Update on neonatal and infantile onset epilepsies

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Purpose of review
Neonatal and infantile epilepsies represent a diverse group of disorders with significant neurodevelopmental impact, necessitating early diagnosis, and tailored treatment. Recent advancements in genetic research, phenotyping, and therapeutic development have reshaped the understanding and management of these conditions, making this review both timely and relevant.

Recent findings
Next-generation sequencing has emerged as a cornerstone for diagnosing neonatal and infantile epilepsies, offering high diagnostic yields and enabling identification of etiology-specific phenotypes. Precision therapies, including sodium channel blockers, ganaxolone, and mammalian target of rapamycin (mTOR) inhibitors, target specific molecular mechanisms. Early initiation of treatment in conditions with a high risk of progressing to epilepsy, like vigabatrin in tuberous sclerosis complex, lower the incidence of infantile spasms and improve developmental outcomes. Drug repurposing has also provided effective options, such as fenfluramine in Dravet syndrome, with promising outcomes. Gene-based therapies, including antisense oligonucleotides and gene replacement, represent the new frontier for addressing the root causes of these disorders.

Summary
The integration of genetic and molecular advancements is transforming the management of neonatal and infantile epilepsies, fostering precision-driven care. Continued research and innovation are essential to refine these strategies, optimize patient outcomes, and establish new standards of care.

Keywords
genetic therapies, infantile epilepsy, neonatal epilepsy, precision medicine

INTRODUCTION

Neonatal and infantile epilepsies encompass a wide array of syndromes with diverse etiologies, presenting unique challenges for early diagnosis and effective treatment. The first year of life is particularly critical, as the onset of epilepsy during this period can significantly impact neurodevelopmental outcomes. Recent advancements in genetic research, particularly through next-generation sequencing (NGS), have reshaped our understanding of early-onset epilepsies and established genetic testing as a cornerstone in their evaluation and management. NGS, including multigene panels, exome and genome sequencing, offers broad coverage and a high diagnostic yield, especially within the first year of life when many severe developmental and epileptic encephalopathies (DEE) manifest. Evidence-based guidelines, such as those from the National Society of Genetic Counsellors, advocate for NGS as a first-tier diagnostic tool for unexplained epilepsies, with yields reaching up to 48% in some studies [1]. With the increasing recognition of specific genetic electro-clinical phenotypes, such as KCNQ2-, SCN2A-, CDKL5-, and PRRT2-related epilepsies, the field is progressively shifting towards precision medicine approaches tailored to the specific etiology. These efforts have been supported by initiatives such as those of International League Against Epilepsy (ILAE), which has issued updated classification on neonatal and infantile epilepsy syndromes [2▪▪], as well as updated guidance for treatment of seizures in neonates [3▪▪].

Emerging therapeutic strategies for infantile epileptic spasms syndrome (IESS) emphasize early intervention in high-risk populations, aiming to

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KEY POINTS

- Next-generation sequencing (NGS) has transformed the diagnosis of neonatal and infantile epilepsies, enabling high diagnostic yields and etiology-specific phenotyping.
- Precision therapies, such as sodium channel blockers, ganaxolone, and mTOR inhibitors, target specific molecular mechanisms to improve outcomes.
- Repurposed drugs, including fenfluramine, have demonstrated efficacy in managing rare genetic epilepsies and expanding treatment options.
- Emerging antisense oligonucleotides therapies and adeno-associated virus-mediated gene replacement, hold promise for addressing the root causes of monogenic epilepsies.
- Early diagnosis and personalized treatment are crucial to mitigating seizure burden and optimizing neurodevelopmental outcomes in neonatal and infantile onset epilepsies.

prevent spasms onset through targeted antiepileptic therapies that modulate seizure activity prior to clinical manifestation [4]. In parallel, targeted genetic therapies are under investigation for Dravet syndrome, with efforts concentrated on modifying the disease course by directly addressing the pathogenic variant in *SCN1A* gene.

This review aims to consolidate recent findings on the phenotyping, genetic underpinnings, and emerging targeted therapies for neonatal and infantile epilepsies.

NEONATAL EPILEPSY

Neonatal epilepsies constitute a distinct and complex clinical landscape, with seizures arising from diverse genetic, structural, and metabolic etiologies within the first 28 days of life. The development of neurointensive care nurseries [5] and the implementation of video-EEG have transformed this landscape, allowing for precise electro-clinical characterization that guides both diagnosis and management.

