directing drug selection, by prompting or avoiding particular interventions, by refining prognosis, or by enabling access to targeted therapy and to family counselling (Haviland et al., 2023). The magnitude of the management effect reported across cohorts varies with the population studied and the definition of clinical utility, so the precise proportion of patients whose care is altered should be interpreted with caution, but the direction of the evidence is consistent.

The mechanistic diversity underlying these disorders has direct therapeutic consequences. Implicated genes encode ion channels, presynaptic and vesicle-cycling machinery, transcriptional and developmental regulators, and components of intracellular signalling pathways, so that a common clinical endpoint of severe epilepsy arises from disparate molecular lesions (Guerrini et al., 2023; McTague et al., 2016). This heterogeneity frustrates any single unifying treatment strategy and instead favours mechanism-specific approaches. Complexity is added by somatic mosaicism, in which a pathogenic variant is present in only a proportion of cells, and by the observation that inherited and de novo mechanisms both contribute, with implications for recurrence risk and family counselling (McTague et al., 2016). Among the many causes, a subset is specifically treatable, including certain metabolic disorders in which substrate provision or dietary therapy addresses the underlying defect, so that their identification carries disproportionate clinical value relative to their frequency (Guerrini et al., 2023). Population-based data reinforce the point that a meaningful fraction

of early-onset epilepsies have a determinable and sometimes actionable cause, which strengthens the argument for systematic rather than selective aetiological investigation (Symonds et al., 2019).

Several caveats temper the enthusiasm for aetiology-driven care. Diagnostic yield remains well short of complete, so that a large minority of children have no molecular diagnosis despite thorough testing, and the yield reported in individual studies is sensitive to cohort selection, testing strategy, and variant-interpretation practices (Sheidley et al., 2022). Genotype-phenotype relationships are frequently imperfect: the same gene may cause disorders ranging from mild epilepsy to severe encephalopathy, identical variants may produce different severity, and the mechanistic direction of a variant, whether loss or gain of function, can determine opposite treatment recommendations, as in the contrasting responses of loss-of-function and gain-of-function sodium-channel disorders to sodium-channel blockers (Guerrini et al., 2023; McTague et al., 2016). Structural, metabolic, and acquired causes remain important, particularly for the epileptic spasms phenotype and for Lennox-Gastaut syndrome, and should not be neglected in the pursuit of a genetic diagnosis. Table 3 summarises representative aetiological categories, their characteristic associations, and their therapeutic relevance, while emphasising that these associations are probabilistic rather than deterministic.

Table 3. Representative aetiological categories in the severe childhood epilepsies and their therapeutic relevance

Aetiological category	Representative examples and phenotypic associations	Therapeutic relevance	Supporting references
Ion-channel genes	*SCN1A* (Dravet syndrome), *KCNQ2*, *SCN2A*, *SCN8A*, *KCNT1*; span self-limited to severe encephalopathy	Direction of channel dysfunction can determine choice of, or avoidance of, sodium-channel blockers	Claes et al., 2001; McTague et al., 2016
Synaptic and regulatory genes	*STXBP1*, *CDKL5*, *PCDH19*; early refractory seizures with global impairment	Some are targets for emerging precision or neurosteroid therapy	Guerrini et al., 2023; Pestana Knight et al., 2022
Structural and neurocutaneous	Tuberous sclerosis complex, malformations of cortical development	mTOR inhibition in tuberous sclerosis; surgical candidacy for focal lesions	Dwivedi et al., 2017; French et al., 2016
Metabolic	Glucose transporter deficiency and other treatable metabolic disorders	Aetiology-specific dietary or substrate therapy where identified	Guerrini et al., 2023
Unknown	No molecular, structural, or metabolic cause identified despite testing	Management remains syndrome-directed and empirical	Sheidley et al., 2022; Symonds et al., 2019

The categories in Table 3 are neither mutually exclusive nor static, since continued gene discovery reclassifies cases previously labelled as of unknown cause, and the therapeutic relevance of a given aetiology depends on the mechanistic detail of the variant rather than the gene alone. The overall picture is of a field in which aetiological diagnosis has genuine and growing clinical value, tempered by an incomplete diagnostic reach and by the imperfect and sometimes counter-intuitive relationship between molecular findings and clinical behaviour.

