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Received: 14 January 2026 | Revised: 15 April 2026 | Accepted: 15 April 2026

DOI: 10.1002/epi.70271

Epilepsia®

CRITICAL REVIEW

Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep: Pathophysiological insights and treatment options

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Funding information
Ministero della Salute, Grant/Award Number: Current Research Funds;

Abstract

Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS) represents a rare but severe group of childhood onset epilepsies characterized by sleep-potentiated epileptiform activity, seizures, and developmental stagnation or regression affecting cognition, language, and behavior. Once considered a self-limited electroencephalographic (EEG) phenomenon, D/EE-SWAS is now recognized as a disorder of brain network dysfunction in which

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Ministero dell'Università e della Ricerca, Grant/Award Number: MNESYS (PE0000006)

persistent epileptiform discharges during non-rapid eye movement sleep disrupt synaptic plasticity, sleep-dependent memory consolidation, and neurodevelopmental trajectories. This review synthesizes recent advances in clinical phenotyping, genetics, neurophysiology, and therapeutics. Etiologically, D/EE-SWAS is highly heterogeneous, with pathogenic variants identified in nearly half of affected individuals, including copy number variants and single-gene disorders involving ion channels, synaptic proteins, and transcriptional regulators. *GRIN2A* is the most frequently implicated gene, although marked intrafamilial and interfamilial variability underscores the role of modifying genetic and network-level factors. Structural lesions—particularly those affecting thalamocortical circuits—represent another major disease substrate and are critical for treatment stratification. At the mechanistic level, abnormal thalamocortical oscillations, impaired sleep architecture, and disruption of slow-wave and spindle activity provide a pathophysiological framework linking EEG abnormalities to cognitive and behavioral deterioration. Neuroimaging and EEG–functional magnetic resonance imaging studies support a model of widespread network inhibition and disconnection extending beyond the primary epileptogenic zone. Therapeutically, corticosteroids currently represent the most effective first-line treatment, demonstrating superior cognitive outcomes compared with benzodiazepines, although relapse after tapering is common, and optimal dosing strategies remain undefined. Precision medicine approaches, including N-methyl-D-aspartate receptor-targeted therapies for *GRIN* variants and channel-specific treatments such as primidone for *TRPM3* gain of function, offer promising avenues toward disease modification. Epilepsy surgery should be considered early in children with unilateral structural etiologies, where it can provide substantial neurodevelopmental benefit. Future priorities include standardized outcome measures, integration of sleep-based biomarkers, refinement of steroid protocols, and international collaborative trials to improve long-term neurodevelopmental outcomes in this vulnerable population.

KEYWORDS

benzodiazepines, continuous spike–wave during slow sleep, corticosteroids, developmental and epileptic encephalopathy, epilepsy surgery, neurodevelopmental outcomes, pediatric epilepsy, precision medicine, spike-and-wave activation in sleep

1 | INTRODUCTION

Developmental and/or epileptic encephalopathy with spike–wave activation in sleep (D/EE-SWAS) is a rare childhood epilepsy syndrome that is estimated to account for approximately 1% of pediatric epilepsies and is characterized by developmental stagnation or regression, seizures and epileptic activity with striking increment during sleep, and onset in infancy or early childhood.[1,2]

Terminology in this field has evolved and has been inconsistent. Historically, electrical status epilepticus in sleep (ESES) referred to the electroencephalographic (EEG) pattern of near-continuous spike–wave activity during non-rapid eye movement (NREM) sleep, whereas continuous spike-and-wave during slow sleep (CSWS) variably described the EEG pattern or the electroclinical syndrome.[3–5] In the current International League Against Epilepsy (ILAE) classification, these conditions fall under D/EE-SWAS, which we adopt throughout this review while retaining historical terms when referring to earlier literature,[6] and which represents a spectrum of rare conditions that may lead to long-lasting developmental deficits.[7]

Developmental and epileptic encephalopathy with spike–wave activation in sleep (DEE-SWAS) and epileptic

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Key points

- D/EE-SWAS is a network disorder that disrupts synaptic plasticity, learning, and cognitive maturation.
- Nearly half of patients have an identifiable genetic etiology, most commonly involving *GRIN2A*, ion channels, and transcriptional regulators.
- Corticosteroids are the most effective first-line therapy for improving cognition and EEG abnormalities, outperforming benzodiazepines.
- Precision medicine is emerging as a disease-modifying strategy, with targeted therapies for *GRIN* and *TRPM3* variants showing promise.
- Early etiologic stratification is essential to optimize long-term neurodevelopmental outcomes.

encephalopathy with spike–wave activation in sleep (EE-SWAS) have overlapping manifestations, with cognitive, language, behavioral, and motor regression or stagnation, whose occurrence is temporally related to the appearance of pronounced spike–wave activation during NREM sleep.[8] DEE-SWAS is distinguished from EE-SWAS by the presence of a preexisting developmental impairment before the onset of SWAS, whereas in EE-SWAS, development is initially normal until the cognitive regression or plateauing in relation to the syndrome.[4,6,8] Most individuals experience seizures, which can be present even before the characteristic cognitive regression seen in these syndromes, and very few do not. Landau–Kleffner syndrome (LKS) is a prototypical EE-SWAS, characterized by acquired language regression in previously typically developing children, often with infrequent or absent seizures. In the ILAE framework, developmental impairment in LKS is considered primarily driven by sleep-activated epileptiform activity rather than an underlying developmental disorder. Seizures may be absent before the cognitive disorder or may be misdiagnosed or underdiagnosed.[6] Even after seizure remission and resolution of SWAS, developmental deficits often persist, despite improvement, in DEE-SWAS but may completely resolve in EE-SWAS, mainly with the efficacy of therapies. The patients require time to recapture their previous developmental state, which impacts their academic achievement.[9] Both syndromes are highly heterogeneous in their etiologies. A recent study identified a genetic etiology in approximately 46% of the core cohort,[7] expanding the understanding of DEE-SWAS with newly described pathogenic variants.[10]