Historically, early myoclonic encephalopathy (EME) and Ohtahara syndromes, now grouped under the broader term early infantile developmental and epileptic encephalopathy (EIDEE) [2▪▪], have served as "buckets" for various etiology-specific disorders. Advances in genetic testing, neuroimaging, and continuous video-EEG have enhanced the stratification of neonate with epilepsy, enabling more refined, etiology-specific classifications that support precision-driven care tailored to each disorder's unique genetic and molecular profile. Within the broad category of EIDEE, conditions such as glycine encephalopathy, previously known as nonketotic hyperglycinemia, and pyridoxine-dependent epilepsy illustrate the diversity of underlying causes and markedly different management pathways. Glycine encephalopathy, an autosomal recessive disorder of glycine metabolism, predominantly caused by pathogenic variants in the *GLDC* and *AMT* genes, leading to significant glycine accumulation in the brain presents with early myoclonic seizures and suppression-burst pattern on electroencephalogram (EEG) (Fig. 1). Magnetic resonance spectroscopy shows increased levels of glycine in the

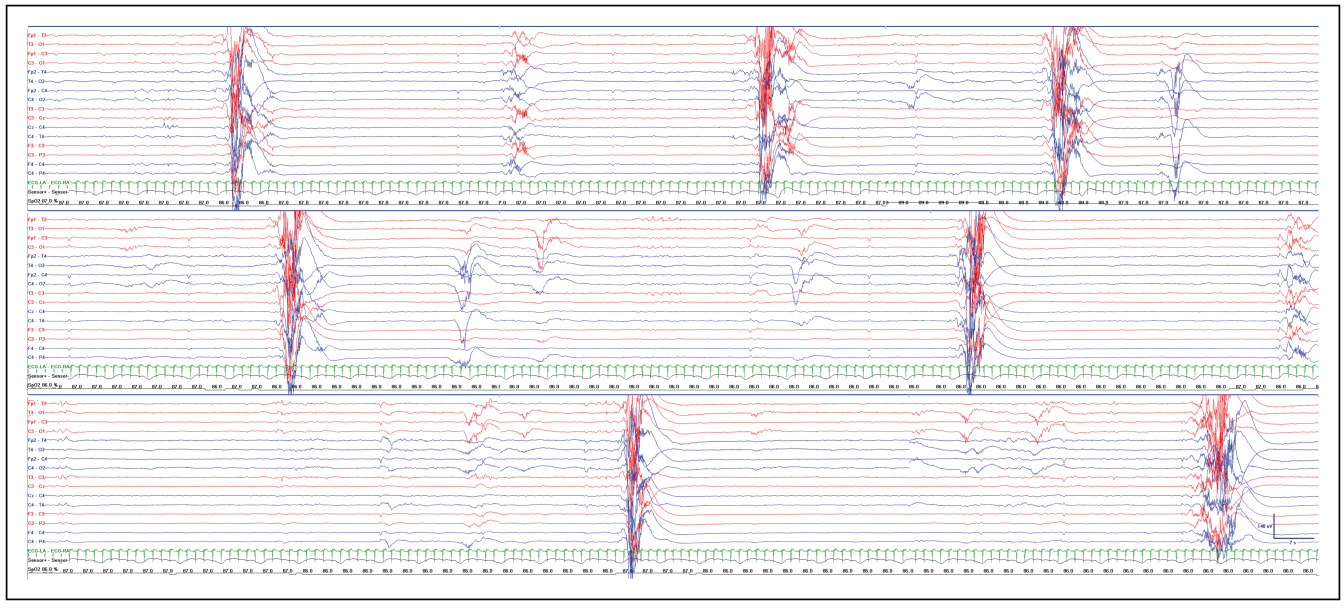

FIGURE 1. EEG of a 3-days-old patient with glycine encephalopathy showing a suppression-burst pattern. Gain, 7 μV/mm; high frequency filter, 70 Hz; paper speed, 15 mm/s.