6. The advancing Therapeutic Landscape

Treatment of the severe childhood epilepsies has moved from empirical polypharmacy toward a more differentiated approach in which the choice of therapy is increasingly informed by syndrome and, where known, by aetiology. The evidence supporting this approach is uneven in quality, ranging from well-conducted randomised controlled trials for a small number of agents to observational data and expert consensus for many others. This section appraises the principal therapeutic categories in turn and evaluates the strength and limitations of the supporting evidence, which is summarised in Table 4.

6.1 Broad-spectrum Antiseizure Medications and the Sodium-channel Caveat

Most children with severe epilepsy syndromes are treated initially with broad-spectrum antiseizure medications such as valproate, clobazam, levetiracetam, and topiramate, chosen empirically according to seizure type and tolerability. The evidence for these agents in the specific severe syndromes is largely extrapolated from broader epilepsy populations and from observational experience rather than from syndrome-dedicated randomised trials, and none reliably achieves sustained seizure freedom in these pharmacoresistant conditions. A clinically important exception to broad-spectrum prescribing is the recognition that sodium-channel-blocking medications, including carbamazepine, oxcarbazepine, phenytoin, and lamotrigine, can aggravate seizures in Dravet syndrome and related *SCN1A* loss-of-function disorders, a caveat that has become a fixed element of syndrome-specific guidance and that illustrates how aetiological understanding refines even the use of established drugs (Wirrell et al., 2017; Wirrell et al., 2022). The same principle operates in reverse for certain gain-of-function channelopathies, where sodium-channel blockade may be beneficial, underscoring the need to interpret drug choice in the light of mechanism rather than seizure type alone.

6.2 Syndrome-specific Pharmacotherapy

The strongest recent advances concern medications evaluated in, and licensed for, specific syndromes. In Dravet syndrome, stiripentol was shown in a small randomised, placebo-controlled trial to produce a marked responder advantage when added to valproate and clobazam, with a large majority of treated children responding compared with almost none receiving placebo, a result

notable both for its effect size and for demonstrating that a syndrome-focused trial in a small, homogeneous population can yield clear conclusions (Chiron et al., 2000). Cannabidiol subsequently produced a significant reduction in convulsive seizure frequency relative to placebo in a randomised trial in Dravet syndrome (Devinsky et al., 2017), and fenfluramine achieved a large placebo-adjusted reduction in convulsive seizure frequency, with the higher dose associated with a reduction of the order of sixty per cent greater than placebo (Lagae et al., 2019). Fenfluramine also demonstrated efficacy when added to stiripentol-inclusive regimens (Nabbout et al., 2020). These trials share a common limitation: they measure short-term convulsive-seizure frequency and provide limited information on developmental trajectory, long-term efficacy, or comparative effectiveness.

In Lennox-Gastaut syndrome, both cannabidiol and fenfluramine have been shown in randomised trials to reduce the frequency of drop seizures relative to placebo, extending the syndrome-specific approach to a disorder without a unifying cause (Devinsky et al., 2018; Knupp et al., 2022; Thiele et al., 2018). Cannabidiol was studied at defined doses added to existing regimens and produced significant reductions in drop-seizure frequency, and fenfluramine similarly reduced drop-seizure frequency, offering additional options for a characteristically refractory condition (Strzelczyk & Schubert-Bast, 2021). In CDKL5 deficiency disorder, ganaxolone, a neuroactive steroid acting at the gamma-aminobutyric-acid type A receptor, produced a modest but statistically significant reduction in major motor seizure frequency compared with placebo, of the order of a thirty-one per cent reduction against a seven per cent reduction, in the first controlled trial of any antiseizure treatment for that disorder (Pestana Knight et al., 2022). The effect sizes across these syndrome-specific agents are clinically meaningful but partial, and seizure freedom remains uncommon, so the therapeutic goal for most children is a reduction in the most disabling seizures rather than their elimination.