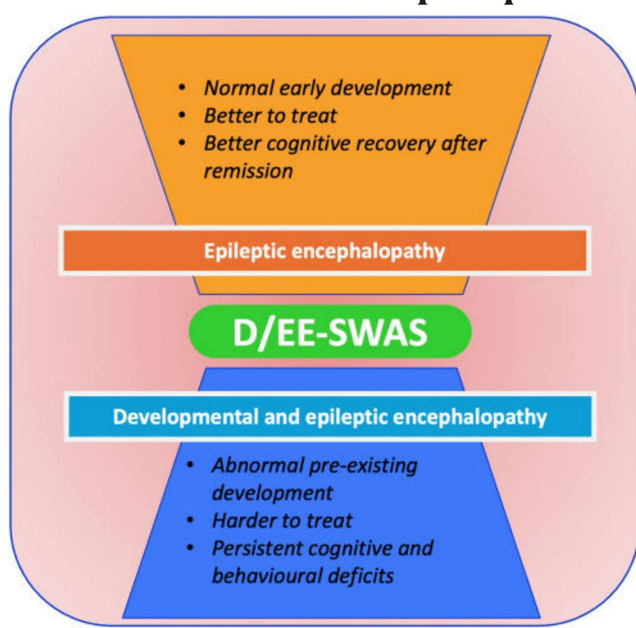

FIGURE 1 Distinguishing features of developmental and/or epileptic encephalopathy with spike–wave activation in sleep (D/EE-SWAS). This figure illustrates the key clinical differences between epileptic encephalopathy with spike-and-wave activation in sleep (EE-SWAS) and developmental and epileptic encephalopathy with spike-and-wave activation in sleep (DEE-SWAS). Children with EE-SWAS typically have normal early development, a more favorable treatment response, and a greater likelihood of full or near-full cognitive recovery after remission. In contrast, DEE-SWAS is characterized by abnormal preexisting neurodevelopment, is more difficult to treat, and is associated with persistent cognitive and behavioral deficits despite seizure remission. The prognosis of D/EE-SWAS is highly dependent of the underlying etiology. This conceptual framework underscores the importance of differentiating between EE-SWAS and DEE-SWAS early, as it influences prognosis, therapeutic decision-making, and counseling of families regarding expected developmental outcomes.

Although developmental regression patterns are similar in DEE-SWAS and EE-SWAS, DEE-SWAS was reported to have a longer duration of the EEG abnormalities and poorer intellectual outcome.[8] The underlying mechanisms remain not fully elucidated. Interictal discharges with disrupting sleep architecture are considered to play a role in the cognitive impairment.[11,12] Spike-and-wave index (SWI) and spike topography can vary across the night in the different sleep cycle.[13] Early reports emphasized the clinical heterogeneity of the syndrome, including diverse seizure types, language regression, and variable cognitive trajectories.[14] Figure 1 is a schematic representation on how to discern between EE-SWAS and DEE-SWAS.

This review represents a narrative synthesis of the literature combined with expert consensus derived from a dedicated international workshop on D/EE-SWAS and highlights the pathophysiological mechanisms of these

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syndromes and of the underlying neurodevelopmental disorders, the underlying etiologies, and the current state of the art of treatment options emphasizing the impact of new antiseizure medications (ASMs) in D/EE-SWAS.

2 | SEARCH STRATEGY

We searched PubMed for peer-reviewed publications published between June 2005 and November 2025 with the terms "electrical status epilepticus in sleep (ESES)", "continuous spikes and waves during sleep (CSWS)", or "spike and wave activation in sleep (SWAS)". This initial search returned 358 potential articles. We then refined our search terms to be "ESES"/"CSWS"/"SWAS" AND (as individual combinatory terms) "epileptic encephalopathy", "developmental encephalopathy", or "developmental and epileptic encephalopathy". Selection criteria were based on the novelty of the study findings and their relevance to neurologists, with inclusion decided collectively by all authors. Relevant historical references were also included. Terminology and diagnostic criteria for D/EE-SWAS have evolved, and much of the earlier literature used heterogeneous definitions such as ESES or CSWS. In this review, older studies were included when the electroclinical context suggested sleep-activated epileptiform activity with developmental regression or plateau consistent with current D/EE-SWAS concepts, although strict retrospective reclassification was not always possible, and cohorts may be heterogeneous.

3 | LINKING EPILEPSY, ABNORMAL SLEEP ARCHITECTURE, DEVELOPMENTAL SLEEP DISRUPTION, AND DEVELOPMENTAL ENCEPHALOPATHY

3.1 | Relationship between epilepsy, sleep, and development in D/EE-SWAS

Abnormal sleep architecture, particularly in NREM sleep, during infancy and early childhood can interfere with key developmental neurobiological processes, including synaptogenesis, myelination, and the pruning of neural connections.[15,16] Sleep disorders in association with the disruption of sleep architecture are commonly observed in patients with DEEs, including DEE-SWAS, significantly impacting their quality of life.[17,18] Many DEEs are characterized by frequent epileptiform EEG abnormalities and seizures that predominantly occur during sleep, potentially affecting the neural networks responsible for regulating sleep. There is a bidirectional interaction between interictal epileptiform discharges (IEDs) and sleep architecture. IEDs and seizures are more frequent during drowsiness and NREM sleep than during REM sleep, with IEDs tending to appear more diffusely during NREM sleep and becoming more localized in REM sleep.[11] Polysomnographic studies in patients with DEEs have shown not only abundant epileptiform activity but also specific disruptions in sleep structure, including reduced total sleep time, increased fragmentation, decreased slow-wave sleep, and abnormal REM sleep patterns.[19–21] In healthy neonatal rabbit models, early life sleep fragmentation has been associated with significant behavioral alterations, in both the short and long term, including signs of neuroinflammation—characterized by changes in microglial morphology and cytokine mRNA expression—and impaired cognitive performance in later life.[22]

Cognitive and behavioral impairments in DEEs may result from disrupted synaptic homeostasis caused by excessive sleep-related epileptic activity, interfering with the physiological processes underlying learning and memory consolidation.[12] Moreover, because NREM sleep plays a key role in modulating synaptic plasticity and coordinating hippocampal–neocortical interactions, its propensity to activate IEDs may further compromise these mechanisms.[23,24] The synchronous maturation of sleep and synaptic physiology is thought to underlie the sleep disturbances observed in DEEs. In D/EE-SWAS, the amplitude and slope of slow waves reflect the synchronicity of neuronal firing and the effectiveness of neuronal interactions, serving as markers of synaptic strength. Studies by Bölsterli and Huber suggest that altered slow wave slopes in children with epilepsy may serve as a noninvasive marker of disrupted cortical function and impaired plasticity.[25] Abundant epileptiform activity may disrupt normal slow-wave dynamics and, along with epileptic spikes that "hijack" thalamocortical circuits involved in sleep spindle generation, interfere with learning and memory consolidation processes.[12,26] Figure 2 shows the peculiar interaction between EEG epileptiform abnormalities, disrupted sleep architecture, and neurodevelopmental arrest or regression.

3.2 | Relationship between sleep discharge in D/EE-SWAS and cognition

The pathophysiological link between this specific EEG pattern and the associated neurodevelopmental abnormalities remains incompletely understood and largely speculative. A proposed key mechanism involves the interaction between excitatory glutamatergic neurons of

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FIGURE 2 Mechanistic links between sleep architecture, synaptic plasticity, and cognitive outcome in developmental and/or epileptic encephalopathy with spike–wave activation in sleep (D/EE-SWAS). This figure summarizes the mechanistic links between spike–wave activation during slow sleep and the neurocognitive phenotype of D/EE-SWAS. Abundant interictal epileptiform discharges (IEDs) during non-rapid eye movement (NREM) sleep disrupt thalamocortical circuits, hijack spindle generation, and alter slow-wave slopes, which are biomarkers of impaired cortical plasticity. These perturbations reduce hippocampocortical information transfer and synaptic downscaling, resulting in impaired learning, memory consolidation, and executive function. Clinically, this manifests as language regression, cognitive plateauing, behavioral dysregulation, and poor school performance. The effects may persist even after seizure remission if untreated, suggesting that prolonged exposure to sleep-potentiated discharges has cumulative neurodevelopmental consequences. This model emphasizes the importance of early sleep electroencephalographic recording, recognition of IEDs, and timely initiation of etiology-driven therapy to limit functional decline and improve long-term outcomes.

