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Unmet needs in epileptic encephalopathy with spike-and-wave activation in sleep: A systematic review

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A B S T R A C T

Introduction: Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS), also referred to as electrical status epilepticus during sleep (ESES) or epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS or EE-CSWS), is a spectrum of rare childhood epileptic encephalopathies that can lead to long-term cognitive impairment. Despite the importance of early diagnosis and intervention for D/EE-SWAS, there is a paucity of well-controlled clinical trial data to inform treatment, and no approved treatments are available. To assess correlations between diagnosis, treatment, and outcomes in D/EE-SWAS, we carried out a systematic review of the literature.

Methods: In August 2020, we conducted comprehensive database searches using search terms including "electrical status epilepticus," "ESES," "CSWS," and "Landau-Kleffner syndrome." Two or more independent reviewers screened titles, abstracts, and full-text articles for those that met the following criteria: prospective studies (randomized controlled trials [RCTs] or open-label trials), retrospective studies (drug evaluations or observational studies/chart reviews), and case series with ≥ 10 participants. Both interventional and non-interventional studies were included (i.e., drug intervention was not an inclusion criterion). Articles published before 2012, review articles, animal studies, and studies of surgical or dietary interventions were excluded. Standardized data extraction templates were used to capture data on study design, patient characteristics, interventions, and outcomes from each of the selected publications. Study quality was assessed using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale (NOS) or the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for retrospective, observational studies.

Results: A total of 34 studies were included for full data extraction, most of which were uncontrolled and observational. Interpretation of study outcomes was limited by small study populations, variability in inclusion criteria, and inconsistency in methods of assessment and reporting of outcomes, which resulted in large heterogeneity in patients and their presenting symptoms. Despite these limitations, some patterns could be discerned. Several studies found that longer duration of ESES and younger age at onset were correlated with more severe language and cognitive deficits. In addition, several studies reported an association between improvement in cognitive outcomes and reduction in electroencephalogram (EEG) abnormalities and/or seizure frequency. In the 16 prospective or retrospective studies that evaluated drug treatments (e.g., antiseizure medications, corticosteroids, and high-dose diazepam), there was some improvement in EEG, seizure, and/or cognitive outcomes, although the specific outcomes and rates of improvement reported varied from study to study.

Conclusion: Long-term cognitive deficits remain common in D/EE-SWAS, and data gaps exist in the literature that preclude an evidence-based approach to managing this complex epilepsy indication. Early intervention with more effective medications is needed to optimize long-term outcomes. Sufficiently powered, randomized, double-blind, controlled trials with standardized methods and predefined primary and secondary outcomes are needed.

1. Introduction

Developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep (D/EE-SWAS) is a rare childhood epilepsy syndrome that is estimated to account for 0.2–1.3% of pediatric epilepsies (Chipaux et al., 2016; Kramer et al., 1998; Sanchez Fernandez et al., 2013a; Sanchez Fernandez et al., 2013c; Specchio et al., 2022; Terney et al., 2016; Van Hirtum-Das et al., 2006). It is characterized by cognitive, language, behavioral, and/or motor regression associated with an electroencephalogram (EEG) pattern of marked spike-and-wave activation in sleep, and seizures in some (but not all) patients (Sanchez Fernandez et al., 2013a; Sanchez Fernandez et al., 2013c; Specchio et al., 2022). Many patients experience developmental delay (encephalopathy) in association with a CSWS EEG pattern, and standard criteria to diagnose such regressions or delays are a major problem in the assessment and management of these patients (Specchio et al., 2022). Much about the physiological underpinning of D/EE-SWAS remains unknown, although structural brain lesions, such as malformations of cortical

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development or early thalamic injury, have been associated with the syndrome (Guerrini et al., 1998; Incorpora et al., 1999; Kelemen et al., 2006; Kersbergen et al., 2013; Monteiro et al., 2001; Sanchez Fernandez et al., 2013a; Specchio et al., 2022). In addition, a growing number of case reports and small case series have described associations with genetic factors such as copy number variations and other mutations in various chromosomes, although the etiological role of these genetic factors is unclear (Sanchez Fernandez et al., 2013a).

Despite the largely unknown pathophysiology of D/EE-SWAS, the disease course has been fairly well characterized (Sanchez Fernandez et al., 2013a; Specchio et al., 2022). Onset of seizures (in those who have seizures) typically occurs between 2 and 12 years of age (peaking at 4–5 years), with the EEG developing spike-and-wave activation in non-rapid eye movement (non-REM) sleep 1–2 years later along with cognitive/-behavioral regression. During the initial phase, seizures are infrequent and drug-responsive in most patients, but typically worsen over time with the evolution of multiple seizure types (Specchio et al., 2022). By adolescence, seizures tend to markedly decrease or resolve, with improvement or resolution of EEG phenotypes also occurring in most patients (Specchio et al., 2022). Reductions in seizure frequency and EEG phenotypes suggest that some symptoms may be self-limiting. Like seizure frequency and EEG phenotypes, cognitive and/or motor deficits may improve over time; however, many patients have residual impairment, and up to half of patients have impairments severe enough to limit independent functioning (Seegmüller et al., 2012; Pera et al., 2013; Sanchez Fernandez et al., 2013a; Specchio et al., 2022; Tassinari and Rubboli, 2006). The degree of long-term cognitive dysfunction is largely determined by etiology (Fejerman et al., 2012; Pera et al., 2013; Caraballo et al., 2013b; Chen et al., 2014; Arhan et al., 2015; Gong et al., 2018; Cao et al., 2019; Saraf et al., 2020) as well as the onset and duration of D/EE-SWAS, with earlier onset and longer duration associated with poorer outcomes (Nickels and Wirrell, 2008; Oztoprak et al., 2021; Van Bogaert, 2013). Poorer cognitive outcomes are also associated with higher percentages of slow-wave sleep occupied by continuous spike-and-wave activity (Maltoni et al., 2016). Thus, early diagnosis, regardless of etiology, and effective treatments are essential for minimizing long-term cognitive deficits (Specchio et al., 2022).

A major obstacle in the study of D/EE-SWAS is the heterogeneous use of terminology for the condition and its identifying characteristics (Berg et al., 2010; Sanchez Fernandez et al., 2013c; Specchio et al., 2022). Since the term “electrical status epilepticus during sleep” (ESES) was first used in the 1970s to describe an EEG pattern of continuous spike-and-waves during slow-wave sleep in children with cognitive dysfunction (Patry et al., 1971; Sanchez Fernandez et al., 2013c), the terminology has continued to evolve (Berg et al., 2010; Sanchez Fernandez et al., 2013c; Specchio et al., 2022). Until recently, another term, “epilepsy with continuous spike-and-wave during sleep” (CSWS or EE-CSWS) was used interchangeably with ESES (Berg et al., 2010; Sanchez Fernandez et al., 2013c); however, some researchers differentiated these terms by using ESES to refer to the EEG pattern of frequent spike-waves or to the associated epileptic encephalopathy with global developmental regression, and CSWS or EE-CSWS to refer to the most severe form of the associated epileptic encephalopathy (Sanchez Fernandez et al., 2013c). In 2022, the International League Against Epilepsy (ILAE) task force on the nosology of childhood epilepsy (Specchio et al., 2022) proposed the terms “developmental epileptic encephalopathy with spike-and-wave activation in sleep”, or DEE-SWAS, to refer to patients with pre-existing neurodevelopmental disorders prior to cognitive regression, and “epileptic encephalopathy with spike-and-wave activation in sleep”, or EE-SWAS, for patients with pre-existing normal development prior to cognitive regression. For brevity, we will use the term “D/EE-SWAS” to encompass both DEE-SWAS and EE-SWAS throughout this review.

Beyond inconsistencies in terminology, diagnostic criteria have varied over time, additionally confounding the D/EE-SWAS landscape. Most notably, there has been considerable variation in the threshold for the spike-wave index (SWI; typically calculated as the percentage of 1-second bins occupied by at least one spike-wave during EEG tracing [Aeby et al., 2005]) used to define D/EE-SWAS. The SWI threshold for D/EE-SWAS was initially defined as spike-and-wave activity occupying at least 85% of the slow-wave sleep tracing (Patry et al., 1971). In more recent studies, SWI thresholds of 50% (Chen et al., 2014; Gencpinar et al., 2016; Hempel et al., 2019; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; van den Munckhof et al., 2018; Vrielynck et al., 2017) and 85% (Cao et al., 2019; Carvalho et al., 2020; Chen et al., 2015, 2016; Degerliyurt et al., 2015; Fortini et al., 2013; Francois et al., 2014; Gong et al., 2018; Saraf et al., 2020; Sonnek et al., 2021; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014) have been used. In 2 studies based in Turkey, short courses of adrenocorticotropic hormone (ACTH) were administered for ESES when SWI was $\geq$ 15% (Altunel et al., 2017a; Altunel et al., 2017b). This 15% threshold was the lowest SWI in the studies that met our review inclusion criteria. Further complicating the landscape has been the historically ambiguous relationship between this condition and similar childhood electroclinical syndromes such as Lennox-Gastaut syndrome (LGS) and self-limited epilepsy with centrotemporal spikes (SeLECTS). Previously, many epilepsy experts considered D/EE-SWAS to exist on a spectrum with these related electroclinical syndromes (Tenney and Glauser, 2017); in fact, many prevalence estimates of D/EE-SWAS include these related syndromes. However, the current ILAE task force differentiates D/EE-SWAS from the related childhood electroclinical syndromes (Specchio et al., 2022).

Despite the importance of early diagnosis and intervention, there are no approved treatments for D/EE-SWAS, and there is only limited evidence from randomized controlled trial data to inform treatment (Bjørnaes et al., 2013; Larsson et al., 2012). A recent Cochrane review noted that due to the low incidence of D/EE-SWAS, multicenter trials with adequate patient recruitment are needed to provide evidence for the effectiveness of pharmacologic treatments (Moresco et al., 2020). In the absence of an evidence-based approach, children with D/EE-SWAS currently receive a variety of therapies, including high-dose benzodiazepines, antiseizure medications (ASMs), and corticosteroids, often in combination (Baumer et al., 2021; Sanchez Fernandez et al., 2014; Sanchez Fernandez et al., 2013a). Epilepsy surgery has also been used for treatment, but this is less common (Baumer et al., 2021; Sanchez Fernandez et al., 2014; Sanchez Fernandez et al., 2013a). Although these treatments may be effective in reducing seizure frequency and severity in the subset of patients who experience seizures, their effects on normalizing SWI and improving long-term outcomes are less clear.