Interpreting the syndrome-specific trials requires attention to their mechanisms and to the meaning of their effect sizes. Stiripentol acts partly through inhibition of cytochrome-P450 enzymes, potentiating co-administered medications, which explains both its efficacy as an adjunct and the need to adjust concomitant drugs (Chiron et al., 2000). Cannabidiol and fenfluramine act through distinct mechanisms unrelated to sodium-channel blockade, which is consistent with their utility in disorders where sodium-channel blockers are contraindicated (Devinsky et al., 2017; Lagae et al., 2019). The reported reductions in seizure frequency, although statistically robust, are typically partial, and cross-trial comparison is hazardous because baseline severity, concomitant medication, and endpoint definitions differ, so that apparent differences in effect size between agents may be artefactual rather than real (Strzelczyk & Schubert-Bast, 2021). In routine practice these agents are used in combination and in sequence rather than as alternatives, and syndrome-specific consensus guidance has begun to codify a rational ordering of treatments, although this guidance rests substantially on expert opinion where head-to-head evidence is absent (Wirrell et al., 2022).

6.3 Hormonal Therapy and Vigabatrin for Epileptic Spasms

For infantile epileptic spasms syndrome, hormonal therapy with corticotropin or prednisolone and the medication vigabatrin are the established first-line treatments. The International Collaborative Infantile Spasms Study, a large randomised trial, showed that combining vigabatrin with hormonal therapy stopped spasms in a greater proportion of infants than hormonal therapy alone within the early treatment period, with cessation achieved in around seventy-two per cent of infants receiving combination therapy compared with around fifty-seven per cent receiving hormonal therapy alone (O'Callaghan et al., 2017). Vigabatrin is of particular value where tuberous sclerosis complex is the cause. The trial evidence establishes superior early spasm control for combination therapy, but the translation of this early electroclinical response into improved long-term developmental outcome is less certain, and the balance between efficacy and the recognised adverse effects of the constituent treatments requires individual judgement.

6.4 Dietary Therapy, Resective Surgery, and Neuromodulation

Non-pharmacological treatments occupy an established place in the management of drug-resistant childhood epilepsy. The ketogenic diet was shown in a randomised controlled trial to reduce seizure frequency in children with drug-resistant epilepsy, with a significantly greater proportion of children on the diet achieving a meaningful reduction than controls, providing controlled evidence for a long-used intervention (Neal et al., 2008). Dietary therapy is particularly relevant in certain aetiologies, including glucose transporter deficiency, where it addresses the underlying metabolic defect. Resective and disconnective surgery can be transformative where a focal or hemispheric substrate is identified, and a single-centre randomised trial in children with drug-resistant epilepsy demonstrated that surgery produced substantially higher rates of seizure freedom than continued medical therapy over twelve months, albeit with a recognised burden of surgical morbidity (Dwivedi et al., 2017). Neuromodulatory approaches, including vagus nerve stimulation and corpus callosotomy for drop attacks, provide palliative benefit in selected refractory cases, although the controlled evidence for these interventions in the specific severe syndromes is more limited. The overarching message is that appropriate candidates for dietary and surgical treatment are frequently identified late, and that timely evaluation, particularly surgical evaluation, is an underused opportunity.

6.5 Mechanism-based, Preventive, and Disease-modifying Therapies

The most conceptually significant developments seek to modify disease rather than merely suppress seizures. In tuberous sclerosis complex, inhibition of the mTOR pathway with everolimus reduced seizure frequency in a randomised, placebo-controlled trial, with the higher-exposure regimen producing a median reduction of around forty per cent compared with around fifteen per cent for placebo, providing a mechanism-based treatment aligned to the disorder's molecular pathology (French et al., 2016). The logic of intervening before, rather than after, epilepsy becomes established has been tested directly: pre-emptive treatment with vigabatrin in infants with tuberous sclerosis complex, begun on the basis of electroencephalographic change before clinical seizures, altered the epilepsy course in a controlled trial, supporting a preventive paradigm that departs from the traditional reactive model of epilepsy care (Kotulska et al., 2021). Precision diagnosis is a prerequisite for such approaches, reinforcing the clinical case for early genetic and aetiological testing (Haviland et al., 2023; Smith et al., 2023).

The clearest illustration of disease-modifying ambition is antisense oligonucleotide therapy for Dravet syndrome. Zorevunersen, an antisense oligonucleotide designed to increase productive *SCN1A* messenger RNA and thereby raise deficient NaV1.1 sodium-channel expression from the non-mutant allele, was evaluated in open-label, early-phase studies in children and adolescents. Across these studies, treatment was associated with reductions in seizure frequency and with reported improvements in measures of cognition and behaviour, and the principal safety finding was elevation of cerebrospinal-fluid protein consistent with the class effect of intrathecal oligonucleotides (Laux et al., 2026). The approach is important because it targets the causal molecular deficit and because its stated aim extends beyond seizure control to developmental outcome, addressing the developmental component of the encephalopathy that seizure-suppressing drugs cannot reach. The evidence remains early: the pivotal data derive from open-label studies without a concurrent randomised control, sample sizes are small, and the durability of benefit and the effect on long-term development are not yet established. Analogous strategies for other monogenic encephalopathies, including CDKL5 deficiency disorder, are at an earlier stage (Pestana Knight et al., 2022). Table 4 summarises the principal therapeutic options, their level of supporting evidence, and their main limitations.