the dorsal thalamus and inhibitory γ-aminobutyric acidergic neurons of the thalamic reticular nucleus, which may play a central role in the neuroplasticity processes underlying higher cortical functions (see section on thalamic injury).[26] The duration and the localization of interictal epileptiform EEG discharges are relevant in influencing the degree and type of cognitive dysfunction. Initially, persistent discharges were thought to cause a "functional ablation" of critical cortical areas. However, correlations between discharge location and functional deficits are inconsistent, and the timing of EEG abnormalities does not always align with clinical deterioration.[14,27] Functional imaging studies reveal that epileptic foci may exert local and remote inhibitory effects on brain networks, with fluorodeoxyglucose positron emission tomography showing focal hypermetabolism adjacent to hypometabolic regions. These metabolic patterns normalize with clinical remission, indicating that disrupted network connectivity contributes to cognitive deficits. EEG–functional magnetic resonance imaging (fMRI) findings support this, demonstrating perfusion increases at epileptic foci and decreases in functionally connected regions.[28–30]

3.3 | Other factors contributing to cognitive impairment in D/EE-SWAS

Additional contributors likely include the underlying etiology, seizure burden, interictal activity during wakefulness, impaired information processing during discharges, and adverse cognitive effects of polytherapy.[31]

The impact of ASMs is another important confounding factor in the interactions between sleep and epilepsy that should be considered. Some research has shown that certain ASMs negatively affect sleep architecture,[32] including phenobarbital and benzodiazepines (reduced slow-wave and REM sleep), valproate (sleep fragmentation and weight-related sleep-disordered breathing), and topiramate (insomnia and reduced sleep efficiency).[33] Other studies have reported improvements in sleep patterns following corticosteroid treatment in cases of epileptic encephalopathy.[34]

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4 | ETIOLOGIES OF DEE WITH SWAS

The causes of DEE-SWAS and EE-SWAS are numerous and diverse, with genetic factors playing a significant role. Copy number variants (CNVs) and single-gene mutations have been identified as major contributors.

A recent study of 101 selected patients with DEE-SWAS and EE-SWAS highlighted key clinical and etiological differences between the two syndromes.[8] A pathogenic variant was found in 40 of 101 unrelated patients in different genes, with 24 cases being de novo, five inherited maternally, seven inherited paternally, and four of unknown origin. A genetic cause was more frequently identified in DEE-SWAS patients (55%) compared to EE-SWAS patients (15%). In this study, structural abnormalities were found in 11% of DEE-SWAS cases versus 15% in EE-SWAS patients.

Various genes have been associated with D/EE-SWAS. These genes perform various cellular functions, such as ion channel regulation (e.g., *ATP1A2*, *CACNA1A*, *GRIN1*, *GRIN2A*, *SCN1A*, *SCN2A*, *KCNA2*, *KCNH5*, *KCNMA1*, *KCNQ3*, *TRPM3*), transcriptional regulation (e.g., *ARID1B*, *CUL4B*, *MECP2*, *PUF60*, *ZBTB18*, *FOXP1*, *SETD1B*), scaffolding (*CNKSR2*, *DLG4*), mTOR pathway involvement (*TSC*, *NPRL2*), and cell adhesion regulation (*PPFIA3*; Figure 3).[35–40] Notably, clusters of genes are more commonly coexpressed than expected by chance, particularly those encoding ion channels and those involved in transcriptional regulation.[8] Anecdotal cases of SWAS in DEE have also been reported for *PARS2*,[22] *MECP2*,[8] and *KCNA1*.[35]

GRIN2A pathogenic variants are the most frequently identified genetic cause, accounting for up to 23% of genetically resolved cases.[37,41,42] However, significant phenotypic variability exists, both within families and among different families carrying the same pathogenic variant of this gene. Although it has been suggested that *GRIN2A* missense variants in transmembrane and linker domains lead to more severe phenotypes than truncating variants