In order to assess the evidence underlying correlations between diagnosis, treatment, and outcomes in D/EE-SWAS, we carried out a systematic review of the literature. Study designs, patient demographics, treatment patterns, and reported outcomes were analyzed.

2. Methods

2.1. Identification and selection of studies

The methodology of this review was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021). In August 2020, we conducted a PubMed database search to identify studies relevant to the diagnosis, treatment, and outcomes of patients with D/EE-SWAS using search terms including “electrical status epilepticus,” “ESES,” “CSWS,” and “Landau-Kleffner syndrome” (for a full list of search terms see Supplementary Table 1). “ESES” and “CSWS” were used as search terms because they were the predominant terms used for the condition before 2020. In addition, a hand search was conducted using recent high-quality articles and reviews to ensure that all relevant reports were identified. Two independent reviewers with clinical backgrounds in epilepsy screened titles, abstracts, and full-text articles for those that met the following criteria: prospective studies (randomized controlled trials [RCTs] or open-label

trials), retrospective studies (drug evaluations or observational studies/chart reviews), and case series with ≥ 10 participants. Both interventional and non-interventional studies were included (i.e., drug intervention was not an inclusion criterion). There were no constraints on geographic region, but only English-language publications were included. Articles published before 2012 were excluded in order to minimize overlap with a previously published pooled analysis (van den Munckhof et al., 2015) and thereby avoid duplication in individual patient data. Review articles, animal studies, and studies of surgical or dietary interventions were excluded.

2.2. Data extraction

Standardized data extraction templates were developed to capture key data on study design, patient characteristics, interventions, and outcomes from each of the selected publications. A list of the efficacy outcomes of interest is shown in Supplementary Table 2. Data from the studies were extracted by a primary reviewer and checked by at least one secondary reviewer; a third, independent reviewer was consulted if any conflicts arose. Study quality was assessed using the Cochrane Risk of Bias Tool for RCTs (Higgins et al., 2011) and the Newcastle-Ottawa Scale (NOS) (Wells et al.) or Joanna Briggs Institute (JBI) Critical Appraisal Checklist (Munn et al., 2020) for retrospective, observational studies.

3. Results

3.1. Systematic literature review and risk of bias assessment

The initial search yielded 397 hits (Fig. 1). After removal of 141 review articles, duplicates, and non-English language reports, and another 38 records by title/abstract screening, 218 publications remained for full-text screening. Of these, 34 records (4 prospective studies and 30 retrospective, observational studies) were included for data extraction based on defined inclusion and exclusion criteria for this review (Altunel et al., 2017a; Altunel et al., 2017b; Arhan et al., 2015; Bjørnaes et al., 2013; Cao et al., 2019; Caraballo et al., 2014; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Carvalho et al., 2020; Chen et al., 2015, 2016; Chen et al., 2014; Degerliyurt et al., 2015; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Gong et al., 2018; Hempel et al., 2019; Kanmaz et al., 2021; Larsson et al., 2012; Maltoni et al., 2016; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014).

Quality assessments of the reports indicated that the overall risk of bias for one of the prospective RCTs (Bjørnaes et al., 2013) was considered high due to a high risk of attrition bias; there was a low overall risk of bias for the other RCT (Larsson et al., 2012) (Supplementary Table 3). The overall risk of bias in the two prospective, open-label trials (Cao et al., 2019; Chen et al., 2016) was considered moderate (Supplementary Table 4). All but 4 of the retrospective trials (Caraballo et al., 2013a; Carvalho et al., 2020; Fatema et al., 2015; Francois et al., 2014) were considered to have a low or moderate risk of bias (Supplementary Tables 4 and 5).

3.2. Study designs

Of the 34 studies that met inclusion criteria, 4 were prospective in design (Table 1) (Bjørnaes et al., 2013; Cao et al., 2019; Chen et al., 2016; Larsson et al., 2012). Two of the prospective studies were RCTs evaluating the effects of levetiracetam (Bjørnaes et al., 2013; Larsson et al., 2012); both trials evaluated the efficacy of 12 weeks of levetiracetam treatment in a randomized, double-blind, placebo-controlled crossover design with small study populations (18 and 23 participants). The other 2 prospective trials evaluated the effects of ≥ 6 months of open-label treatment with corticosteroids (methylprednisolone plus prednisolone (Cao et al., 2019) or dexamethasone [Chen et al., 2016]); both studies had fewer than 25 participants.

The remaining 30 studies were retrospective in design; of these, 12 evaluated the effects of drug treatments including ASMs (levetiracetam

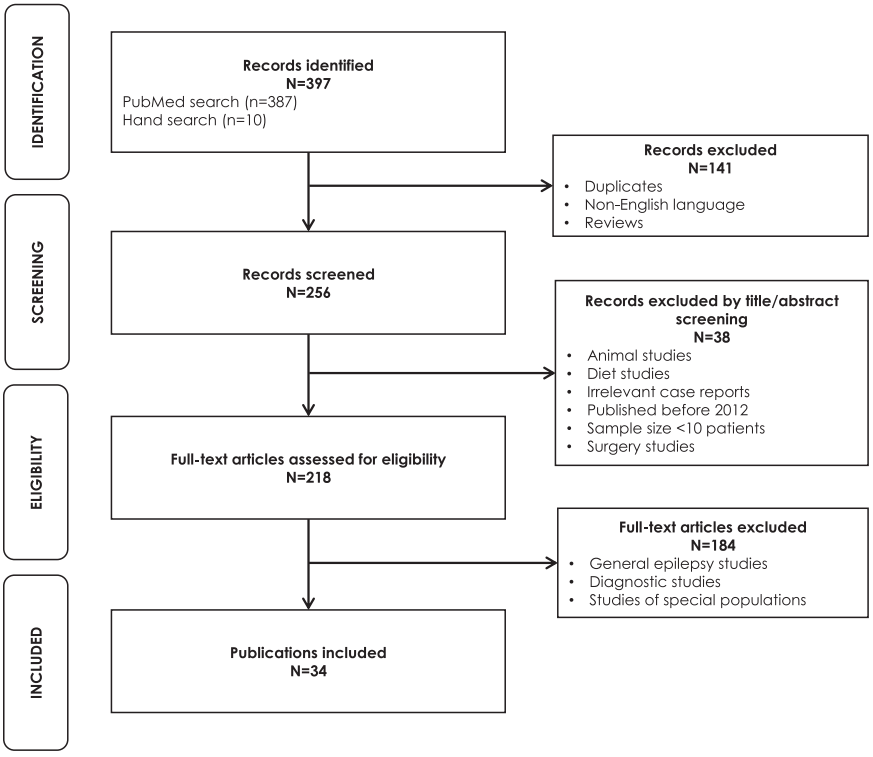

Fig. 1. PRISMA Flow Diagram of Search Strategy.

Table 1
Summary of Prospective Studies.

	Treatment (Dose)	Treatment Duration	Study Outcomes
Randomized, Double-blind			
Bjørnaes et al. (2013) N = 23	Levetiracetam (20–25 mg/kg) vs PBO	12 wk[a]	• Greater reduction in mean SWI for levetiracetam vs PBO (40% vs 17%) • In pts with available data, levetiracetam had no significant effect on behavior (n = 12–15), vigilance (n = 11–13), or memory (n = 12–13); outcomes in the PBO arm were not reported • No correlation between reduced SWI and cognitive status
Larsson et al. (2012) N = 18	Levetiracetam (20–25 mg/kg) vs PBO	12 wk[a]	• Greater reduction in mean SWI for levetiracetam vs PBO (44% vs 8%) • 9 (50%) pts had > 50% SWI reduction
Open-label			
Cao et al. (2019) N = 22	Methylprednisolone (15 mg/kg); prednisolone (2 mg/kg)[b]	12 mo[b]	• 7 (32%) pts had ≥ 50% seizure reduction after initial treatment; 4 (18%) were seizure-free • No significant difference in VIQ and PIQ between pts with ≥ 50% vs < 50% SWI reduction • VIQ and PIQ were significantly higher in pts with ≥ 50% vs < 50% seizure reduction ($P < 0.05$)
Chen et al. (2016) N = 15	Dexamethasone (0.15 mg/kg)	6–10 mo[c]	• 5 (33%) pts had ≥ 50% SWI reduction; 2 (13%) had SWI normalization • 4 (27%) pts had > 50% seizure reduction; 3 (20%) were seizure-free • 7 (47%) pts had improvement or resolution of cognitive and/or behavioral impairment

mo, month(s); PBO, placebo; PIQ, performance intelligence quotient; pts, patients; SWI, spike-wave index; VIQ, verbal intelligence quotient; vs, versus; wk, week(s).
[a] This was a crossover study; half of the pts were randomized to LEV for 12 wk, then PBO for 12 wk, while the other half were randomized to PBO then LEV.
[b] Participants received 3 consecutive courses of intravenous methylprednisolone (15 mg/kg) for 3 days, then oral prednisolone (2 mg/kg) for 4 days. After 3 consecutive courses, oral prednisolone (1–2 mg/kg) was started and eventually tapered for a total combined treatment of 6 mo. Participants who responded to the initial course of treatment were followed for up to 12 mo.
[c] After the 6–10 mo treatment period, participants were followed for up to 7 years.

[Chen et al., 2015; Chen et al., 2014], sulthiame [Fejerman et al., 2012; Kanmaz et al., 2021], topiramate [Vrielynck et al., 2017]), benzodiazepines (high-dose diazepam [Francois et al., 2014; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b]), corticosteroids (prednisone [Hempel et al., 2019]) and others (ACTH [Altunel et al., 2017a; Altunel et al., 2017b]; amantadine [Wilson et al. (2018)]) (Table 2). For most long-term studies, the treatment dose and concomitant medications were allowed to be adjusted during the follow-up period to best treat the patient. Two of the studies evaluated different outcomes (short- vs long-term effects of diazepam treatment) in the same patient population (Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b). Patient populations in these studies ranged from 17 to 75 participants, with only 4 studies following more than 50 patients (Altunel et al., 2017a; Chen et al., 2015; Chen et al., 2014; Fejerman et al., 2012). Duration of follow-up periods ranged from 1 month to 16 years, except for 1 study that assessed short-term outcomes after 24 h of diazepam treatment.