Table 4. Principal therapeutic options for severe childhood epilepsy syndromes, evidence, and limitations

Intervention	Principal indication	Nature of supporting evidence	Key limitation of the evidence	Supporting references
Stiripentol	Dravet syndrome (adjunctive)	Small randomised placebo-controlled trial with large responder advantage	Small sample; short-term seizure endpoint	Chiron et al., 2000
Cannabidiol	Dravet and Lennox-Gastaut syndromes	Randomised placebo-controlled trials showing reduced target seizures	Partial effect; limited developmental outcome data	Devinsky et al., 2017; Devinsky et al., 2018; Thiele et al., 2018
Fenfluramine	Dravet and Lennox-Gastaut syndromes	Randomised placebo-controlled trials with substantial seizure reduction	Cardiac monitoring required; short-term endpoints	Knupp et al., 2022; Lagae et al., 2019; Nabbout et al., 2020
Ganaxolone	*CDKL5* deficiency disorder	First randomised placebo-controlled trial in the disorder	Modest effect; seizure freedom uncommon	Pestana Knight et al., 2022
Hormonal therapy plus vigabatrin	Infantile epileptic spasms syndrome	Large randomised trial favouring combination for early spasm cessation	Uncertain long-term developmental benefit	O'Callaghan et al., 2017
Ketogenic diet	Drug-resistant childhood epilepsy	Randomised controlled trial showing reduced seizures	Adherence demands; heterogeneous populations	Neal et al., 2008
Resective surgery	Focal or hemispheric substrate	Randomised trial showing high seizure-freedom rate	Surgical morbidity; requires suitable substrate	Dwivedi et al., 2017
mTOR inhibition (everolimus)	Tuberous sclerosis complex	Randomised placebo-controlled trial	Partial effect; adverse events dose-related	French et al., 2016
Pre-emptive vigabatrin	Tuberous sclerosis complex (before seizure onset)	Controlled trial of a preventive paradigm	Applicable to a defined aetiology; requires early detection	Kotulska et al., 2021
Antisense oligonucleotide (zorevunersen)	Dravet syndrome (*SCN1A* haploinsufficiency)	Open-label early-phase studies with seizure and cognitive signals	No concurrent randomised control; durability unknown	Laux et al., 2026

Table 4 shows a therapeutic landscape stratified by evidence quality. A small number of syndrome-specific pharmacological agents and non-pharmacological interventions rest on randomised evidence, whereas the most conceptually promising disease-modifying approaches, which target the causal defect and aspire to developmental benefit, remain supported chiefly by early-phase or mechanism-based data. The recurring limitation across the table is the dominance of short-term seizure endpoints, which constrains what can be concluded about the effect of any of these treatments on the developmental component of the encephalopathy.

7. Comorbidity, Mortality, and Sudden Unexpected Death in Epilepsy

Seizures are only one component of the burden imposed by severe childhood epilepsies. Intellectual disability, motor impairment, behavioural and psychiatric difficulty, sleep disturbance, and, in some syndromes, progressive decline are common and contribute substantially to the impact on children and families (Cardenal-Muñoz et al., 2022; Guerrini et al., 2023). These comorbidities are partly intrinsic to the underlying aetiology and partly related to the epilepsy itself, and their management requires multidisciplinary care that extends well beyond seizure control. The developmental and epileptic encephalopathy construct is again relevant, because it predicts that even effective seizure treatment will leave a residual developmental burden attributable to the cause, a prediction

consistent with the observation that seizure reduction in trials has rarely been accompanied by demonstrable normalisation of development.