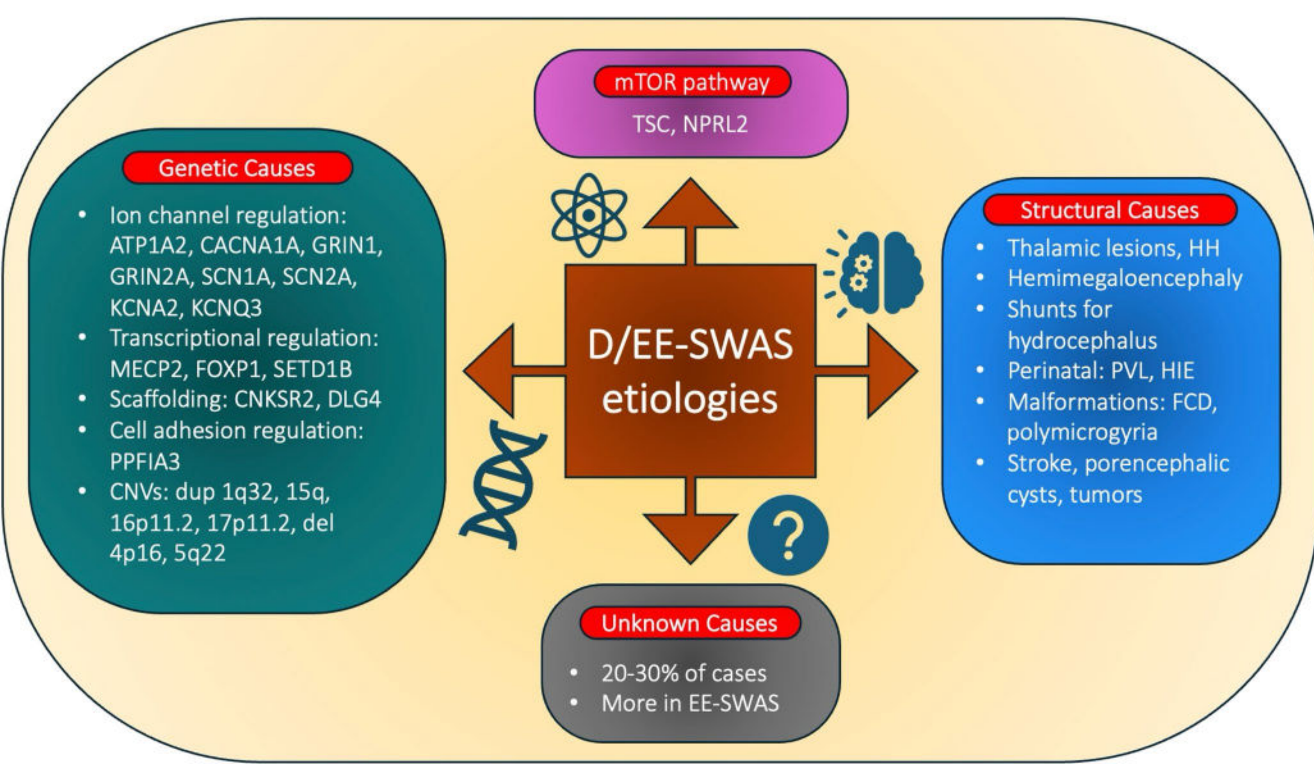

FIGURE 3 Etiological spectrum of developmental and/or epileptic encephalopathy with spike–wave activation in sleep (D/EE-SWAS). This figure summarizes the main causes of D/EE-SWAS. Genetic causes include pathogenic variants affecting ion channel regulation (e.g., *ATP1A2*, *CACNA1A*, *GRIN1*, *GRIN2A*, *SCN1A*, *SCN2A*, *KCNA2*, *KCNQ3*), transcriptional regulators (*MECP2*, *FOXP1*, *SETD1B*), scaffolding proteins (*CNKSR2*, *DLG4*), and cell adhesion molecules (*PPFIA3*). Copy number variants (CNVs) involving 1q32, 15q, 16p11.2, and 17p11.2 duplications, or 4p16 and 5q22 deletions, are also reported. Structural causes include thalamic lesions, hypothalamic hamartoma (HH), hemimegaloencephaly, patients with shunts for hydrocephalus, other perinatal brain injuries, cortical malformations, ischemic or hemorrhagic stroke in early life/porencephalic cysts, and low-grade glioneuronal tumors. mTOR-pathway related lesions (e.g., TSC, NPRL2) can be associated with an SWAS phenotype. In 20%–30% of cases, the etiology remains unknown, particularly in epileptic encephalopathy with spike–wave activation in sleep (EE-SWAS), highlighting the need for advanced genetic testing and neuroimaging to refine diagnosis and personalize treatment strategies. FCD, focal cortical dysplasia; HIE, hypoxic–ischemic encephalopathy; PVL, periventricular leukomalacia.

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or missense variants in other domains, this correlation is not absolute. Thus, factors beyond variant location and functional effect likely contribute to phenotypic diversity. Understanding this variability is essential for accurate genetic counseling.

CNVs are identified in approximately 16% of cases. Previously described CNVs associated with DEE-SWAS and EE-SWAS include duplications at 1q32, 15q, 16p11.2, and 17p11.2, as well as deletions at 4p16 and 5q22. Additionally, DEE-SWAS is a recognized feature of Xp11.23-p11.22 duplication syndrome.[8]

4.1 | Structural abnormalities in relation to D/EE-SWAS

DEE-SWAS is also associated with various structural brain abnormalities. Identifying them through appropriate brain neuroimaging studies (MRI) is crucial for guiding treatment decisions, which may include surgical options in some drug-resistant cases. These structural etiologies typically affect the corticothalamic circuits involved in sleep-related epileptiform activity.[43,44]

The most common structural causes are the following: (1) thalamic lesions, including early thalamic injuries (hemorrhagic and ischemic) and hypothalamic hamartoma; (2) hemimegaloencephaly; (3) patients with shunts for hydrocephalus; (4) other perinatal brain injuries (e.g., periventricular leukomalacia, hypoxic–ischemic encephalopathy); (5) cortical malformations, such as focal cortical dysplasia and polymicrogyria; (6) ischemic or hemorrhagic stroke in early life/porencephalic cysts; and (7) low-grade glioneuronal tumors (e.g., gangliogliomas, dysembryoplastic neuroepithelial tumors; Figure 3).

Recent high-resolution neuroimaging and electrophysiological work has further highlighted the role of pathological thalamocortical oscillations and disrupted brain networks in mediating the neurocognitive deficits associated with DEE-SWAS, providing a mechanistic framework for targeted interventions.[45]

Structural DEE-SWAS is associated with a higher likelihood of early onset clinical epilepsy, language regression, drug resistance, and dependency on ASM polytherapy at 1 year.[46]

With advanced imaging and genetic testing, the number of unsolved cases is decreasing, now accounting for 20%–30% of cases, more often in those with EE-SWAS. Reported genetic diagnostic yields are largely derived from tertiary or research-enriched cohorts and may therefore overestimate the likelihood of identifying a molecular etiology in unselected clinical populations.

5 | NEURODEVELOPMENT AND SWAS

Disabilities caused by SWAS may affect multiple cognitive domains, including intelligence, language and communication, learning disorders, visuospatial orientation, attention, and social interaction.

An overall decrease in intelligence quotient (IQ) is frequently present, and a marked discrepancy between verbal and performance quotients is often reported. Importantly, beyond cognitive regression, a stagnation in development—particularly in the language domain—can also occur.[5,47]

A recent work analyzed the phenotypic differences between DEE-SWAS and EE-SWAS.[8] All 101 patients included in the study had regression or plateauing in at least one domain, and 14 had regression across all domains. The most frequently affected were speech and language (78/101, 77%), followed by cognition (61/101, 60%). Intellectual outcome was better in patients with EE-SWAS (92% normal intellect or mild intellectual disability) compared with those who had DEE-SWAS (49% moderate to profound intellectual disability).

Neurodevelopmental disorders are observed in 50%–90% of patients with D/EE-SWAS, with attention-deficit/hyperactivity disorder symptoms being the most common (50%–70%), followed by irritability and externalizing behavior (25%–35%), poor social interaction (16%), and anxiety (6%). There is also a notable overlap between SWAS and autism spectrum disorder (23%–35%), with up to 70% of affected children exhibiting autistic traits such as impaired social interaction, repetitive behaviors, and restricted interests.[7,48–50]

Some studies suggest also that neurobehavioral consequences in SWAS are particularly resistant to treatment and may even worsen over time, independently from cognitive evolution.[5]

Within the D/EE-SWAS spectrum, LKS highlights the vulnerability of language networks to sleep-activated epileptiform activity, leading to prominent receptive and expressive language regression with relative preservation of nonverbal abilities. Despite remission of epileptiform activity in many cases, persistent language and academic difficulties are common, especially with delayed treatment.[51]

Nevertheless, delays in treatment have been linked to poorer outcomes, in addition to etiologies, emphasizing the need for early diagnosis and intervention. Patients with unknown etiology generally have better outcomes than those with structural brain abnormalities or genetic DEE-SWAS, where psychiatric disorders tend to be more severe and often necessitate assistance with daily functioning (up to 65% of patients; Figure 4).[52,53]

FIGURE 4 Neurocognitive and psychiatric outcomes and prognostic factors in developmental and/or epileptic encephalopathy with spike–wave activation in sleep. Developmental arrest or regression is seen in nearly all children, with language regression/stagnation in ~77% and global cognitive impairment in ~60%. Neurodevelopmental comorbidities include attention-deficit/hyperactivity disorder (ADHD; 50%–70%), irritability and externalizing behavior (25%–35%), and autism spectrum disorder (ASD) overlap (23%–35%; autistic traits up to 70%). Prognosis is influenced by etiology (genetic/structural vs. unknown), duration of spike–wave activation in sleep (SWAS), and time to treatment initiation. Children with epileptic encephalopathy with SWAS (EE-SWAS) generally have a better intellectual outcome and a higher likelihood of complete recovery, particularly if treated early, emphasizing the importance of timely diagnosis and individualized management.