The other 18 retrospective studies were observational studies/chart reviews. These observational studies were not designed to evaluate specific treatments; rather, the objective of the studies was to evaluate changes over time in specific characteristics associated with D/EE-SWAS, such as SWI/EEG, seizure frequency, cognitive/behavioral outcomes, treatment patterns, and/or prognosis. Duration of follow-up in these studies ranged from 2 weeks to 22 years, with 8 studies following patients for ≤ 2 years (Table 3) (Carvalho et al., 2020; Fatema et al., 2015; Gencpinar et al., 2016; Gong et al., 2018; Raha et al., 2012; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018) and 10 studies following patients longer than 2 years (Table 4) (Arhan et al., 2015; Caraballo et al., 2014; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Degerliyurt et al., 2015; Fortini et al., 2013; Maltoni et al., 2016; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014). The observational study populations ranged from 10 to 117 patients, with 4 studies following fewer than 20 patients (Caraballo et al., 2015; Fatema et al., 2015; Raha et al., 2012; Yilmaz et al., 2014).

3.3. Inclusion criteria

Key inclusion criteria are shown in Supplementary Table 6. All studies required the presence of continuous spike-and-wave discharges during slow-wave sleep as an inclusion criterion; however, we did not use specific attributes of SWI (such as minimum specific inclusion criteria, calculation methods, or definition) to exclude studies that met search criteria. The minimum SWI percentage of non-REM sleep required for inclusion varied from 15% to 85%, and 3 studies did not specify a threshold (Caraballo et al., 2013a; Fatema et al., 2015; Fejerman et al., 2012). Methods of calculating and/or defining SWI also varied widely among the studies, and most of the studies did not provide specific details for the calculation. In 9 studies, SWI was defined only as "the percentage of epileptiform or spike-wave activity" during N-REM sleep (Altunel et al., 2017a; Altunel et al., 2017b; Chen et al., 2015, 2016; Chen et al., 2014; Gong et al., 2018; Hempel et al., 2019; Sonnek et al., 2021; Yilmaz et al., 2014), with no further information on the exact method of calculation (3 of these studies specified that the measurement occurred during the first N-REM sleep cycle (Chen et al., 2015, 2016) or the first ≥ 10 min of sleep [Sonnek et al., 2021]). Another 8 studies defined SWI only as the "number of spike-waves per unit of time" during N-REM sleep (Arhan et al., 2015; Caraballo et al., 2014; Caraballo et al., 2015; Caraballo et al., 2013b; Degerliyurt et al., 2015; Fortini et al., 2013; Francois et al., 2014; Maltoni et al., 2016); of these, 2 studies defined the unit of time as 1 s (Degerliyurt et al., 2015) or 1 min (Maltoni et al., 2016), and 1 study measured the spike-waves during 15-second intervals over 100 pages of EEG recordings (Francois et al., 2014). Three studies did not include any information on how SWI was defined (Caraballo et al., 2013a; Fatema et al., 2015; Fejerman et al., 2012).

Of the studies that provided more detail on SWI calculation, 9 defined SWI as the percentage of 1-second bins with ≥ 1 spike-wave during N-REM sleep (Cao et al., 2019; Kanmaz et al., 2021; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018; Wiwattanadittakul et al., 2020), 6 of which specified the duration of measurement as 5 min (Cao et al., 2019; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b), 10 min (van den Munckhof et al., 2018), ≥ 30 min (Raha et al., 2012), or 1 h (Vrielynck et al., 2017). In 2 studies, SWI was calculated as the percentage of time with < 3 s between spikes in 10-minute epochs of N-REM sleep (Bjørnaes et al., 2013; Larsson et al., 2012). The remaining 3 studies calculated SWI as either the total minutes of spike and slow waves divided by the total duration of N-REM sleep (Gencpinar et al., 2016), the average number of spike-wave complexes per 100 s (Saraf et al., 2020), and the percentage of 3-second bins with ≥ 1 spike-wave during the first sleep cycle using automatic spike matching to hand-selected template spikes (Carvalho et al., 2020).

Table 2
Summary of Retrospective Studies Evaluating Drug Treatments.

	Treatment (Dose)	Treatment/ Follow-up, Mean (Range)	Study Outcomes
ASMs			
Chen et al. (2014) N = 73	Levetiracetam (30–60 mg/kg)	19 mo (6 mo-2 yr)[a]	• 15 (21%) pts had ≥ 50% SWI reduction • Of 52 pts with seizures, 22 (42%) had reduced seizures; 11 (21%) were seizure-free
Chen et al. (2015) N = 71	Levetiracetam (30–50 mg/kg)	3 mo-6.3 yr[a]	• 24 (34%) pts had SWI normalization • Of 50 pts with seizures, 25 (50%) were seizure-free; 10 (20%) had > 50% seizure reduction • 13 (18%) returned to BL cognitive function; 11 (15%) had > 50% improvement • Symptomatic etiology, longer duration of ESES, and younger age at ESES onset were associated with poor response
Fejerman et al. (2012) N = 53	Sulthiame (5–30 mg/kg)	1.5–16 yr[a]	• 15 (28%) pts had normalization of EEG • 31 (58%) had seizure freedom • Seizure freedom/ reduction was associated with cognitive improvement
Kanmaz et al. (2021) N = 29	Sulthiame (6–17 mg/kg)	5 mo-4 yr[a]	• 1 (3%) pt had > 50% SWI reduction; 6 (21%) had EEG normalization • Of 19 pts with seizures, 8 (42%) were seizure-free; 4 (21%) had > 50% seizure reduction • 11 (38%) pts had cognitive/behavioral improvement
Vrielynck et al. (2017) N = 21	Topiramate (2–5.5 mg/kg)	12 mo[a]	• 10 (48%) pts had improved sleep EEG grade; of these 9 (90%) showed cognitive/ behavioral improvement • Of 13 pts with seizures, 6 (46%) were seizure-free, 4 (31%) had seizure reduction
Benzodiazepines			
Francois et al. (2014) N = 42	Diazepam (0.2–2 mg/kg)	10 mo-2 yr[a]	• Of 26 pts with available SWI data, 18 (69%) had > 50% SWI reduction; 65% reduction in mean SWI • Of 17 pts with difficulties in problem solving, 8 (47%) improved by study end
Sanchez Fernandez et al. (2012a) N = 29[b]	Diazepam (1 mg/kg)	24 hr[c]	• 15 (52%) pts had ≥ 50% SWI reduction; 47% reduction in mean SWI
Sanchez Fernandez et al. (2013b) N = 29[b]	Diazepam (0.5–1 mg/kg)	4 wk[d]/6 mo	• 12 (41%) pts had ≥ 25% SWI reduction; 8 (28%) had ≥ 50% SWI reduction; 3 (10%) had ESES resolution • 14 (48%) pts were seizure-free • 14 (48%) improved in language; 11 (38%) in cognitive abilities; 4 (14%) in behavior
Corticosteroids			
Hempel et al. (2019) N = 17	Prednisone (2 mg/kg)	10 mo (1 mo-2.3 yr)[a]	• Trend towards a correlation between improvement in language/behavior and ESES resolution
Other			
Altunel et al. (2017a) N = 75	ACTH (0.03–1 mg/kg)	6–15 d/13 mo	• 59% reduction in mean SWI • Of 42 pts with seizures, seizure frequency was reduced by 90%; 24 (57%) pts were seizure-free • 67% improvement in ADHD symptoms
Altunel et al. (2017b) N = 25	ACTH (0.03 mg/kg)	6–10 d/13 mo	• 51% reduction in median SWI • Of 10 pts with seizures, 7 (70%) were seizure-free; 3 (30%) had reduced seizures • Stuttering resolved in 12 (48%) pts; 72% improvement in ADHD/ASD symptoms • Improvements in ADHD/ASD symptoms correlated with reduced seizures ($P = 0.004$)
Wilson et al. (2018) N = 20	Amantadine (3–11 mg/kg)	11.5 mo[d] (2 mo-6 yr)[a]	• 47% reduction in median SWI • Of 16 pts with available data, 11 (69%) had language, cognitive, or behavioral improvement

ACTH, adrenocorticotropic hormone; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; ASMs, antiseizure medications; BL, baseline; d, day(s); EEG(s), electroencephalogram(s); ESES, electrical status epilepticus during slow-wave sleep; hr, hour(s); mo, month(s); pts, patients; SWI, spike-wave index; wk, week(s); yr, year(s).

[a] Duration of treatment and follow up periods were the same.

[b] Sanchez Fernandez 2012a and Sanchez Fernandez 2013b evaluated different outcomes (short- vs long-term treatment effects) in the same patient population.

[c] Outcomes were assessed 24 h after administering one dose of diazepam (1 mg/kg).

[d] Median value; mean was not reported.

The presence of seizures was required for inclusion in less than half of the included studies (Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2015; Caraballo et al., 2013b; Chen et al., 2015; Chen et al., 2014; Degerliyurt et al., 2015; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Gong et al., 2018; Kanmaz et al., 2021; Saraf et al., 2020). In 19 studies, cognitive impairment, functional deterioration, aphasia, or behavioral disorders were specified as inclusion criteria (Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2014; Caraballo et al., 2015; Caraballo et al., 2013b; Carvalho et al., 2020; Chen et al., 2015, 2016; Degerliyurt et al., 2015; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Gong et al., 2018; Kanmaz et al., 2021;

Table 3
Summary of Retrospective, Observational Studies With Follow-up Times ≤ 2 Years[a].