The impact of these syndromes extends to families and carers, who bear a substantial and sustained burden encompassing constant supervision, disrupted sleep, and the emotional weight of a chronic, life-limiting condition, alongside significant economic and social costs (Cardenal-Muñoz et al., 2022). Effective care is therefore necessarily multidisciplinary, combining epilepsy management with developmental, behavioural, nutritional, and palliative support, and with structured counselling about risks including sudden unexpected death in epilepsy. A recurring shortcoming of the evidence base is that these dimensions of impact are seldom captured in trials, which have concentrated on seizure counts to the near-exclusion of validated measures of development, adaptive function, and quality of life (Guerrini et al., 2023). This mismatch between what is measured and what matters most to families is a central theme of the critical appraisal offered here, and it constrains the extent to which current evidence can guide the choices that families and clinicians actually face.

Premature mortality is elevated across the severe syndromes, and sudden unexpected death in epilepsy is a leading contributor. In Dravet syndrome specifically, early death is well documented, with sudden unexpected death and status epilepticus recognised as principal mechanisms (Sakauchi et al., 2011). Across paediatric epilepsy more broadly, the incidence of sudden unexpected death in epilepsy in children has been estimated at approximately 0.22 per 1000 patient-years, lower than in adults, although more recent analyses suggest that this figure may underestimate the true burden and that paediatric rates may approach adult rates in some populations (Harden et al., 2017; Whitney et al., 2023). The most consistently identified risk factor is the occurrence and frequency of generalised tonic-clonic seizures, which provides a rationale for optimising seizure control as a means of risk reduction, alongside attention to nocturnal supervision and treatment adherence (Harden et al., 2017; Whitney et al., 2023). The evidence on prevention is largely indirect: reducing generalised convulsive seizures is expected to reduce risk, but demonstrating a mortality benefit from any specific intervention is difficult given the rarity of the outcome and the ethical and practical constraints on trials. This gap between plausible mechanism and demonstrated preventive efficacy is one of the most consequential in the field, because mortality, unlike seizure count, is the outcome families most fear.

8. Methodological Quality and Coherence of the Evidence Base

A critical reading of the literature on severe childhood epilepsies reveals recurrent methodological constraints that limit the confidence attainable in many conclusions. The rarity of individual syndromes forces reliance on small samples, which reduces statistical power, widens confidence intervals, and makes subgroup and comparative analyses unreliable. Even the pivotal randomised trials, which represent the strongest evidence in the field, have typically enrolled modest numbers and have measured short-term seizure frequency rather than developmental or functional outcomes (Chiron et al., 2000; Lagae et al., 2019; Pestana Knight et al., 2022). The near-universal use of seizure count as the primary endpoint is a structural weakness, because it privileges the epileptic component of the encephalopathy over the developmental component that families and clinicians most wish to influence, and because seizure diaries are themselves subject to measurement error.

Table 5. Methodological limitations of the evidence base and the research priorities they imply

Limitation	Consequence for interpretation	Implied research priority	Supporting references
Small samples inherent to rare syndromes	Low power; unreliable subgroup and comparative inference	Multicentre and international consortia; adaptive and platform trial designs	Chiron et al., 2000; Pestana Knight et al., 2022
Reliance on short-term seizure count as endpoint	Developmental and functional effects poorly captured	Validated developmental and quality-of-life outcome measures	Lagae et al., 2019; Laux et al., 2026
Population and outcome heterogeneity	Impedes comparison and pooling across studies	Standardised core outcome sets and aetiology-stratified analysis	Sheidley et al., 2022; Symonds et al., 2019
Referral-cohort ascertainment bias	Distorted prevalence and prognosis estimates	Population-based prospective cohorts	Symonds et al., 2019
Predominance of observational treatment data	Susceptibility to bias and confounding	Randomised or rigorously controlled comparative studies	Guerrini et al., 2023; Strzelczyk & Schubert-Bast, 2021
Rarity of mortality outcomes	Preventive efficacy hard to demonstrate directly	Registry-based and surrogate-endpoint approaches to SUDEP risk	Harden et al., 2017; Whitney et al., 2023

Heterogeneity compounds these problems. Populations differ in aetiology, age, and prior treatment; interventions and comparators vary; and outcomes are defined inconsistently across studies, from proportional seizure reduction to responder thresholds to drop-seizure counts, which impedes direct comparison and pooling. Much of the aetiological and prognostic evidence derives from referral cohorts subject to ascertainment bias, so that population-based estimates such as those from prospective national cohorts carry particular weight (Symonds et al., 2019). Genotype-phenotype studies are frequently retrospective and vulnerable to publication and reporting bias, and reported diagnostic yields are sensitive to cohort selection and to evolving variant-interpretation standards (Sheidley et al., 2022). Observational reports of treatment benefit, especially for older or off-label agents, are difficult to separate from regression to the mean, placebo response, and the natural fluctuation of seizure frequency.