6 | CURRENT TREATMENT STRATEGIES FOR DEE WITH SWAS

Figure 5 reports a stepwise treatment algorithm for D/EE-SWAS.

Treatment recommendations in D/EE-SWAS derive from evidence of varying strength—including randomized trials, observational studies, and expert consensus—reflecting the limited high-quality data available.

6.1 | Pharmacological treatment

6.1.1 | Corticosteroids

A first multicenter, randomized controlled trial[34] was performed between 2014 and 2022 comparing corticosteroids (either continuous treatment with 1–2 mg/kg per day of prednisolone orally or pulse treatment with 20 mg/kg per day of methylprednisolone intravenously for 3 days every 4 weeks) to clobazam (.5–1.2 mg/kg per day orally). The primary outcome measure was cognitive functioning after 6 months of treatment, which was assessed by either the IQ responder rate (defined as improvement of ≥11.25 IQ points) or the cognitive sum score responder rate (defined as improvement of ≥.75 points). Safety was assessed by the number of adverse events and serious adverse events. Among 45 enrolled children, those receiving corticosteroids showed greater IQ improvement (≥11.25 points in 25% vs. 0% with clobazam; $p = .025$), although no difference was observed in cognitive sum score improvement. Adverse events were common in both groups, with weight gain more frequent in corticosteroid users and fatigue or behavioral issues in clobazam users. Despite early trial termination and failure to complete the recruitment, increasing the uncertainty of the results, the findings suggest corticosteroids as a preferred early treatment for D/EE-SWAS. This is consistent with previous retrospective studies[54,55] and literature review ($n = 575$ collected cases).[55]

Corticosteroids showed higher efficacy compared to other ASMs, including benzodiazepines, but also to intravenous immunoglobulins in a large cohort.[55,56]

Different regimens and doses of corticosteroids are reported in the literature, with many monocenter

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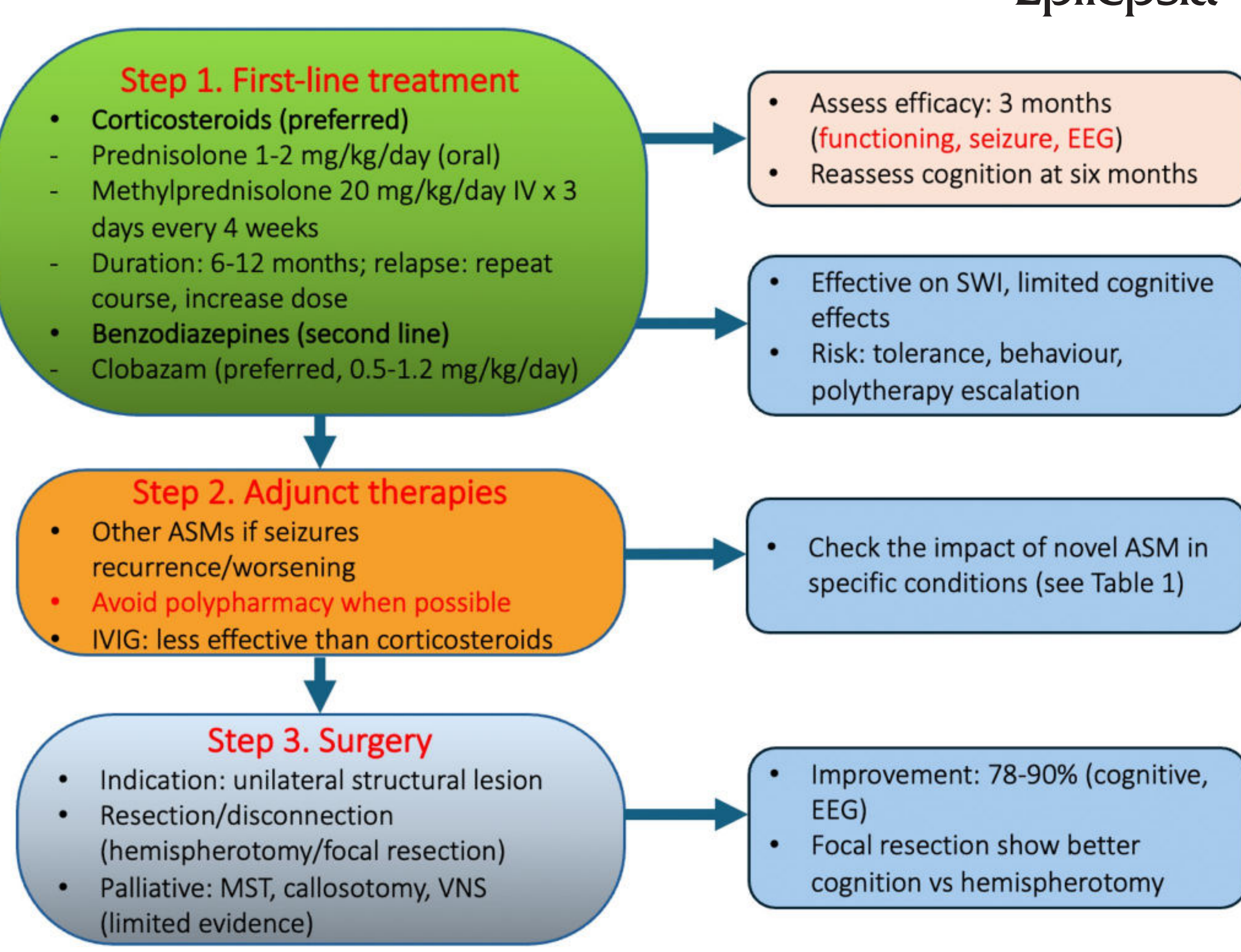

FIGURE 5 Stepwise treatment algorithm for developmental and/or epileptic encephalopathy with spike–wave activation in sleep. This flowchart summarizes a pragmatic three-step approach: (1) first-line corticosteroid therapy—either daily oral prednisolone (1–2 mg/kg/day) or intermittent intravenous methylprednisolone pulses (20 mg/kg/day × 3 days monthly)—with a treatment duration of 6–12 months and repeat courses for relapse; (2) benzodiazepines (e.g., clobazam) as second-line agents; among benzodiazepines, clobazam is generally preferred because of its longer half-life, better tolerability, and lower sedative burden compared with diazepam, allowing more sustained suppression of sleep-activated epileptiform activity; and (3) adjunctive antiseizure medications (ASMs) or intravenous immunoglobulin (IVIG) for refractory cases. Surgery (focal resection, hemispherotomy) should be considered early in children with unilateral structural lesions. Assessment of treatment response should include 3-month electroencephalography (EEG) and seizure monitoring and 6-month neuropsychological evaluation to guide continuation or escalation of therapy. MST, multiple subpial transection; SWI, spike-and-wave index; VNS, vagus nerve stimulation.

retrospective studies on small case series.[57–60] To avoid adverse events of long-term oral corticosteroids, intravenous high-dose intermittent bolus steroid therapy was proposed[59] as well as mixed protocols of high-dose intravenous bolus (15–20 mg/kg daily) for 3 consecutive days with 3 weekly cycles followed by oral prednisolone (2 mg/kg daily for 1 month, then gradually withdrawn).[61]

No corticosteroid regimen has proven superior, and both oral prednisolone or intermittent intravenous methylprednisolone pulses can be utilized, with regimen selection individualized according to disease severity and side effect profile.