	Objective	Follow-up Duration, Mean (Range)	Outcomes
Carvalho et al. (2020) N = 38	Demonstrate value of repeated SWI assessments and validate wearable device in pts with D/EE-SWAS	10.6 mo (5 mo-2.4 yr)	• Of 16 pts with available data, 14 (88%) had reduced SWI; 12 (75%) had detectable improvement in behavior and/or school performance
Fatema et al. (2015) N = 10	Describe clinical spectrum and EEG characteristics in pts with D/EE-SWAS	2 wk-1 yr	• 7 (70%) pts had > 50% SWI reduction; 1 (10%) had normalized SWI • 10 (100%) pts had at least some seizure/ behavioral improvement
Gencpinar et al. (2016) N = 44	Describe EEG spectrum in pts with D/EE-SWAS	≥ 2 yr	• Of 36 pts with available data, 5 (14%) had > 50% SWI reduction; 18 (50%) had normalized SWI • 16 (36%) pts were seizure-free, 11 (25%) had seizure frequency reductions of > 50% • Of 22 patients with available data, 10 (45%) had favorable cognitive outcomes
Gong et al. (2018) N = 21	Investigate HFOs in pts with D/EE-SWAS with different etiologies	NR	• Methylprednisolone treatment significantly reduced HFOs/spikes ($P < 0.05$ both) • Reductions in HFOs/ spikes were larger for genetic/unknown group vs structural group ($P < 0.05$ both)
Raha et al. (2012) N = 14	Assess cognitive and behavioral problems, EEG findings, and treatments in pts with D/EE-SWAS	0.5–8 yr	• Of 11 pts treated with prednisolone, 5 (45%) had reduction of SWI to < 50%; 7 (64%) had improved seizure/ cognitive outcomes
Saraf et al. (2020) N = 52	Analyze EEG, seizure, and language outcomes in pts with D/EE-SWAS	≥ 1 yr	• 13 (25%) pts were seizure-free; seizure freedom was more likely in idiopathic vs symptomatic pts ($P = 0.03$) • 32 (61%) pts had language improvement; pts with ≥ 3 favorable EEG markers had better language outcomes
Sonnek et al. (2021) N = 95	Describe clinical spectrum, etiologies, and treatment effects in pts with D/EE-SWAS or near-D/ EE-SWAS	NR	• Significant EEG improvement with steroids ($P < 0.01$) and surgery ($P < 0.05$) • 53% and 30% of treatments were associated with reduced seizures and cognitive improvement, respectively
van den Munckhof et al. (2018) N = 47	Examine association between EEG improvement and cognition in pts with D/EE-SWAS and cognitive deficits	13.1 mo	• 24% reduction in median SWI • 45% of treatments resulted in cognitive improvement • Median SWI reductions were greater in patients with cognitive improvement ($P = 0.002$) • In 7 pts with available data, SWI change was correlated with IQ change ($P = 0.014$)

D/EE-SWAS, developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep; EEG(s), electroencephalogram(s); HFOs, high-frequency oscillations; IQ, intelligence quotient; mo, month(s); NR, not reported; pts, patients; SWI, spike-wave index; vs, versus; wk, week(s); yr, year(s).
[a] Based on mean follow-up time; if mean follow-up was not reported, then minimum follow-up time was used.

Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; van den Munckhof et al., 2018; Vrielynck et al., 2017).

3.4. Outcomes assessed

Just 16 of the 34 studies assessed all 3 main efficacy outcomes of interest: SWI/EEG, seizure (in patients with seizures), and cognitive outcomes (Altunel et al., 2017a; Altunel et al., 2017b; Arhan et al., 2015; Caraballo et al., 2015; Caraballo et al., 2013b; Chen et al., 2015, 2016; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Gencpinar et al., 2016; Kanmaz et al., 2021; Raha et al., 2012; Sanchez Fernandez et al., 2013b; Sonnek et al., 2021; Vrielynck et al., 2017) (Supplementary Table 7). SWI and/or EEG results were reported in the majority of studies; however, the outcomes were reported using a variety of different metrics, including percent reduction in median or mean SWI, percent of patients with reduction of SWI by a given percentage (e.g., ≥ 50% or ≥ 75%), percent of patients with normalization or resolution of SWI, ESES, or EEG, and/or percent of patients with EEG improvement or EEG abnormalities. In the 23 studies that reported seizure outcomes in the patients with seizures (Altunel et al., 2017a; Altunel et al., 2017b; Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2014; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Chen et al., 2015, 2016; Chen et al., 2014; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Gencpinar et al., 2016; Kanmaz et al., 2021; Raha et al., 2012; Sanchez Fernandez et al., 2013b; Saraf et al., 2020; Sonnek et al., 2021; Vrielynck et al., 2017; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014), the results were typically reported as percentages of patients with reduced seizure frequency and/or seizure freedom.

Cognitive outcomes were reported in 28 of the 34 studies (Altunel et al., 2017a; Altunel et al., 2017b; Arhan et al., 2015; Bjørnaes et al., 2013; Cao et al., 2019; Caraballo et al., 2014; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Carvalho et al., 2020; Chen et al., 2015, 2016; Degerliyurt et al., 2015; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Hempel et al., 2019; Kanmaz et al., 2021; Maltoni et al., 2016; Raha et al., 2012; Sanchez Fernandez et al., 2013b; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018); however, a wide variety of metrics and/or instruments were used (Supplementary Table 7). Of the 28 studies that reported cognitive outcomes, only 12 used a standardized testing instrument, such as the Wechsler Intelligence Scale, the Strengths and Difficulties Questionnaire, and/or the Terman-Merrill Scales (Arhan et al., 2015; Bjørnaes et al., 2013; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Degerliyurt et al., 2015; Kanmaz et al., 2021; Maltoni et al., 2016; Raha et al., 2012; Saraf et al., 2020; Sonnek et al., 2021). Ten studies relied partly or wholly on subjective reports from parents, teachers, and/or clinicians of improvements in behavior, school achievement, and/or cognitive status (Altunel et al., 2017a; Altunel et al., 2017b; Caraballo et al., 2014; Chen et al., 2015, 2016; Francois et al., 2014; Gencpinar

Table 4
Summary of Retrospective, Observational Studies With Follow-up Times > 2 Years[a].

	Objective	Follow-up, Mean (Range)	Outcomes
Arhan et al. (2015) N = 59	Evaluate EEG features, treatment effectiveness, and outcomes in pts with D/EE-SWAS	4.5 (1–6) yr	• 18 (31%) pts had normalized EEG and were seizure-free; 32 (54%) had > 50% SWI and seizure reduction • Cognitive performance improved in patients with > 75% seizure reduction • Correlation between longer ESES duration and more severe cognitive deficits
Caraballo et al. (2013a) N = 66[b]	Analyze EEG features, treatment, and outcomes in pts with unilateral PMG	13.5 (3–20) yr	• In 43 pts with D/EE-SWAS; 3 (7%) had seizure freedom • Pts with > 75% seizure reduction had improved IQ and school performance
Caraballo et al. (2013b) N = 117	Analyze EEG features, etiology, treatment, and prognosis of pts with D/EE-SWAS	2–22 yr	• 91 (78%) pts had EEG abnormalities; 45 (38%) were seizure-free • Pts with > 75% seizure reduction had improved in school performance and IQ • EEG and cognitive outcomes were better in idiopathic vs non-idiopathic pts
Caraballo et al. (2014) N = 29	Analyze EEG features, etiology, treatment, and prognosis of pts with LKS	12 (3–21) yr	• 26 (90%) pts had seizure freedom; 8 (28%) had completely recovered language • No correlation between treatments, improved SWI, or language/cognitive outcomes • More severe language deficit was correlated with earlier onset and longer duration of D/EE-SWAS
Caraballo et al. (2015) N = 17	Analyze EEG characteristics, etiology, treatment, and prognosis of pts with D/EE-SWAS and unusual EEG features	7.5 (2–10) yr	• 13 (76%) pts had EEG abnormalities; 3 (18%) had seizure freedom • Pts with > 75% seizure reduction had improved school performance and IQ • Seizure outcomes were better in idiopathic vs structural pts • Patients with reduced seizures or seizure freedom had improved school performance and cognitive outcomes
Degerliyurt et al. (2015) N = 22	Evaluate clinical and imaging characteristics, treatment results, and prognosis in pts with D/EE-SWAS	3.8 (0.8–14) yr	• 15 (68%) pts had EEG improvement • Of 15 pts with available data, IQ declined in 10 (67%); in 8 pts with available data, VIQ (but not PIQ) was significantly reduced at follow up ($P < 0.05$)
Fortini et al. (2013) N = 21	Analyze EEG features, etiology, treatment, and prognosis of pts with hemi-ESES	8 (2–15) yr	• 3 (14%) pts had > 75% SWI and seizure reduction; 8 (38%) had SWI and seizure normalization • Pts with seizure freedom or > 75% seizure reduction improved in school performance and IQ • More favorable outcomes in patients with unilateral polymicrogyria
Maltoni et al. (2016) N = 61	Identify neuropsychological variables that predict outcomes in pts with D/EE-SWAS	7.3 yr	• Higher SWI significantly correlated with lower IQ ($P < 0.05$), VIQ, and PIQ (both $P < 0.01$) • Increased duration of SWI ≥ 25 correlated with poorer cognitive outcomes ($P < 0.0001$)
Wiwattanadittakul et al. (2020) N = 33	Assess treatment patterns and outcomes in pts with SWI ≥ 85%	33 mo[c] (5 mo-11.9 yr)	• 21 (64%) pts had resolution of ESES; 18 (55%) were seizure-free • Seizure-free pts were more likely to have ESES resolution ($P = 0.003$)
Yilmaz et al. (2014) N = 14	Examine characteristics and	2–4 yr	• 7 (50%) pts had normal EEGs; 12

(continued on next page)

Table 4 (*continued*)

	Objective	Follow-up, Mean (Range)	Outcomes
	treatment outcomes in pts with D/EE-SWAS		(86%) pts were seizure-free • No correlation between ESES duration and IQ ($P > 0.05$)

D/EE-SWAS, developmental and/or epileptic encephalopathy with spike-and-wave activation in sleep; EEG(s), electroencephalogram(s); ESES, electrical status epilepticus during sleep; IQ, intelligence quotient; LKS, Landau–Kleffner syndrome; mo, month; PIQ, performance intelligence quotient; pts, patients; PMG, polymicrogyria; SWI, spike wave index; VIQ, verbal intelligence quotient; vs, versus; yr, year.

[a] Based on mean follow-up; if mean follow-up was not reported, then minimum follow-up time was used.

[b] A total of 66 pts were included in the study; 53 had epilepsy and 43 had D/EE-SWAS.

[c] Median value; mean was not reported.

et al., 2016; Hempel et al., 2019; van den Munckhof et al., 2018; Vrielynck et al., 2017), and 6 studies did not define the method of cognitive assessment (Carvalho et al., 2020; Fatema et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Sanchez Fernandez et al., 2013b; Wilson et al., 2018).

3.5. Patient and disease characteristics

Patient and disease characteristics of the 1293 total patients included in the studies are summarized in Supplementary Table 8. Mean patient age was reported in 26 studies and ranged from 6.1 to 15 years (Altunel et al., 2017a; Altunel et al., 2017b; Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Carvalho et al., 2020; Chen et al., 2016; Chen et al., 2014; Fatema et al., 2015; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Gong et al., 2018; Hempel et al., 2019; Kanmaz et al., 2021; Larsson et al., 2012; Maltoni et al., 2016; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018; Yilmaz et al., 2014). In patients who experienced seizures, mean age at seizure onset ranged from 2.0 to 6.5 years. Mean age at diagnosis of D/EE-SWAS was reported in 17 studies and ranged from 5.4 to 7.8 years (Arhan et al., 2015; Chen et al., 2015, 2016; Chen et al., 2014; Degerliyurt et al., 2015; Fortini et al., 2013; Hempel et al., 2019; Kanmaz et al., 2021; Maltoni et al., 2016; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014). In almost all the studies, the majority of patients were male. In the 21 studies that reported D/EE-SWAS etiology, a variety of descriptors were used including symptomatic, idiopathic, cryptogenic, genetic, structural/lesional, and unknown (Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Chen et al., 2015; Chen et al., 2014; Degerliyurt et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Gong et al., 2018; Hempel et al., 2019; Kanmaz et al., 2021; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018; Yilmaz et al., 2014). Seizure types were reported in most studies, with the most common being focal. Supplementary Table 9 shows the reported comorbidities and ASMs. Most studies reported at least some comorbidities, including developmental impairment, cognitive impairment, cerebral palsy, behavioral disturbances, and attention deficit hyperactivity disorder (ADHD). Almost all the publications reported at least some information about ASMs; the most common were valproic acid and levetiracetam.