Several tensions in the literature reflect these limitations rather than genuine biological disagreement. Apparent inconsistencies in genotype-phenotype correlation often arise from differences in cohort composition and variant classification; discrepancies in reported treatment effect sizes frequently reflect differences in endpoint definition and baseline severity; and divergent estimates of the incidence of sudden unexpected death in epilepsy in children reflect differing case-ascertainment methods (Harden et al., 2017; Whitney et al., 2023). Recognising these sources of variation is essential to avoid manufacturing consensus where none exists or, conversely, over-interpreting differences that are methodological in origin. Table 5 summarises the principal methodological limitations, their consequences, and the related research priorities that follow from them.

Table 5 links each limitation to a concrete research priority, and taken together these priorities define the methodological agenda for the field: larger and better-coordinated studies, outcomes that reflect development and function rather than seizure count alone, standardised definitions that permit comparison, and designs capable of testing prevention and disease modification. The next section develops these priorities substantively.

9. Future Directions

The first priority is to close the diagnostic gap and to shorten the interval to aetiological diagnosis. A substantial minority of children with severe epilepsy remain without a molecular cause despite testing, and diagnosis is often reached late, after opportunities for aetiology-specific and preventive treatment have passed (Sheidley et al., 2022; Symonds et al., 2019). The unresolved problem is both technical, in that current sequencing does not detect all causal variation, and systemic, in that access, turnaround, and interpretation are uneven. The most appropriate response combines broader first-tier genome-level testing with reanalysis of undiagnosed cases as knowledge advances, embedded in care pathways that deliver rapid results early in the illness. Population-based rather than referral-based study designs are needed to establish the true diagnostic yield and the real-world effect of early diagnosis on management and outcome, and outcome measures should capture changes in treatment and prognosis, not diagnosis alone (Haviland et al., 2023).

A second priority is to reorient therapeutic evaluation toward outcomes that reflect the developmental component of the encephalopathy. Current evidence rests overwhelmingly on short-term seizure frequency, leaving the effects of treatment on cognition, adaptive behaviour, communication, and quality of life largely unquantified (Lagae et al., 2019; Pestana Knight et al., 2022). Future trials should incorporate validated, developmentally appropriate outcome measures and longer follow-up, and should adopt standardised core outcome sets to permit comparison across studies. Because individual syndromes are rare, this will require multicentre and international collaboration and trial designs suited to small populations, including adaptive and platform approaches that can evaluate several interventions efficiently. Head-to-head comparisons of the licensed syndrome-specific agents, which are almost entirely lacking, would materially assist clinical decision-making.

A third priority concerns disease-modifying and preventive therapy. The emergence of mTOR inhibition, pre-emptive treatment before seizure onset, and antisense oligonucleotide therapy signals a shift from seizure suppression toward altering disease course, but the evidence is early and, for the genetic therapies, derives largely from open-label studies (French et al., 2016; Kotulska et al., 2021; Laux et al., 2026). The key unresolved questions are whether these approaches produce durable benefit, whether they improve development rather than only seizures, and how early they must be applied to be effective. Addressing these questions requires randomised or rigorously controlled designs with developmental endpoints, careful attention to the timing of intervention relative to disease onset, long-term safety surveillance appropriate to interventions intended for chronic use in children, and equitable frameworks for access given the likely cost and complexity of such treatments. Extending the antisense and gene-directed paradigm beyond Dravet syndrome to other monogenic encephalopathies is a natural next step, contingent on demonstrating both mechanistic tractability and clinical benefit.

A fourth priority, distinguished as a longer-term rather than immediate need, is to translate the plausible link between seizure control and reduced mortality into demonstrated preventive strategies. Sudden unexpected death in epilepsy remains insufficiently mitigated, and its rarity makes conventional trials of prevention impractical (Harden et al., 2017; Whitney et al., 2023). Registry-based studies, validated surrogate markers of risk, and evaluation of monitoring and supervision strategies offer more feasible routes to progress, and should be pursued alongside continued efforts to optimise control of generalised convulsive seizures, the most consistent modifiable risk factor. Progress on each of these fronts would materially advance the field, moving it from the reduction of seizures toward the protection of development and life.