Another retrospective study with 147 treatments (43 steroid-based and 104 nonsteroid) showed that cognitive improvement was reported in 36% of cases at first follow-up and 45% at last follow-up. Steroid treatment was the most effective, however, significantly increasing the odds of cognitive improvement at first follow-up (odds ratio [OR] = 2.5, 95% confidence interval [CI] = 1.1–5.7). The data of this study also support the importance of SWI reduction as a key indicator of treatment efficacy,[55] although this is not supported by other observations.[62]

Effectiveness of corticosteroids is often first assessed at 3 months, evaluating seizure reduction/control, daily functioning, and sleep EEG. Neuropsychological evaluation is advised to be performed at 6 months to prevent retest effects. The treatment duration is often not clearly defined, and it is unknown when to expect improvement of cognition, but a

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duration of at least 6 months to 1 year is likely necessary.[63] Relapses when corticosteroids are reduced or discontinued are common. They manifest as impairment of daily functioning/cognition or behavior associated with reactivation of spike and wave during sleep. Usually, a second course of therapy is considered or a return to the previous higher dose if this recurrence occurs during drug withdrawal with a slower withdrawal regimen. In the case of seizure recurrence or increase in frequency, other ASMs can be added.

The usual investigations and preventive measures for high-dose/long-duration steroids must be considered. High-dose or prolonged corticosteroid therapy requires monitoring due to frequent adverse effects, including weight gain, hypertension, mood changes, hyperglycemia, infection risk, and—over longer courses—growth suppression, osteoporosis, cataracts, and adrenal suppression. Periodic assessment of blood pressure, weight, glucose, and growth is recommended, with supplementation and gradual tapering to reduce complications and relapse.

Accumulating evidence supports the use of steroids over benzodiazepines as the preferred first-line treatment for D/EE-SWAS, particularly in improving cognitive outcomes.

Corticosteroids might have a spectrum of effects such as reducing neuroinflammation or enhancing an antiseizure effect via hormonal and neurotransmitter pathways.[64] Notably, a recent study demonstrated ongoing inflammatory processes in D/EE-SWAS, which appeared to decrease in parallel with clinical and electroencephalographic improvement, suggesting a possible link between inflammation and syndrome activity.[65]

6.1.2 | Benzodiazepines

The effectiveness of benzodiazepines in treating D/EE-SWAS has been recognized since the 1970s, with early reports showing complete suppression of epileptiform EEG activity after benzodiazepine administration. Among different benzodiazepines, clobazam has been preferred based on its longer half-life (36–42 h) and its favorable tolerability, since Larrieu et al.[66] documented seizure cessation and EEG normalization in a child with ESES following clobazam initiation.

Although benzodiazepines are effective in reducing SWI, their impact on long-term cognitive outcomes remains unclear. A retrospective study of 81 children (11 US centers, 2014–2016) analyzed treatment strategies for D/EE-SWAS. Benzodiazepines (62%) were the most common first-line therapies. Benzodiazepines (OR = 3.32, $p = .002$) and steroids (OR = 4.04, $p = .01$) showed greater odds of clinical subjective improvement than common ASM.[54]

Multiple concerns arise regarding the long-term use of benzodiazepines, particularly concerning their cognitive adverse effects, behavioral side effects, and sedative properties. In adults, chronic benzodiazepine use has been linked to an increased risk of dementia.[67] However, data on the cognitive and behavioral impact of benzodiazepines in children with epilepsy remain scarce. In addition, the pharmacological characteristics of benzodiazepines raise concerns about withdrawal effects, which could lead to seizure recurrence or worsening, potentially necessitating an escalation of the ASM regimen in benzodiazepine users. A 5-year cohort study using the French national health care data system found that the likelihood of transitioning from dual therapy to polytherapy was influenced by the inclusion of a benzodiazepine in the initial regimen. Specifically, patients on a dual therapy including a benzodiazepine were more likely to require polytherapy (subdistribution hazard ratio = 1.20, 95% CI = 1.03–1.39).[68,69]

The reviewed studies did not report on total duration of benzodiazepines to assure lasting effectiveness.

Although benzodiazepines may effectively reduce SWI, their impact on cognition and behavior and the risk for polytherapy escalation are concerning. Given the evolving benefit–risk balance, benzodiazepines should be considered second-line treatments after steroids for D/EE-SWAS, and treatment longer than 2 years likely should be avoided.

Relapse during corticosteroid or benzodiazepines tapering can be seen; in clinical practice, this is often managed by slower dose reduction, adjunct ASM, or re-escalation of steroids or benzodiazepines if cognitive or functional deterioration recurs.

6.1.3 | Impact of novel ASM

The identification of an increasing number of genetic causes of D/EE-SWAS has led to precision medicine as an alternative to syndrome-driven treatments with steroids and benzodiazepines, which have been considered for the general D/EE-SWAS population.[34]

Among the genetic causes of D/EE-SWAS, variants in *GRIN2A* are the most frequently identified, reported in up to 20% of cases in previous studies,[8] although this is likely an overestimation due to selection bias. The *GRIN2A* gene encodes the GluN2A protein, a subunit of the N-methyl-D-aspartate receptor (NMDAR), which plays a key role in glutamatergic synapses. The different gene variants can have gain-of-function (GoF) or loss-of-function (LoF) effects with associated phenotypes.

For patients with LoF variants, the NMDAR coagonist L-serine may be an effective treatment.[70] A recent nonrandomized, open-label, single-arm trial on L-serine in children with *GRIN* genetic variants leading to LoF (*GRIN1*, *GRIN2A*, and *GRIN2B*), but no reported phenotype of

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TABLE 1 Emerging precision medicine approaches and targeted therapies.

Targeted therapy	Gene/mechanism	Functional effect	Reported clinical impact
L-serine (NMDAR coagonist)	*GRIN2A* (loss of function)	Reduced NMDAR activity	Improved adaptive behavior, motor function, and quality of life; seizure reduction or resolution in some cases
Memantine or amantadine (NMDAR antagonists)	*GRIN2A* (gain of function)	Increased NMDAR activity	Reduced spike–wave index; subjective improvements in cognition, language, and behavior
Radiprodil (GluN2B negative allosteric modulator)	*GRIN2A* (gain of function)	Increased NMDAR activity (GluN2B specific)	Seizure reduction demonstrated in animal models of *GRIN2A*-related encephalopathy (not yet trialed in DEE-SWAS)
Primidone	*TRPM3* (gain of function)	Increased *TRPM3* activity	Halted developmental regression, improved neurodevelopment, disappearance of CSWS

Note: This table highlights novel strategies tailored to underlying genetic etiologies. Examples include L-serine supplementation for *GRIN1*/*2A*/*2B* loss-of-function variants, NMDAR antagonists (memantine, amantadine) for gain-of-function variants, and primidone for *TRPM3* gain-of-function mutations; each is associated with clinical and EEG improvement in case series. These therapies represent a shift toward disease-modifying interventions, complementing traditional syndrome-driven treatments such as corticosteroids and benzodiazepines. The figure underscores the need for genotype–phenotype correlation studies, prospective trials, and biomarker development to integrate precision medicine into standard care.