3.6. Study outcomes

In the 2 prospective, crossover RCTs of levetiracetam (20–25 mg/kg), the percent reductions from baseline in mean SWI after 12 weeks of treatment for levetiracetam versus placebo were 40% versus 17% (Bjørnaes et al., 2013) and 44% versus 8% (Larsson et al., 2012). Neither of these studies assessed the effects of levetiracetam on seizure frequency and only 1 of the studies (Bjørnaes et al., 2013) evaluated cognitive effects (no significant effects were observed for levetiracetam, and outcomes in the placebo arm were not reported) (Table 1). In a prospective, open-label study evaluating treatment with 3 consecutive rounds of methylprednisolone (15 mg/kg for 3 days) plus prednisolone (2 mg/kg for 4 days) (Cao et al., 2019), 50% of patients had $\geq$ 50% seizure reduction or were seizure-free after up to 1 year of follow up (Table 1). In a prospective, open-label study of dexamethasone (0.15 mg/kg) (Chen et al., 2016), 47% of patients had $\geq$ 50% reduction or normalization in SWI, 47% had $>$ 50% reduction in seizures or were seizure-free, and 47% had improvement or resolution of cognitive and/or behavioral impairment.

Similarly, the 12 retrospective drug evaluation studies reported some improvements in SWI/EEG, seizure, and cognitive outcomes for the treatments assessed, including ASMs (levetiracetam [2 studies], sulthiame [2 studies], topiramate [1 study]), benzodiazepines (high-dose diazepam [3 studies]), corticosteroids (prednisone [1 study]), and other treatments (ACTH [2 studies], amantadine [1 study]) (Table 2). In the levetiracetam studies, 21% of patients had $\geq$ 50% SWI reduction after up to 2 years of levetiracetam (30–60 mg/kg) (Chen et al., 2014), and 34% of patients had SWI normalization after up to 6 years of levetiracetam (30–50 mg/kg) (Chen et al., 2015). Of patients with seizures, 63% (Chen et al., 2014) and 70% (Chen et al., 2015) had reduced seizures or were seizure-free. In addition, 1 study (Chen et al., 2015) reported that 34% of patients had improvement or returned to baseline in cognitive function. In the 2 studies with sulthiame, 28% patients had normalization of EEG after up to 16 years of sulthiame (5–30 mg/kg) (Fejerman et al., 2012) and 24% had $>$ 50% reduction or normalization of SWI after up to 4 years of sulthiame (6–17 mg/kg) (Kanmaz et al., 2021); additionally, 58% (Fejerman et al., 2012) and 63% (Kanmaz et al., 2021) of patients with seizures had reduced seizures or were seizure-free. In 1 of these studies (Kanmaz et al., 2021), 38% of patients had cognitive and/or behavioral improvement after sulthiame treatment. In the single topiramate study (Vrielynck et al., 2017), 48% of patients had improved EEG grade after up to 1 year of treatment with topiramate (2–5.5 mg/kg), 9 (90%) of whom had cognitive/behavioral improvement; in 13 patients with seizures, 10 (77%) had seizure reduction or were seizure-free.

In 3 retrospective studies with high-dose diazepam (0.2–2 mg/kg) (Francois et al., 2014; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b), 28–69% of patients had $\geq$ 50% reduction in SWI, with 65% (Francois et al., 2014) and 47% (Sanchez Fernandez et al., 2012a) reductions from baseline in mean SWI. In 1 of the diazepam studies, 8 of 17 patients (47%) with difficulties in problem-solving had improvements (Francois et al., 2014). In another study (Sanchez Fernandez et al., 2013b), 48% of patients had improvements in language, 38% had improvements in cognition, and 14% improved in behavior. In the single study with the corticosteroid prednisone (2 mg/kg) (Hempel et al., 2019), a trend was observed towards a correlation between improvement in language/behavior and ESES resolution.

In 2 retrospective studies of ACTH (0.3–1 mg/kg) (Altunel et al., 2017a; Altunel et al., 2017b), SWI was reduced by 59% (Altunel et al., 2017a) and 51% (Altunel et al., 2017b) after up to 13 months of follow up, and 57% (Altunel et al., 2017a) and 70% (Altunel et al., 2017b) of patients with seizures were seizure-free. In 1 study (Altunel et al., 2017a), there was a 67% improvement in ADHD symptoms; in the other study (Altunel et al., 2017b), 72% of patients had improvements in ADHD symptoms. In a single study of amantadine (3–11 mg/kg) (Wilson et al., 2018), there was a 47% reduction from baseline in median SWI

after up to 6 years of follow up, and 11 of 16 patients with available data (69%) had language, cognitive, or behavioral improvement.

The retrospective, observational studies also reported some improvements in their patient populations (Tables 3 and 4); however, as previously discussed, the outcomes reported varied widely in the studies, and the outcomes assessed were generally not associated with a specific drug or therapy, as these studies were not designed to evaluate particular treatments.

Of note, 1 drug evaluation study (Chen et al., 2015) and 3 observational studies (Arhan et al., 2015; Caraballo et al., 2014; Maltoni et al., 2016) found that more severe cognitive or language impairment was correlated with increased duration of ESES and younger age at onset, although 1 small observational study (n = 14) found no correlation between ESES duration or age at onset and intelligence quotient (IQ) (Yilmaz et al., 2014). In addition, 1 drug evaluation study and 1 observational study found that EEG improvements were associated with improvements in IQ (van den Munckhof et al., 2018) or language and behavior (Hempel et al., 2019); another observational study reported that patients with at least 3 out of 4 favorable EEG features (i.e., spike wave frequency <170 per 100 s, absence of frontal spikes, normal background, presence of generalized spikes) had better language outcomes (Saraf et al., 2020). In contrast, 2 prospective drug evaluation studies (Bjørnaes et al., 2013; Cao et al., 2019) and 1 observational study (in patients with Landau-Kleffner syndrome [LKS]) (Caraballo et al., 2014) found no correlation between improved SWI and cognitive outcomes.

Etiological data were reported in 21 studies (Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2013b; Caraballo et al., 2015; Chen et al., 2014; Chen et al., 2015; Degerliyurt et al., 2015; Fejerman et al., 2012; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Gong et al., 2018; Hempel et al., 2019; Kanmaz et al., 2021; Saraf et al., 2020; Sonnek et al., 2021; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wilson et al., 2018; Yilmaz et al., 2014) (Supplementary Table 10). Nineteen of these studies included patients with lesional etiologies (also referred to as structural, known, or symptomatic) and non-lesional etiologies (also referred to as unknown, idiopathic, or cryptogenic); the other 2 studies only included patients with structural/symptomatic etiology. Among 11 studies that reported outcomes by etiology, 10 showed more favorable outcomes in patients with non-lesional etiology and 1 favored those with lesional etiology.

Finally, a correlation between seizure control and improvements in cognitive outcomes was observed in a number of the studies (Altunel et al., 2017b; Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Fejerman et al., 2012; Fortini et al., 2013). For example, in 1 observational study of 59 patients with D/EE-SWAS, patients with a > 75% reduction in seizure frequency had significantly improved cognitive outcomes on the Wechsler Intelligence Scale for Children-Revised, Stanford-Binet Intelligence Scale, and/or subjective teacher/caregiver reports at last follow-up (mean follow-up, 4.5 years; range, 1–6 years) (Arhan et al., 2015).

Of the 16 prospective and retrospective studies evaluating a drug treatment, 11 reported information on adverse events (Altunel et al., 2017a; Cao et al., 2019; Chen et al., 2015, 2016; Chen et al., 2014; Fejerman et al., 2012; Francois et al., 2014; Kanmaz et al., 2021; Sanchez Fernandez et al., 2012a; Vrielynck et al., 2017; Wilson et al., 2018). Overall, the adverse events that were reported were inconsistent from study to study; however, there were a few studies in which similar adverse events were reported for the same treatment. In 2 prospective, open-label studies evaluating corticosteroids (methylprednisolone plus prednisolone (Cao et al., 2019) or dexamethasone (Chen et al., 2016)), Cushing syndrome was reported in > 70% of patients and hypertension in 9% and 29% of patients. In 2 retrospective studies evaluating levetiracetam, 7% and 24% of patients experienced anorexia (Chen et al., 2015; Chen et al., 2014). In 2 studies with sulthiame, 6% and 14% of patients experienced agitated respiration/hyperventilation (Fejerman et al., 2012; Kanmaz et al., 2021). Finally, irritability, hyperactivity, or agitation were also reported in 2 diazepam studies (Francois et al., 2014; Sanchez Fernandez et al., 2012a). Similar to the lack of data on adverse events, just 10 reports provided data on the number of, or the reasons for, treatment discontinuation (Bjørnaes et al., 2013; Cao et al., 2019; Chen et al., 2016; Chen et al., 2014; Kanmaz et al., 2021; Larsson et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; Vrielynck et al., 2017; Wilson et al., 2018).

4. Discussion

The objective of this systematic literature review was to assess correlations between diagnosis, treatment, and outcomes in D/EE-SWAS. Our review of the 34 studies that met the criteria for inclusion indicated a lack of standardized study designs, including inclusion criteria and trial outcomes. Reduction in SWI (variably defined) and/or seizure frequency were the most common outcome measures reported, while correlation with improved cognition was variable. Although the prognosis for seizure frequency and severity in patients with D/EE-SWAS who experience seizures is generally favorable, long-term cognitive deficits make independent living impossible for many patients (Tenney and Glauser, 2017). Delays in treatment have been associated with poorer outcomes (Altunel et al., 2017a; Arhan et al., 2015; Kramer et al., 2009; Pera et al., 2013), making early diagnosis and treatment critical. However, no clear consensus exists on optimal treatment for children with D/EE-SWAS, leaving clinicians to make treatment decisions based on anecdotal evidence and their own clinical experience (Sanchez Fernandez et al., 2014; Veggiotti et al., 2016). More high-quality evidence from well-controlled studies is necessary for the creation of evidence-based treatment guidelines, potentially allowing for earlier and more effective interventions. Until such high-quality data are available, it is useful to examine the existing literature to evaluate possible correlations between diagnosis, treatment, and outcomes in D/EE-SWAS.