10. Conclusions

The severe epilepsy syndromes of childhood have been transformed over two decades by a revised classification, by the identification of numerous monogenic causes, and by a succession of syndrome-specific and mechanism-based therapies. The available evidence supports several defensible conclusions. The developmental and epileptic encephalopathy construct, which separates the developmental burden intrinsic to the cause from the additional harm of ongoing epileptic activity, is a useful and now widely adopted framework, and it reframes both the goals of treatment and the interpretation of therapeutic trials. Aetiological diagnosis, particularly through broad genetic testing, has moved from a diagnostic to a management tool, because a molecular cause increasingly guides drug selection, prognosis, and access to targeted therapy, even though a diagnostic gap persists and genotype maps imperfectly onto phenotype and treatment response.

Confidence is strongest for the proposition that a small number of syndrome-specific agents reduce disabling seizures in Dravet syndrome, Lennox-Gastaut syndrome, and CDKL5 deficiency disorder, and that combination first-line treatment improves early control of epileptic spasms. Confidence is weaker, because the evidence is thinner or of lower design quality, for the comparative

effectiveness of these agents, for their effects on development and survival, and for the durability and developmental impact of the emerging disease-modifying therapies. The shift toward mechanism-based, preventive, and disease-modifying strategies is the most significant conceptual advance, since it targets the causal defect and aspires to alter developmental outcome rather than only seizure frequency, but the supporting evidence remains preliminary and must not be over-interpreted. Premature mortality, including sudden unexpected death in epilepsy, remains inadequately prevented, and the link between seizure control and reduced mortality, though plausible, is largely indirect.

The broader significance of this synthesis is that the field is moving from the empirical suppression of seizures toward an aetiology-informed and increasingly disease-directed model of care, while the evidence base has not yet caught up with this ambition. The dominant reliance on short-term seizure count as an outcome constrains what can be concluded about the interventions that matter most, and the rarity of these disorders imposes structural limits on study size and design. Integrating early aetiological diagnosis, developmentally meaningful outcomes, and rigorously designed trials of disease modification represents the clearest path from the present position, in which seizures can often be reduced but development and survival remain difficult to protect, toward genuinely disease-altering care.

11. Limitations

This review is a critical narrative synthesis and is therefore subject to the interpretive and selection limitations intrinsic to that design. Despite a transparent search approach and explicit appraisal criteria, the identification, selection, and weighting of sources involved judgement, and the possibility of selection and interpretive bias cannot be excluded. The synthesis was not conducted as a systematic review, no exhaustive record-count screening was performed, and no formal risk-of-bias scoring or quantitative pooling was undertaken, so the conclusions reflect a reasoned integration of the evidence rather than a statistically aggregated estimate.

Access to the literature was constrained in ways that may have affected coverage. Subscription-only indexing platforms were not directly searched, and the review relied on openly accessible bibliographic resources, verified records, and hand-searching; some relevant sources may therefore have been missed. Consideration was limited to publications available in English or with an adequate English-language abstract, which may have introduced a language bias and under-represented evidence published in other languages. The evidence base itself imposes further limitations that the review inherits rather than creates. The rarity of the syndromes means that much evidence comes from small studies and observational cohorts; study designs, populations, interventions, and outcomes are heterogeneous and often not directly comparable; long-term and developmental outcome data are scarce; and quantitative synthesis was neither feasible nor appropriate. The field is developing rapidly, particularly in genetics and disease-modifying therapy, so some conclusions may be superseded as new evidence emerges. These constraints should be borne in mind when applying the interpretations offered here.

Consent and Ethical Approval

It is not applicable.

Declaration of AI Use

This manuscript was prepared through the combined contributions of all author(s), including contributions to the study design, data, content development, results, interpretation, and related scholarly work. The author(s) acknowledge the use of Grammarly and ChatGPT to assist with grammar checking, language refinement, reference formatting. These AI-assisted tools were not used as authors and did not replace the intellectual contributions or scholarly judgment of the author(s). All AI-assisted outputs, including content, references, and interpretations, were carefully reviewed, revised, verified, and approved by the author(s). The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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