Abbreviations: CSWS, continuous spike-and-wave during slow sleep; DEE-SWAS, developmental and epileptic encephalopathy with spike–wave activation in sleep; NMDAR, N-methyl-D-aspartate receptor.

DEE-SWAS, showed improvements in adaptive behavior, motor function, and quality of life. In this study, L-serine was also effective in epilepsy; five of 18 patients (28%) experienced a complete resolution of epileptic EEG activity, and one of three patients (33%) had a significant reduction in seizure frequency (75%–90% responder rate).[71]

More rarely, the DEE-SWAS phenotype is associated with GoF, in which NMDAR antagonist medications—such as memantine and amantadine—have been considered a therapeutic option.[72]

Amantadine has been tried in 20 patients with D/EE-SWAS with different etiologies (structural, genetic, and mostly unknown), with a reduction of median baseline spike–wave index from 76% (baseline) to 53%; moreover, 30% patients exhibited complete (or nearly complete) resolution of SWAS. The majority of patients reported subjective improvements in cognitive, linguistic, or behavioral functioning.[73]

More recently, radiprodil, a selective GluN2B negative allosteric modulator, demonstrated seizure reduction in mice with *GRIN2A*-related DEE.[74]

Another suggested example of precision medicine was reported in *SCN2A* LoF variants, which might also be associated with a DEE-SWAS phenotype. In these cases, avoiding sodium channel blockers in addition to conventional D/EE-SWAS treatment, such as steroids, benzodiazepine, or valproate may be effective.[75]

Finally, an example of a targeted therapy is the use of primidone in DEE-SWAS associated with *TRPM3* pathogenic variants with a GoF effect.[76] Based on in vitro studies demonstrating an inhibitory effect of primidone on *TRPM3*, two patients started individualized therapy with this drug. In both children, developmental regression was halted, neurodevelopment improved, and SWAS was no longer detectable.[76] Table 1 summarizes the novel ASMs and their role in specific etiologies.

Although most of the previously mentioned examples of precision therapy are etiology-driven, in most cases they do not specifically take the SWAS phenotype into account. Therefore, we currently lack data on the clear efficacy of targeted therapies in monogenic patients with this specific electroclinical phenotype.

6.2 | Nonpharmacological treatment options

6.2.1 | Epilepsy surgery

Epilepsy surgery may be a safe and effective treatment for carefully selected children with D/EE-SWAS with a causative unilateral structural etiology. Timely intervention can reduce seizures and epileptiform discharges, maximizing developmental potential and allowing a reduction in ASM.[77]

Among D/EE-SWAS therapeutic strategies, surgery has long been underutilized or considered only in later stages of D/EE. This choice was probably due to the presumed self-limiting nature of the electrophysiological pattern or the presence of generalized epileptiform discharges,

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fearing more widespread than just unilateral pathology and thus poor surgical candidacy.[9,78]

A pooled individual patient data analysis showed surgery being the most effective treatment for D/EE-SWAS syndrome, in terms of cognitive or EEG improvement, in up to 90% of patients who were candidates for epilepsy surgery.[56]

A recent meta-analysis of 131 cases (95% with structural lesion on MRI)[79] also demonstrated a high efficacy of surgery in improvement in neurocognitive and neurobehavioral functions as well as in controlling seizures, ranging from 78% to 80% for resective surgeries (hemispherotomy in unilateral cases or focal resection/disconnection), with hemispherotomy being the most frequently performed surgery (53%).[79]

Despite a comparable seizure freedom rate, focal resections have shown a higher improvement in neurocognitive abilities compared to HT (71.4% vs. 58%), most likely related to the etiology indicating the type of surgery and not to resolution of SWAS.

Palliative surgical techniques have been reported. Multiple subpial transection is the only surgical procedure employed to treat LKS, but efficacy in terms of language and behavior outcomes is inconsistent.[75,76,80,81] Corpus callosotomy has been associated with up to 27% seizure reduction and up to 16.7% neurocognitive and behavioral improvement in D/EE-SWAS.[79–81] Vagus nerve stimulation in SWAS patients was reported only in single case reports, with good results in terms of sleep EEG improvement, postulating its possible influence in thalamocortical projections.[82] These treatments need further evaluation with more robust study designs. As for medical treatment, normal development before the onset of EE-SWAS was also found to be a significant predictor of favorable neurodevelopmental outcome following surgery.[56] Previous studies[83] have reported poorer outcome in patients with duration of SWAS longer than 2 years, but this finding was not confirmed as a negative prognostic factor in surgical cohorts.[79] Neurostimulation approaches—including vagus nerve stimulation, noninvasive cortical stimulation, and thalamic deep brain stimulation—remain investigational in D/EE-SWAS, with only limited case-level evidence and no controlled studies demonstrating efficacy.

Importantly, in selected children with unilateral structural etiologies, epilepsy surgery may be considered even when clinical seizures are infrequent or well controlled, if SWAS is associated with ongoing cognitive or developmental deterioration. As a main limitation, surgery is only applicable in patients with a structural unilateral lesion; thus, many D/EE-SWAS patients are not surgical candidates. However, to avoid underutilization of surgery, all patients should be investigated to consider whether they are surgical candidates, with a focus on structural unilateral lesion accessible for resection or disconnection.

7 | CURRENT CHALLENGES AND FUTURE DIRECTIONS

Long-term cognitive deficits remain a significant concern in children with D/EE-SWAS. Despite progress in understanding the syndrome, there is still a lack of robust evidence to guide standardized, early management. Timely identification and prompt initiation of effective, personalized treatment are crucial to reducing the cumulative burden of epileptiform activity on the developing brain. Where appropriate, etiology-based approaches such as resective surgery should be considered early in the disease course, particularly in children with unilateral structural lesions. Diagnostic challenges continue to hinder optimal care. Sleep EEG is not consistently performed in children with language regression or unexplained cognitive plateau, and EEG abnormalities alone do not meet diagnostic criteria; evidence of developmental slowing or regression is essential. Broader dissemination and adoption of diagnostic criteria are urgently needed. A persistent barrier to clinical trials and therapeutic optimization is the absence of standardized, clinically meaningful outcome measures. Cognitive and behavioral improvement is often prioritized over seizure freedom, but the heterogeneity of D/EE-SWAS means that relevant outcomes differ among patients. Subjective reports from caregivers are valuable but may not align with objective neuropsychological metrics, leading to under- or overestimation of treatment benefit. Development of individualized, functionally relevant, and statistically robust outcome measures—incorporating both cognitive trajectories and quality-of-life indices—will be crucial to accurately evaluating treatment response and informing shared decision-making. Importantly, reduction of SWAS or spike–wave index alone should not be considered a sufficient therapeutic outcome, and in the absence of parallel cognitive or functional improvement clinicians should reassess etiology, comorbidities, and treatment strategy, recognizing that SWAS may be epiphenomenal in some cases.