In the 34 studies in D/EE-SWAS that we identified in our systematic literature review, there was wide variability in the study designs, including inclusion criteria and follow-up durations. While all the studies required the presence of continuous SWI discharges during slow-wave sleep as an inclusion criterion, the SWI thresholds used for inclusion ranged from 15% to 85%. SWI criteria were provided in 31 studies, 20 of which included patients with SWI ≥ 50% (Cao et al., 2019; Caraballo et al., 2015; Carvalho et al., 2020; Chen et al., 2014; Chen et al., 2015; Chen et al., 2016; Degerliyurt et al., 2015; Fortini et al., 2013; Francois et al., 2014; Gencpinar et al., 2016; Gong et al., 2018; Hempel et al., 2019; Raha et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b; Saraf et al., 2020; van den Munckhof et al., 2018; Vrielynck et al., 2017; Wiwattanadittakul et al., 2020; Yilmaz et al., 2014) (Supplementary Table 6). In addition, the methods of calculating and/or defining SWI varied widely, with many studies providing little or no detail on how SWI was measured. Additionally, only 19 of the 34 studies specified cognitive, functional, or behavioral regression for inclusion, and those that did used a variety of different metrics for assessment. Finally, the treatment and/or follow-up durations in the studies varied from 24 h to 16 years.

Further complicating interpretation of the studies is the inconsistency across studies in the methods for assessing and reporting study outcomes. For example, SWI and/or EEG results were reported using a range of metrics, including percent reduction in median or mean SWI; percent of patients with reduction of SWI by a given percentage (e.g., ≥ 50%); percent of patients with normalization or resolution of SWI, ESES, or EEG; and/or percent of patients with EEG improvement or EEG abnormalities. In addition, of the 28 studies that reported cognitive outcomes, only 12 used a standardized testing instrument, with the remainder either relying on subjective reports from parents, teachers, and/or clinicians or not defining the assessment method. This inconsistency reflects the lack of a standard cognitive testing battery in D/EE-SWAS. Even if a standard battery were to be agreed upon, the conduct of

the trial must address test/re-test effects, appropriate duration of follow-up for each cognitive assessment, and how changes in concomitant medications may have impacted testing. In addition, formal testing is time-intensive, not always accessible, and often has restricted insurance coverage; thus, cognitive testing is not routinely administered in clinical practice (Triplett and Asato, 2015). Moreover, etiology is not consistently assessed and reported in clinical studies, despite being an important consideration for treatment and prognosis. These factors are also likely barriers to appropriate diagnosis, treatment, and care for patients with D/EE-SWAS. Moving forward, consensus regarding some basic parameters would improve the broader clinical value of the data collected, such as use of consensus guidelines to define the patient population (e.g., ILAE); consistent report of etiology of disease; a standard battery of cognitive assessments for appropriate duration; consistent, data-driven, and consensus-based definitions of biological outcomes (e.g., SWI); and additional validated clinical and biomarker outcomes.

Although the interpretation of outcomes is limited by differences in study design and reporting of outcomes, some patterns could be discerned. Of the 16 prospective or retrospective studies that evaluated drug treatments (e.g., ASMs, corticosteroids, and high-dose diazepam), 7 studies reported mean or median reductions in SWI ranging from 40% to 65% (Altunel et al., 2017a; Altunel et al., 2017b; Bjørnaes et al., 2013; Francois et al., 2014; Larsson et al., 2012; Sanchez Fernandez et al., 2012a; Wilson et al., 2018). In addition, 7 studies reported $\geq$ 50% reduction in SWI/EEG in 3–69% of patients (Chen et al., 2016; Chen et al., 2014; Francois et al., 2014; Kanmaz et al., 2021; Larsson et al., 2012; Sanchez Fernandez et al., 2012a; Sanchez Fernandez et al., 2013b), and 5 studies reported that 10–34% of patients had normalization of SWI, EEG, or ESES (Chen et al., 2015, 2016; Fejerman et al., 2012; Kanmaz et al., 2021; Sanchez Fernandez et al., 2013b). Some groups have observed that SWI assessments may be better used as an intrapatient measure of change rather than as a fixed threshold across all patients (Sanchez Fernandez et al., 2012b). Improvements in seizure outcomes were also reported in 10 studies reporting that 47–100% of patients with seizures had reductions in seizure frequency and/or seizure freedom (Altunel et al., 2017a; Altunel et al., 2017b; Cao et al., 2019; Chen et al., 2015, 2016; Chen et al., 2014; Fejerman et al., 2012; Kanmaz et al., 2021; Sanchez Fernandez et al., 2013b; Vrielynck et al., 2017). When outcomes were stratified by etiology, the idiopathic/non-lesional group generally had a better prognosis than those in the lesional group (Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Chen et al., 2014; Chen et al., 2015; Fejerman et al., 2012; Francois et al., 2014; Gong et al., 2018; Saraf et al., 2020).

Notably, several studies found that longer duration of ESES and younger age at onset were correlated with more severe cognitive and language deficits (Arhan et al., 2015; Caraballo et al., 2014; Chen et al., 2015; Maltoni et al., 2016). One mechanistic hypothesis for the association between duration of ESES and cognitive outcomes is that abnormal neuronal activity during a critical period of synaptogenesis leads to aberrant synapse formation (Arhan et al., 2015). In addition, several studies also reported an association between cognitive outcomes and reductions in SWI (Hempel et al., 2019; Saraf et al., 2020; van den Munckhof et al., 2018) or seizure frequency (Altunel et al., 2017b; Arhan et al., 2015; Cao et al., 2019; Caraballo et al., 2013a; Caraballo et al., 2015; Caraballo et al., 2013b; Fejerman et al., 2012; Fortini et al., 2013). In contrast, 3 studies found no association between SWI reduction and cognitive improvement (Bjørnaes et al., 2013; Cao et al., 2019; Caraballo et al., 2014). Given the variation among the studies in inclusion criteria, follow-up duration, and assessment of outcomes, it is difficult to interpret these contrasting findings. However, it is worth noting that the 3 studies that did not observe correlations between SWI reduction and cognitive improvement included fewer than 30 patients; thus, the studies may not have been adequately powered to detect possible correlations. In addition, 1 of the studies that did not observe a correlation had a follow-up period of only 12 weeks (Bjørnaes et al., 2013), which may not have been long enough to observe possible changes in cognitive outcomes. For any study, treatment duration and follow-up must be long enough to ensure that between-group differences can be expected for primary outcomes, and preferably all tested outcomes. Another study included patients with LKS, a specific subtype of D/EE-SWAS in which regression affects mainly language with auditory aphasia (Caraballo et al., 2014); thus, it is possible that the lack of correlation between EEG and cognitive improvements might be due to differences in this specific patient population.

Another challenge in synthesizing information from the included studies is the retrospective design of all but 4 of the studies. Retrospective studies are prone to publication and/or selection biases, as well as retrospective bias, where a pattern is discerned that may in actuality be random noise (Shafer and Dexter, 2012). Moreover, the patient populations in the studies were relatively small, ranging from 10 to 117 patients. The 2 prospective RCTs included a combined total of only 41 patients, greatly limiting the ability to interpret or generalize the findings (Bjørnaes et al., 2013; Larsson et al., 2012). Aside from these 2 RCTs, no study included a control group (including a historical control group), and no studies specified a primary outcome. For the long-term retrospective treatment studies reporting EEG-SWI as an outcome measure, these results can be confounded by the decrease of epileptiform activity in puberty seen in the natural progression of D/EE-SWAS. Finally, interpretation of retrospective studies is complicated by heterogeneous endpoints that do not always proceed in parallel (e.g., changes in EEG parameters, seizure counts, cognitive and/or behavioral outcomes), polypharmacy that may confound EEG outcomes or cognitive testing, and natural fluctuations in disease course that may be difficult to differentiate from treatment effects (particularly in studies without a comparator group) (Sanchez Fernandez et al., 2014).

Our review of the D/EE-SWAS literature reveals significant data gaps that preclude an evidence-based approach to this complex epilepsy indication and highlights the need for high-quality controlled trials with fit-for-purpose clinical outcome assessments (COAs) that capture relevant cognitive domains and consistent thresholds and definitions for SWI. However, it is worth nothing that advances in D/EE-SWAS research may be occurring, as suggested by recent studies. In an ongoing open-label extension study (Neurocrine Biosciences NCT05301894) that included patients who completed a Phase 2 study (Neurocrine Biosciences NCT04625101), the long-term safety and tolerability of a triple T-type calcium channel blocker (NBI-827104) are being evaluated, with secondary endpoints evaluating effects on SWI and global improvement. In another ongoing study (University Medical Center Utrecht ISRCTN42686094), the effects of corticosteroids are being compared with clobazam on cognitive function (IQ or development quotient) and secondary endpoints including change in SWI. Finally, the effects of cannabidiol 10 mg/kg (recommended maintenance dose) on SWI and behavior are being evaluated in an ongoing placebo-controlled trial (Northwell Health NCT04721691).

This review had several limitations. First, like all systematic literature reviews, this review has the potential for selection bias when choosing studies for inclusion. Second, although we identified an abundance of D/EE-SWAS studies during literature searches and many were not considered to be appropriate for inclusion in our review (e.g., diet studies), it is possible that some studies were missed during the screening process. Third, the lack of consistent terminology and criteria for D/EE-SWAS may have complicated our literature search and confounded some of our interpretations. Fourth, since no specific quality assurance measures were required for inclusion and no weighting for quality was performed, there is a risk that low-quality studies may have biased our results. Fifth, in the absence of unique patient identifiers across studies, it is theoretically possible that individual patient data may be represented in more than one trial. Finally, as previously discussed, the lack of well-controlled studies and variability of inclusion criteria and outcomes assessed in the studies limit our ability to draw conclusions.