brain, and the cerebrospinal fluid (CSF) analysis, elevated CSF/serum glycine ratio. The diagnosis is confirmed by genetic analysis. Glycine is a co-agonist at N-methyl-D-aspartate (NMDA) receptors. One hypothesis of the purported neurotoxicity of elevated glycine in the pathogenesis of the encephalopathy is based on overstimulation of the NMDA type of glutamate receptors. Despite intervention strategies aimed at reducing glycine levels in both blood and CSF through sodium benzoate, which results in the conversion of glycine to hippurate in mitochondria, and dextromethorphan which downstream effects with NMDA receptor antagonists, patients lacking residual enzyme activity face a high likelihood of severe neurologic impairment, which may lead to discussions regarding the continuation of life-sustaining therapies [6]. In contrast, pyridoxine-dependent epilepsy, resulting from pathogenic variants in *ALDH7A1* gene, follows a different therapeutic trajectory. Prompt recognition and diagnosis through a pyridoxine trial, consisting in the administration of intravenous or oral pyridoxine to assess for clinical and EEG responsiveness, enable targeted chronic treatment with vitamin B6. Although up to 75% of patients still experience some degree of neurodevelopmental impairments, such as intellectual disability and motor or speech delays, early treatment has been correlated with a better overall outcome compared to untreated cases [7]. Emerging strategies, such as combining pyridoxine with a lysine-restricted diet and L-arginine supplementation, may offer additional benefits by reducing toxic metabolites and potentially further improve long-term outcomes [8]. These contrasting examples underscore how precise, etiology-specific diagnosis informs distinct management approaches – offering the potential for improved quality of life in some cases, while guiding realistic prognostic expectations in others.

Differentiating acute provoked seizures, often triggered by reversible insults like hypoxic-ischemic encephalopathy, stroke or transient metabolic disorders, from neonatal-onset epilepsies, which are typically genetic and demand longer-term treatment, is now a cornerstone for the management of seizures in neonates [9▪▪,10▪▪]. Seizures in neonates should be regarded as a symptom of different diseases, and their characterization together with the associated signs, may contribute further to the delineation of the etiology-specific phenotypes. This approach has allowed for the early recognition of rare and ultra-rare entities, previously underdiagnosed. A recent study on BRAT1 encephalopathy highlights the diagnostic importance of associated signs, such as neonatal hypertonia and nonepileptic multifocal myoclonus that, together with the EEG features, may prompt the clinical diagnosis and direct genetic testing. Neonates with BRAT1 encephalopathy typically develop intractable multifocal seizures only after the second week of life, followed by severe encephalopathy, acquired microcephaly, and prolonged episodes of apnea and bradycardia leading to early death [11]. For instance, KCNH5-related encephalopathy, caused by gain-of-function variants in Kv10.2, may range from mild infantile epilepsy to severe DEE. In this context, the presence of nonepileptic myoclonus during the neonatal period may represent a prognostic marker for severe neurologic impairment, as observed in KCNH5-related encephalopathies, where affected neonates progressed to profound DEE and early death [12]. Similarly, in neonatal-onset SCN8A-DEE the presence of complex movement disorder and apnea, may indicate a severe phenotype as observed in one neonate with a *de novo SCN8A* variant (c.3979A > G p.I1327 V) [13].

Early and accurate etiology-specific interventions are transforming neonatal epilepsy care, reducing seizure burden and improving neurodevelopmental outcomes through personalized, mechanism-based treatments. These approaches will be explored in greater detail in the subsequent sections on targeted and repurposed therapies.

PREVENTING INFANTILE ONSET EPILEPSY

In neonates with acute symptomatic seizures, evidence consistently supports that these seizures typically resolve once the acute period has passed, negating the need for prolonged antiseizure medication (ASM) treatment. A recent study demonstrated no benefit regarding neurodevelopment or the development of postneonatal epilepsy in maintaining ASM treatment after resolution of acute symptomatic neonatal seizures [14], and current recommendations advocate for discontinuation of ASMs before hospital discharge, irrespective of MRI or EEG findings [3▪▪]. In addition, phenobarbital, the most commonly prescribed ASM for neonatal seizures has been associated with neurotoxic effects, such as increased apoptosis, impaired neurogenesis, and lower cognitive scores with prolonged use [15–18].

In contrast, emerging data highlight the importance of rapid seizure management. A study by Pavel *et al.* showed that neonates with acute symptomatic seizures, mainly due to HIE and stroke, treated within one hour of seizure onset experienced significantly better seizure control and shorter seizure burden than those with delayed treatment [19]. Prompt and effective intervention appears to be pivotal in mitigating the risk of secondary epilepsy and improving neurodevelopmental outcomes.