One of the most important advances in recent years is the earlier identification of genetic etiologies and biomarkers that may precede the appearance of SWAS. This has opened the door to precision medicine approaches, including gene-specific therapies or rational drug selection based on molecular mechanisms. For example, recognition of *GRIN2A*-related disorders or mTOR pathway variants may influence first-line treatment choices. Nevertheless, SWAS remains a potentially reversible

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TABLE 2 A practical "decision framework" for the use of high-dose steroids or benzodiazepines.

Clinical domain	Features supporting treatment targeting SWAS (e.g., steroids/benzodiazepines)	Features favoring caution or conservative approach	Suggested clinical approach when uncertain
Developmental trajectory	Clear loss of previously acquired skills or new developmental stagnation temporally associated with SWAS	Long-standing static developmental impairment without clear change	Establish objective baseline (neuropsychology, language, behavior, adaptive skills)
Functional impact	Decline in language, attention, learning, or behavior affecting daily or school function (reported by caregivers/teachers/therapists)	No observable functional deterioration despite SWAS	Define individualized treatment goals and outcome measures
EEG evolution	New onset or marked worsening of SWAS coinciding with clinical change	Stable SWAS pattern over time without clinical correlation	Repeat sleep EEG to confirm persistence and quantify burden
Timing	Short interval between SWAS emergence and developmental change	Long duration of developmental impairment preceding SWAS recognition	Consider time-limited therapeutic trial if plausible temporal link
Comorbidity and risk	Acceptable risk profile for steroids/ benzodiazepines	Medical or psychiatric comorbidities increasing treatment risk	Prefer less burdensome options first (e.g., ASM adjustment, sleep optimization)
Response to prior therapy	Prior improvement of cognition/behavior with SWAS reduction	EEG improvement without functional benefit after adequate trial	Discontinue/taper if no meaningful clinical gain

Note: This framework reflects expert clinical reasoning in the absence of definitive evidence and aims to balance potential reversibility of SWAS-related dysfunction against treatment burden.

Abbreviations: ASM, antiseizure medication; EEG, electroencephalographic; SWAS, spike-and-wave activation in sleep.

condition, and optimizing treatment timing is essential to maximize cognitive recovery.

Current treatment protocols remain heterogeneous. Corticosteroids are the preferred first-line therapy, but questions remain regarding optimal dose, duration, and tapering strategy, particularly in patients with a high risk of relapse. Benzodiazepines and other ASMs are widely used but may have limited cognitive benefit, and their long-term impact on development is unclear. Surgery continues to be underutilized despite evidence that early resection or disconnection can significantly improve neurodevelopmental outcomes in children with focal structural etiologies. In the absence of a clear functional decline, we consider high-dose steroids or prolonged benzodiazepines only selectively appropriate, ideally as a time-limited, goal-directed trial with objective outcome measures. A practical "decision framework" for the use of high-dose steroids or benzodiazepines is provided in Table 2.

Future priorities include dissemination of consensus diagnostic criteria, systematic evaluation of sleep architecture beyond SWI, and development of interventions to improve sleep quality—such as melatonin, sleep hygiene programs, or neuromodulation—which may have downstream benefits on cognition and seizure control. Large-scale genetic studies, functional assays, and advanced neuroimaging approaches, including EEG-fMRI and network connectivity analyses, are needed to define biomarkers of disease activity and to develop individualized risk profiles. Given the rarity of D/EE-SWAS, multicenter collaborations will be essential to generate high-quality data and to evaluate therapeutic strategies in sufficiently powered cohorts. Comprehensive care should extend beyond seizure control to include rehabilitation, neuropsychological support, and family counseling, aiming to preserve neurodevelopment and optimize quality of life.

AUTHOR CONTRIBUTIONS

Nicola Specchio and Stéphane Auvin contributed to writing the manuscript, including literature search and preparation of figures and tables. All authors independently reviewed the results of the search of published work, read all selected articles, and revised and approved the final version. Paolo Curatolo designed the study, contributed to writing the manuscript, reviewed the literature search, and coordinated the entire work.

ACKNOWLEDGMENTS

The authors have nothing to report.

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FUNDING INFORMATION

This work was supported by the Italian Ministry of Health with Current Research Funds.

CONFLICT OF INTEREST STATEMENT

N.S. has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, LivaNova, and Sanofi; has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. S.A. has served as a consultant or received honoraria for lectures from Biocodex, BioMarin, Encoded, Eisai, GRIN Therapeutics, Jazz Pharmaceuticals, Neuraxpharm, Nutricia, Orion, Proveca, Supernus, Stoke, Takeda, UCB Pharma, Xenon, and Zogenix. He has been an investigator for clinical trials for Eisai, Proveca, Takeda, and UCB Pharma. A.B. has received honoraria for presenting at educational events, serving on advisory boards, and consultancy work for Biocodex, Jazz/GW Pharma, Encoded Therapeutics, Stoke Therapeutics, Nutricia, and UCB/Zogenix. V.D.G. has served on scientific advisory boards for Longboard Pharmaceuticals and Dr. Schar Kanso, and has received grants from Jazz Pharmaceuticals. V.D.M. reports no conflict of interests. E.G. has served on scientific advisory boards for UCB, Neurocrine Bioscience, and Encoded Therapeutics and has received speaker honoraria from Eisai, Jazz/GW Pharma, and UCB. F.E.J. has served as consultant/advisor for UCB, GW Pharma (now Jazz Pharmaceuticals), GRIN Therapeutics, Longboard, and Novartis, for which remuneration was made to the department, outside of the submitted work. R.N. has served as principal investigator in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, and LivaNova. She has received consulting and lecturer honoraria from BioGene, BioMarin, Praxis, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, Neuraxpharma, Takeda, Nutricia, Biocodex, Advicennes, and Eisai. She has received unrestricted research grants from Eisai, UCB, LivaNova, and GW Pharma and academic research grants from EJP-RD (Horizons 2020). C.P. reports no conflict of interests. G.R. has received speaker fees from UCB and Angelini and has participated on advisory boards for Angelini and UNEEG. M.T. has received speaker fees or funding from or has participated on advisory boards for BioMarin and Biocodex. P.C. has served on a scientific advisory board for Novartis, has received speaker honoraria from Jazz Pharmaceuticals and ItalFarmaco, and has served as an investigator for clinical trials for Novartis. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Specchio N, Auvin S, Brunklaus A, De Giorgis V, Di Micco V, Gardella E, et al. Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep: Pathophysiological insights and treatment options. Epilepsia. 2026;00:1–17. https://doi.org/10.1002/epi.70271

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