In conclusion, this systematic review of published D/EE-SWAS studies has illustrated a lack of high-quality evidence, which makes it difficult to fully appraise correlations between treatments, EEG changes, and clinical outcomes. Although the current data suggest that the evaluated treatment approaches (ASMs, corticosteroids, and benzodiazepines) may be associated with varying degrees of efficacy in terms of SWI improvement and seizure reduction, cognitive deficits can persist after D/EE-SWAS resolves. These long-term cognitive deficits are associated with disease duration, suggesting that early intervention with more effective medications is needed to optimize long-term outcomes. Sufficiently powered, randomized, double-blind, controlled trials with standardized methods and predefined primary and secondary outcomes are needed. Additionally, adequately designed natural history studies with longitudinal follow-up measures are critical to characterize outcomes in patients with D/EE-SWAS. Even while we acknowledge the need for stringent adherence to a global standard for D/EE-SWAS trials, we cannot lose sight of the individual patient. The large heterogeneity in etiology and presenting symptoms will often necessitate a tailored approach to treatment. Just as clinically relevant outcomes are not identical for all patients, neither can there be a one-size-fits-all treatment.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eplepsyres.2023.107278.

References

Aeby, A., Poznanski, N., Verheulpen, D., Wetzburger, C., Van Bogaert, P., 2005. Levetiracetam efficacy in epileptic syndromes with continuous spikes and waves during slow sleep: experience in 12 cases. Epilepsia 46, 1937–1942.

Altunel, A., Altunel, E.O., Sever, A., 2017a. Response to adrenocorticotropic in attention deficit hyperactivity disorder-like symptoms in electrical status epilepticus in sleep syndrome is related to electroencephalographic improvement: a retrospective study. Epilepsy Behav. 74, 161–166.

Altunel, A., Sever, A., Altunel, E.O., 2017b. ACTH has beneficial effects on stuttering in ADHD and ASD patients with ESES: a retrospective study. Brain Dev. 39, 130–137.

Arhan, E., Serdaroglu, A., Aydin, K., Hirfanoglu, T., Soysal, A.S., 2015. Epileptic encephalopathy with electrical status epilepticus: an electroclinical study of 59 patients. Seizure 26, 86–93.

Baumer, F.M., McNamara, N.A., Fine, A.L., Pestana-Knight, E., Shellhaas, R.A., He, Z., Arndt, D.H., Gaillard, W.D., Kelley, S.A., Nagan, M., Ostendorf, A.P., Singhal, N.S., Speltz, L., Chapman, K.E., 2021. Treatment practices and outcomes in continuous spike and wave during slow wave sleep: a multicenter collaboration. J. Pedia 232, 220–228 e223.

Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, J.H., van Emde Boas, W., Engel, J., French, J., Glauser, T.A., Mathern, G.W., Moshe, S.L., Nordli, D., Plouin, P., Scheffer, I.E., 2010. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on Classification and Terminology, 2005-2009. Epilepsia 51, 676–685.

Bjørnaes, H., Bakke, K.A., Larsson, P.G., Heminghyt, E., Rytter, E., Brager-Larsen, L.M., Eriksson, A.S., 2013. Subclinical epileptiform activity in children with electrical status epilepticus during sleep: effects on cognition and behavior before and after treatment with levetiracetam. Epilepsy Behav. 27, 40–48.

Cao, D., Chen, Y., Liao, J., Nariai, H., Li, L., Zhu, Y., Zhao, X., Hu, Y., Wen, F., Zhai, Q., 2019. Scalp EEG high frequency oscillations as a biomarker of treatment response in epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS). Seizure 71, 151–157.

Caraballo, R.H., Cejas, N., Chamorro, N., Kaltenmeier, M.C., Fortini, S., Soprano, A.M., 2014. Landau-Kleffner syndrome: a study of 29 patients. Seizure 23, 98–104.

Caraballo, R.H., Fortini, S., Flesler, S., Pasteris, M.C., Caramuta, L., Portuondo, E., 2015. Encephalopathy with status epilepticus during sleep: unusual EEG patterns. Seizure 25, 117–125.

Caraballo, R.H., Cersosimo, R.O., Fortini, P.S., Ornella, L., Buompadre, M.C., Vilte, C., Princich, J.P., Fejerman, N., 2013a. Congenital hemiparesis, unilateral polymicrogyria and epilepsy with or without status epilepticus during sleep: a study of 66 patients with long-term follow-up. Epileptic Disord. 15, 417–427.

Caraballo, R.H., Veggiotti, P., Kaltenmeier, M.C., Piazza, E., Gamboni, B., Lopez Avaria, M.F., Noli, D., Adi, J., Cersosimo, R., 2013b. Encephalopathy with status epilepticus during sleep or continuous spikes and waves during slow sleep syndrome: a multicenter, long-term follow-up study of 117 patients. Epilepsy Res 105, 164–173.

Carvalho, D., Mendes, T., Dias, A.I., Leal, A., 2020. Interictal spike quantification in continuous spike-wave of sleep (CSWS): Clinical usefulness of a wearable EEG device. Epilepsy Behav. 104, 106902.

Chen, J., Cai, F., Jiang, L., Hu, Y., Feng, C., 2015. Levetiracetam efficacy in children with epilepsy with electrical status epilepticus in sleep. Epilepsy Behav. 44, 73–77.

Chen, J., Cai, F., Jiang, L., Hu, Y., Feng, C., 2016. A prospective study of dexamethasone therapy in refractory epileptic encephalopathy with continuous spike-and-wave during sleep. Epilepsy Behav. 55, 1–5.

Chen, X.Q., Zhang, W.N., Yang, Z.X., Zhao, M., Cai, F.C., Huang, S.P., Gao, L., Pang, B.D., Chen, X., Zou, L.P., 2014. Efficacy of levetiracetam in electrical status epilepticus during sleep of children: a multicenter experience. Pedia Neurol. 50, 243–249.

Chipaux, M., Szurhaj, W., Vercueil, L., Milh, M., Villeneuve, N., Cances, C., Auvin, S., Chassagnon, S., Napuri, S., Allaire, C., Derambure, P., Marchal, C., Caubel, I., Ricard-Mousnier, B., N'Guyen The Tich, S., Pinard, J.M., Bahi-Buisson, N., de Barace, C., Kahane, P., Gautier, A., Hamelin, S., Coste-Zeitoun, D., Rosenberg, S.D., Clerson, P., Nabbout, R., Kuchenbuch, M., Picot, M.C., Kaminska, A., Group, G., 2016. Epilepsy diagnostic and treatment needs identified with a collaborative database involving tertiary centers in France. Epilepsia 57, 757–769.

Degerliyurt, A., Yalnizoglu, D., Bakar, E.E., Topcu, M., Turanli, G., 2015. Electrical status epilepticus during sleep: a study of 22 patients. Brain Dev. 37, 250–264.

Fatema, K., Rahman, M.M., Begum, S., 2015. Characteristics and management of children with continuous spikes and waves during slow sleep. Mymensingh Med J. 24, 806–812.

Fejerman, N., Caraballo, R., Cersosimo, R., Ferraro, S.M., Galicchio, S., Amartino, H., 2012. Sulthiame add-on therapy in children with focal epilepsies associated with encephalopathy related to electrical status epilepticus during slow sleep (ESES). Epilepsia 53, 1156–1161.

Fortini, S., Corredera, L., Pastrana, A.L., Reyes, G., Fasulo, L., Caraballo, R.H., 2013. Encephalopathy with hemi-status epilepticus during sleep or hemi-continuous spikes and waves during slow sleep syndrome: a study of 21 patients. Seizure 22, 565–571.

Francois, D., Roberts, J., Hess, S., Probst, L., Eksioglu, Y., 2014. Medical management with diazepam for electrical status epilepticus during slow wave sleep in children. Pedia Neurol. 50, 238–242.

Gencpinar, P., Dundar, N.O., Tekgul, H., 2016. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: An electroclinical evaluation according to the EEG patterns. Epilepsy Behav. 61, 107–111.

Gong, P., Xue, J., Qian, P., Yang, H., Liu, X., Cai, L., Bian, K., Yang, Z., 2018. Scalp-recorded high-frequency oscillations in childhood epileptic encephalopathy with continuous spike-and-wave during sleep with different etiologies. Brain Dev. 40, 299–310.

Guerrini, R., Genton, P., Bureau, M., Parmeggiani, A., Salas-Puig, X., Santucci, M., Bonanni, P., Ambrosetto, G., Dravet, C., 1998. Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. Neurology 51, 504–512.

Hempel, A., Frost, M., Agarwal, N., 2019. Language and behavioral outcomes of treatment with pulse-dose prednisone for electrical status epilepticus in sleep (ESES). Epilepsy Behav. 94, 93–99.

Higgins, J.P., Altman, D.G., Gotzsche, P.C., Juni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A., Cochrane Bias Methods, G., Cochrane Statistical Methods, G., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343, d5928.