For conditions with a high risk of epilepsy, such as tuberous sclerosis complex (TSC), preventive

strategies have shown promise. Preventive treatment in TSC focuses on early intervention to reduce epilepsy risk and its developmental impact. Vigabatrin, started at the appearance of epileptic discharges on EEG, has been shown to lower the incidence of infantile spasms and improve developmental outcomes [4]. Additionally, mammalian target of rapamycin (mTOR) inhibitors like everolimus, which target the core dysregulated pathway in TSC, offer potential as preventive therapies. The EXIST-3 trial demonstrated seizure reductions of up to 40% in patients with refractory epilepsy. However, rates of seizure freedom were limited, possibly due to the late onset of treatment, as patients were started on everolimus at a median age of 10 years [20]. New evidence suggests that starting mTOR inhibitors earlier, before epileptogenesis progresses, could delay seizure onset and reduce the risk of refractory epilepsy [21]. Therefore, it is possible that combining early mTOR inhibition with vigabatrin may optimize prevention strategies in TSC-related epilepsy.

TARGETED AND REPURPOSED THERAPIES: A NEW ERA OF PRECISION TREATMENT

Progress in genetic and molecular research has reshaped the treatment landscape for neonatal and infantile epilepsies, paving the way for more precise and strategic approaches (Table 1). These breakthroughs have fostered the targeted use of existing ASMs in specific genetic epilepsies, revealed the potential of repurposing drugs initially designed for other conditions, and motivated the development of new precision therapies.

Sodium channel blockers (SCBs), including carbamazepine and oxcarbazepine, have shown efficacy in patients carrying *SCN1A*, *SCN2A*, and *SCN8A* gain-of-function pathogenic variants [22–24], and *PRRT2* gene defects [25]. Initiation of SCBs has been shown to be associated with dramatic seizure control in infants with *KCNQ2* loss-of-function pathogenic variants [26–28]. Ezogabine, a potassium channel opener, has shown promise both reducing seizure frequency and enhancing developmental outcomes in KCNQ2-DEE, though it has a lower response rate compared to SCBs [29].

Several drugs, initially marketed for other conditions, have shown efficacy in treating genetic epilepsies, illustrating the value of drug repurposing. Vinpocetine, a cognition-enhancing drug repurposed for a patient with GABRB3-DEE due to loss-of-function variants, demonstrated a dose-dependent reduction in epileptiform activity on EEG, and improvement in language, behavior, and overall clinical function, likely through its enhancement of GABAergic activity and modulation of sodium

Table 1. Genes, mechanisms, established and potential treatments in genetic neonatal and infantile epilepsies

Gene	Mechanism	Treatment	Status as precision medicine treatment
SCN1A, SCN2A, SCN8A GoF variants	GoF in Nav1.1, Nav1.2, and Nav1.6 channels	SCBs	Established
SCN1A LoF variants	LoF in Nav1.1 channel	Stiripentol Fenfluramine ASO-STK-001	Established Established Hypothetical
KCNQ2 LoF variants	LoF in Kv7.2 channel	SCBs Ezogabine	Established Potential
KCNA2 GoF variants	LoF in Kv1.2 channel	4-Aminopyridine	Hypothetical
KCNT1	Increase current amplitude via enhanced cooperativity among SLACK channel	Quinidine	Potential
PRRT2	Increased Nav1.2/Nav1.6 excitability [41]	SCBs	Established
GABRB3 LoF variants	Ligand-gated channelopathy Disruption of GABA-A receptor function	Vinoceptine	Potential
CDKL5	Disruption of synaptic signaling and neurodevelopment	Ganaxolone	Established
TSC	Disinhibition of mTOR pathway	mTOR inhibitors Everolimus	Established
GATOR complex genes (*DEPDC5, NPRL2, NPRL3*) LoF variants	Disinhibition of mTOR pathway	mTOR inhibitors Everolimus	Potential

ASO, antisense oligonucleotide; GATOR, GAP Activity Towards Rags complex 1; GoF, gain-of-function; LoF, loss-of-function; SCBs, sodium channel blockers; SLACK, sequence like a calcium-activated potassium channel.