Incorpora, G., Pavone, P., Smilari, P.G., Trifiletti, R., Parano, E., 1999. Late primary unilateral thalamic hemorrhage in infancy: report of two cases. Neuropediatrics 30, 264–267.
Kanmaz, S., Simsek, E., Serin, H.M., Yilmaz, S., Aktan, G., Tekgul, H., Gokben, S., 2021. Sulthiame add-on treatment in children with epileptic encephalopathy with status epilepticus: an efficacy analysis in etiologic subgroups. Neurol. Sci. 42, 183–191.
Kelemen, A., Barsi, P., Gyorsok, Z., Sarac, J., Szucs, A., Halasz, P., 2006. Thalamic lesion and epilepsy with generalized seizures, ESES and spike-wave paroxysms–report of three cases. Seizure 15, 454–458.
Kersbergen, K.J., de Vries, L.S., Leijten, F.S., Braun, K.P., Nievelstein, R.A., Groenendaal, F., Benders, M.J., Jansen, F.E., 2013. Neonatal thalamic hemorrhage is strongly associated with electrical status epilepticus in slow wave sleep. Epilepsia 54, 733–740.
Kramer, U., Nevo, Y., Neufeld, M.Y., Fatal, A., Leitner, Y., Harel, S., 1998. Epidemiology of epilepsy in childhood: a cohort of 440 consecutive patients. Pedia Neurol. 18, 46–50.
Kramer, U., Sagi, L., Goldberg-Stern, H., Zelnik, N., Nissenkorn, A., Ben-Zeev, B., 2009. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). Epilepsia 50, 1517–1524.
Larsson, P.G., Bakke, K.A., Bjornaes, H., Heminghyt, E., Rytter, E., Brager-Larsen, L., Eriksson, A.S., 2012. The effect of levetiracetam on focal nocturnal epileptiform activity during sleep–a placebo-controlled double-blind cross-over study. Epilepsy Behav. 24, 44–48.
Maltoni, L., Posar, A., Parmeggiani, A., 2016. Long-term follow-up of cognitive functions in patients with continuous spike-waves during sleep (CSWS). Epilepsy Behav. 60, 211–217.
Monteiro, J.P., Roulet-Perez, E., Davidoff, V., Deonna, T., 2001. Primary neonatal thalamic haemorrhage and epilepsy with continuous spike-wave during sleep: a longitudinal follow-up of a possible significant relation. Eur. J. Paediatr. Neurol. 5, 41–47.
Moresco, L., Bruschettini, M., Calevo, M.G., Siri, L., 2020. Pharmacological treatment for continuous spike-wave during slow wave sleep syndrome and Landau-Kleffner Syndrome. Cochrane Database Syst. Rev. 11, CD013132.
Munn, Z., Barker, T.H., Moola, S., Tufanaru, C., Stern, C., McArthur, A., Stephenson, M., Aromataris, E., 2020. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evid. Synth. 18, 2127–2133.
Neurocrine Biosciences NCT04625101. Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects With Epileptic Encephalopathy With Continuous Spike-and-Wave During Sleep. ClinicalTrials.gov identifier: NCT04625101. Updated November 14, 2022. Accessed June 19, 2023. ⟨https://ClinicalTrials.gov/show/NCT04625101⟩.
Neurocrine Biosciences NCT05301894. Extension Study to Evaluate NBI-827104 in Pediatric Subjects With Epileptic Encephalopathy With Continuous Spike-and-Wave During Sleep. ClinicalTrials.gov identifier: NCT05301894. Updated January 23, 2023. Accessed June 19, 2023. ⟨https://clinicaltrials.gov/ct2/show/NCT05301894⟩.
Nickels, K., Wirrell, E., 2008. Electrical status epilepticus in sleep. Semin Pedia Neurol. 15, 50–60.
Northwell Health NCT04721691. ESES. ClinicalTrials.gov identifier: NCT04721691. Updated February 24, 2023. Accessed April 20, 2023. ⟨https://clinicaltrials.gov/show/NCT04721691⟩.
Oztoprak, U., Yayici Koken, O., Aksoy, E., Yuksel, D., 2021. Spike-wave index assessment and electro-clinical correlation in patients with encephalopathy associated with epileptic state during slow sleep (ESES / CSWS); single-center experience. Epilepsy Res 170, 106549.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hrobjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.
Patry, G., Lyagoubi, S., Tassinari, C.A., 1971. Subclinical "electrical status epilepticus" induced by sleep in children. A clinical and electroencephalographic study of six cases. Arch. Neurol. 24, 242–252.
Pera, M.C., Brazzo, D., Altieri, N., Balottin, U., Veggiotti, P., 2013. Long-term evolution of neuropsychological competences in encephalopathy with status epilepticus during sleep: a variable prognosis. Epilepsia 54 (Suppl 7), 77–85.
Raha, S., Shah, U., Udani, V., 2012. Neurocognitive and neurobehavioral disabilities in Epilepsy with Electrical Status Epilepticus in slow sleep (ESES) and related syndromes. Epilepsy Behav. 25, 381–385.
Sanchez Fernandez, I., Chapman, K.E., Peters, J.M., Harini, C., Rotenberg, A., Loddenkemper, T., 2013a. Continuous Spikes and Waves during Sleep: Electroclinical Presentation and Suggestions for Management. Epilepsy Res Treat. 2013, 583531.
Sanchez Fernandez, I., Chapman, K., Peters, J.M., Klehm, J., Jackson, M.C., Berg, A.T., Loddenkemper, T., 2014. Treatment for continuous spikes and waves during sleep (CSWS): survey on treatment choices in North America. Epilepsia 55, 1099–1108.
Sanchez Fernandez, I., Peters, J.M., An, S., Bergin, A.M., Takeoka, M., Rotenberg, A., Kothare, S.V., Riviello Jr., J.J., Loddenkemper, T., 2013b. Long-term response to high-dose diazepam treatment in continuous spikes and waves during sleep. Pedia Neurol. 49, 163–170 e164.
Sanchez Fernandez, I., Peters, J., Hadjiloizou, S., Prabhu, S.P., Zarowski, M., Stannard, K., Takeoka, M., Rotenberg, A., Kothare, S.V., Loddenkemper, T., 2012b. Clinical staging and electroencephalographic evolution of continuous spikes and waves during sleep. Epilepsia 53, 1185–1195.
Sanchez Fernandez, I., Hadjiloizou, S., Eksioglu, Y., Peters, J.M., Takeoka, M., Tas, E., Abdelmoumen, I., Rotenberg, A., Kothare, S.V., Riviello Jr., J.J., Loddenkemper, T., 2012a. Short-term response of sleep-potentiated spiking to high-dose diazepam in electric status epilepticus during sleep. Pedia Neurol. 46, 312–318.
Sanchez Fernandez, I.S., Chapman, K.E., Peters, J.M., Kothare, S.V., Nordli Jr., D.R., Jensen, F.E., Berg, A.T., Loddenkemper, T., 2013c. The tower of Babel: survey on concepts and terminology in electrical status epilepticus in sleep and continuous spikes and waves during sleep in North America. Epilepsia 54, 741–750.
Saraf, U.U., Asranna, A., Menon, R.N., Mohan, P.M., Vp, V., Radhakrishnan, A., Cherian, A., S, V.T., 2020. Predictors of one-year language and seizure outcomes in children with epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS). Seizure 81, 315–324.
Seegmüller, C., Deonna, T., Mayor Dubois, C., Valenti-Hirsch, M.-P., Hirsch, E., Metz-Lutz, M.-N., de Saint Martin, A., Roulet-Perez, E., 2012. Long-term outcome after cognitive and behavioral regression in nonlesional epilepsy with continuous spike-waves during slow-wave sleep. Epilepsia 53, 1067–1076.
Shafer, S.L., Dexter, F., 2012. Publication bias, retrospective bias, and reproducibility of significant results in observational studies. Anesth. Analg. 114, 931–932.
Sonnek, B., Doring, J.H., Mutze, U., Schubert-Bast, S., Bast, T., Balke, D., Reuner, G., Schuler, E., Klabunde-Cherwon, A., Hoffmann, G.F., Kolker, S., Syrbe, S., 2021. Clinical spectrum and treatment outcome of 95 children with continuous spikes and waves during sleep (CSWS). Eur. J. Paediatr. Neurol. 30, 121–127.
Specchio, N., Wirrell, E.C., Scheffer, I.E., Nabbout, R., Riney, K., Samia, P., Guerreiro, M., Gwer, S., Zuberi, S.M., Wilmshurst, J.M., Yozawitz, E., Pressler, R., Hirsch, E., Wiebe, S., Cross, H.J., Perucca, E., Moshe, S.L., Tinuper, P., Auvin, S., 2022. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia 63, 1398–1442.
Tassinari, C.A., Rubboli, G., 2006. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 47 (Suppl 2), 40–43.
Tenney, J.R., Glauser, T., 2017. Electroclinical Syndromes: Childhood Onset, in: Swaiman, K.F., et al. (Ed.), Pediatric Neurology: Principles and Practice Elsevier, Edinburgh, pp. 569–575.
Terney, D., Kolmel, M., Khinchi, P., Olsen, G.T., Nikanorova, M., Olofsson, K., Kjelgaard, B.D., Moller, S.R., Alving, J., Pavlidis, E., 2016. Clinico-neurophysiological and genetic features of ESES/CSWS in Denmark, Epilepsia. Wiley 111 River St, Hoboken 07030–5774, NJ USA, pp. 12–12.
Triplett, R.L., Asato, M.R., 2015. Brief cognitive and behavioral screening in children with new-onset epilepsy: a pilot feasibility trial. Pedia Neurol. 52, 49–55.
University Medical Center Utrecht (Netherlands). RESCUE ESES: a Randomized European trial of Steroids versus Clobazam Usage for Encephalopathy with Electrical Status Epilepticus in Sleep. ISRCTN Registry identifier: ISRCTN42686094. Updated January 2, 2021. Accessed January 12, 2022. ⟨https://www.isrctn.com/ISRCTN42686094⟩.
Van Bogaert, P., 2013. Epileptic encephalopathy with continuous spike-waves during slow-wave sleep including Landau-Kleffner syndrome. Handb. Clin. Neurol. 111, 635–640.
van den Munckhof, B., Alderweireld, C., Davelaar, S., van Teeseling, H.C., Nikolakopoulos, S., Braun, K.P.J., Jansen, F.E., 2018. Treatment of electrical status epilepticus in sleep: clinical and EEG characteristics and response to 147 treatments in 47 patients. Eur. J. Paediatr. Neurol. 22, 64–71.
van den Munckhof, B., van Dee, V., Sagi, L., Caraballo, R.H., Veggiotti, P., Liukkonen, E., Loddenkemper, T., Sanchez Fernandez, I., Buzatu, M., Bulteau, C., Braun, K.P., Jansen, F.E., 2015. Treatment of electrical status epilepticus in sleep: a pooled analysis of 575 cases. Epilepsia 56, 1738–1746.
Van Hirtum-Das, M., Licht, E.A., Koh, S., Wu, J.Y., Shields, W.D., Sankar, R., 2006. Children with ESES: variability in the syndrome. Epilepsy Res 70 (Suppl 1), S248–S258.
Veggiotti, P., Pera, M.C., Olivotto, S., De Giorgis, V., 2016. How to Manage Electrical Status Epilepticus in Sleep. J. Clin. Neurophysiol. 33, 3–9.
Vrielynck, P., Marique, P., Ghariani, S., Lienard, F., de Borchgrave, V., van Rijckevorsel, K., Bonnier, C., 2017. Topiramate in childhood epileptic encephalopathy with continuous spike-waves during sleep: A retrospective study of 21 cases. Eur. J. Paediatr. Neurol. 21, 305–311.
Wells, G.A., Shea B., O'Connell D., et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Accessed August 9, 2021. ⟨https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp⟩.
Wilson, R.B., Eliyan, Y., Sankar, R., Hussain, S.A., 2018. Amantadine: A new treatment for refractory electrical status epilepticus in sleep. Epilepsy Behav. 84, 74–78.
Wiwattanadittakul, N., Depositario-Cabacar, D., Zelleke, T.G., 2020. Electrical status epilepticus in sleep (ESES) - Treatment pattern and EEG outcome in children with very high spike-wave index. Epilepsy Behav. 105, 106965.
Yilmaz, S., Serdaroglu, G., Akcay, A., Gokben, S., 2014. Clinical characteristics and outcome of children with electrical status epilepticus during slow wave sleep. J. Pedia Neurosci. 9, 105–109.