channels [30]. 4-Aminopyridine, traditionally used for multiple sclerosis, repurposed for KCNA2-related DEE with gain-of-function variants, significantly reduced seizure frequency, improved ataxia, and enhanced cognition and speech in responsive patients [31]. Fenfluramine, initially marketed as an appetite suppressant, has been repurposed as an effective treatment for seizures in patients with Dravet syndrome. In clinical trials, fenfluramine significantly reduced seizure burden, with up to 62.3% reduction in mean monthly convulsive seizure frequency compared to placebo [32]. Furthermore, 54% of patients achieved a remarkable $\geq$75% reduction in seizures, compared to only 2% in the placebo group [33]. Beyond seizure frequency, fenfluramine extended seizure-free intervals and provided prolonged periods of convulsive seizure-free days, contributing to improved quality of life for patients and their families. In addition, it has been demonstrated that patients with Dravet syndrome treated with fenfluramine use less rescue medications and require less hospital admissions, compared to pretreatment period [34]. Ganaxolone, a neuroactive steroid positively modulating GABAA receptors, has been recently approved for seizures associated with CDKL5 deficiency disorder (CDD). Phase 3 trials demonstrated a 30.7% median reduction in seizure frequency compared to placebo [35]. Quinidine, a class I antiarrhythmic drug, was repurposed for the treatment of KCNT1-related epilepsies, targeting gain-of-function pathogenic variants in the *KCNT1* gene by blocking the abnormal potassium currents they generate. While early studies suggested its potential in reversing channel overactivity *in vitro*, clinical trials have shown inconsistent results. Notably, infants treated with quinidine, even early in the disease course, demonstrated no therapeutic benefit, likely due to insufficient drug levels reaching the brain and significant cardiac side effects limiting dose escalation [36]. This underscores the challenges in translating *in vitro* efficacy to clinical setting.

Expanding the indications of precision therapies for diseases with shared mechanisms is crucial in advancing personalized medicine. Everolimus, an mTOR inhibitor validated for TSC [20], offers potential for GATOR1 complex-related epilepsies, which share a similar mechanism of mTORC1 hyperactivation due to loss of inhibition. Pathogenic variants in *DEPDC5*, *NPRL2*, and *NPRL3*, which encode components of the GATOR1 complex, result in focal epilepsies, often associated with cortical dysplasia. Recent studies have shown promising results with mTOR inhibitors in these conditions, highlighting the need for further clinical investigations to evaluate their therapeutic potential [37].

Looking ahead, future therapies for neonatal and infantile epilepsies aim to push the boundaries of current treatments by addressing the underlying genetic causes with unprecedented precision. Antisense oligonucleotides (ASO) represent a cutting-edge precision therapy targeting the genetic underpinnings of various developmental and epileptic encephalopathies (DEEs). These molecules operate by binding to RNA sequences through Watson-Crick base pairing, enabling them to modulate gene expression at the posttranscriptional level. The mechanisms of ASOs include splicing modulation to promote productive mRNA synthesis, inhibition of translation by masking specific RNA sequences, and degradation of target RNA through RNase H1 recruitment [38].

For loss-of-function pathogenic variants, such as those in *SCN1A* causing Dravet syndrome, targeted augmentation of nuclear gene output (TANGO)-based ASOs upregulate the translation of functional mRNA from the unaffected allele, restoring deficient protein levels. This technology has shown preclinical efficacy in models like SCN1A-haploinsufficient mice, where ASOs increased NaV1.1 protein expression, reduced seizure frequency, and extended survival [39]. Ongoing studies on STK-001, an investigational ASO, offer a novel approach to Dravet syndrome therapy by addressing the root genetic cause through upregulation of NaV1.1 protein.

Preclinical studies using an AAV9.Syn.hCDKL5 vector have shown promise in gene replacement therapy for CDD, demonstrating reduced pathology and improved behavior in *Cdkl5* knockout mice with efficient neuronal transfection [40].

These therapies underscore the transformative potential of precision medicine and repurposed drugs in neonatal and infantile epilepsies. Continued advancements in genetic research, clinical trials, and translational approaches will further refine these strategies, improving outcomes for patients with these severe disorders.

CONCLUSION

Advancements in genetic research, precision medicine, and targeted therapies have revolutionized the understanding and management of neonatal and infantile epilepsies, offering new hope for improved outcomes. Early and accurate identification of infants with genetic disorders is critical for implementing etiology-specific treatments, which can mitigate seizure burden and support neurodevelopment. The potential of repurposed drugs and emerging gene-based therapies highlights the importance of integrating translational research into clinical practice. However, gaps remain in understanding

long-term efficacy and optimizing early intervention strategies. Future research should focus on refining preventive approaches, and resources should be allocated to optimize access to genetic testing. In term of innovative gene therapies, it is likely that earlier treatment maximizes the therapeutic effects and the logical progression in treating younger patients is the implementation of better diagnostic algorithms.

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Conflicts of interest

There are no conflicts of interest.

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