Title

Treatment Practices and Outcomes in Continuous Spike and Wave during Slow Wave Sleep: A Multicenter Collaboration.

Authors

Baumer, Fiona
McNamara, Nancy
Fine, Anthony
et al.

Publication Date

2021-05-01

DOI

10.1016/j.jpeds.2021.01.032

Peer reviewed

HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

J Pediatr. 2021 May ; 232: 220–228.e3. doi:10.1016/j.jpeds.2021.01.032.

Treatment Practices and Outcomes in Continuous Spike and Wave During Slow Wave Sleep (CSWS): A Multicenter Collaboration

Fiona M. Baumer, MD[1], **Nancy A. McNamara, MD**[2], **Anthony L. Fine, MD**[3], **Elia Pestana-Knight, MD**[4], **Renée A. Shellhaas, MD**[2], **Zihuai He, PhD**[1], **Daniel H. Arndt, MD**[5], **William D. Gaillard, MD**[6], **Sarah A. Kelley, MD**[7], **Margot Nagan, MD**[8], **Adam P. Ostendorf, MD**[9], **Nilika S. Singhal, MD**[10], **Laura Speltz, MD**[11], **Kevin E. Chapman, MD**[8]

[1]Department of Neurology, Stanford University School of Medicine, Palo Alto, CA

[2]Department of Pediatrics, Michigan Medicine, University of Michigan, Ann Arbor, MI

[3]Department of Neurology, Divisions of Epilepsy & Child Neurology, Mayo Clinic, Rochester, MN

[4]Epilepsy Center, Cleveland Clinic Neurological Institute, Cleveland Clinic Lerner College of Medicine, Cleveland, OH

[5]Beaumont Children's, Oakland University William Beaumont School of Medicine, Royal Oak, MI

[6]Center for Neuroscience, Children's National Hospital, George Washington University, Washington, DC

[7]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD

[8]Department of Pediatrics & Neurology, University of Colorado, Aurora, CO

[9]Department of Pediatrics, Nationwide Children's Hospital, Ohio State University, Columbus, OH

[10]UCSF Weill Institute for Neurosciences, UCSF School of Medicine, San Francisco, CA

[11]Department of Neurology, University of Minnesota School of Medicine, Minneapolis, MN

Abstract

Objectives: To determine how Continuous Spike and Wave during Slow Wave Sleep (CSWS) is currently managed and to compare the effectiveness of current treatment strategies using a database from 11 pediatric epilepsy centers in the United States.

Study design: This retrospective study gathered information on baseline clinical characteristics, CSWS etiology, and treatment(s) in consecutive patients seen between 2014–2016 at 11 epilepsy referral centers. Treatments were categorized as benzodiazepines, steroids, other antiseizure medications (ASMs), or other therapies. Two measures of treatment response [clinical

Corresponding Author: Fiona M. Baumer, MD, 750 Welch Road, Ste. 317, Palo Alto, CA 94304, fbaumer@stanford.edu, P: 650-468-7535; F: 650-723-7299.

Conflicts of Interest: None. A segment of the results in this article was previously presented in poster format at the American Epilepsy Society National Meeting.

improvement as noted by the treating physician; and EEG improvement] were compared across therapies, controlling for baseline variables.

Results: Eighty-one children underwent 153 treatment trials during the study period (68 trials of benzodiazepines, 25 of steroids, 45 of ASMs, 14 of other therapies). Children most frequently received benzodiazepines (62%) or ASMs (27%) as first line therapy. Treatment choice did not differ based on baseline clinical variables, nor did these variables correlate with outcome. After adjusting for baseline variables, children had a greater odds of clinical improvement with benzodiazepines (OR 3.32, 95%CI 1.57–7.04, p=0.002) or steroids (OR 4.04, 95%CI 1.41–11.59, p=0.01) than with ASMs and a greater odds of EEG improvement after steroids (OR 3.36, 95% CI 1.09–10.33, p=0.03) than after ASMs.

Conclusions: Benzodiazepines and ASMs are the most frequent initial therapy prescribed for CSWS in the United States. Our data suggests that ASMs are inferior to benzodiazepines and steroids and support earlier use of these therapies. Multicenter prospective studies that rigorously assess treatment protocols and outcomes are needed.

Keywords

Electrical Status Epilepticus of Sleep; ESES; Landau-Kleffner Syndrome; LKS; pediatric; epilepsy; developmental regression

INTRODUCTION

Continuous spike and wave during slow wave sleep (CSWS) is an epilepsy syndrome in which abundant, sleep-potentiated spike waves cause neurocognitive and behavioral deficits. The condition was first recognized by Landau and Kleffner in the 1950s[1], but was more fully described by Tassinari in the 1970s.[2] Though CSWS has been studied for over 50 years, significant debate about the diagnostic criteria and terminology persists.[3] Necessary for the diagnosis is an electrographic pattern called electrical status epilepticus of sleep (ESES), in which spike waves substantially increase in frequency after the patient falls asleep and persist through non-REM sleep.[4] There is not consensus as to whether the ESES pattern seen in a child with cognitive difficulties is sufficient for the diagnosis or whether a history of frank developmental regression is required. Furthermore, diagnosis of the ESES pattern itself is not agreed upon. Most centers base the ESES diagnosis on the spike wave index (SWI) [percent of 1-second bins in non-REM sleep containing at least 1 spike][5], but the diagnostic cut-off is not set. Many centers use a SWI cut-off of at least 50–85%.[6]

Given the association of CSWS with potentially reversible neurodevelopmental disabilities, clinicians have tried multiple treatment modalities.[7] Yet, the ideal treatment approach to patients with ESES has not been established.[3] There are currently four primary treatment strategies: high-dose oral benzodiazepines given before sleep, steroids, other anti-seizure medications (ASMs), or epilepsy surgery.[8] Effectiveness of high-dose benzodiazepines was first reported in the 1970s,[2] and since then various formulations have been tried. Steroids have been given in oral and intravenous (IV) formulations, and other immune-modulating agents including ACTH and IVIG have been administered with varying success.[7] Of ASMs, valproic acid, ethosuximide, and levetiracetam are most commonly prescribed[7,9], but reports

on a variety of ASMs and other agents also exist.[10–12] Surgeries have typically included focal resection for cases of unilateral structural brain lesions (malformations or areas of injury)[13] or multiple subpial transections, a procedure that has fallen out of favor as it was shown to be ineffective at resolving CSWS or enhancing cognitive outcomes or quality of life.[14] In addition, the ketogenic diet has been studied in a number of CSWS patients with varying degrees of success.[15] (Please see Jansen et al. 2019 for a comprehensive review of the treatment literature.[7])

Despite this wide variety of treatment strategies[16], there are few data regarding comparative effectiveness. A pooled analysis of reported cases dating back to 1977 compared benzodiazepines, ASMs, steroids, and surgery.[8] The authors concluded that ASMs were significantly less effective than the other treatment categories (49% response rate), and that benzodiazepines (68% response) were less effective than steroids (81% response) and surgery (90% response). The results of this analysis must be interpreted with caution, however, as they are based only on published cases. Randomized trials or even carefully designed prospective observational studies for this condition are lacking.

Rigorous studies of CSWS treatment strategies are clearly needed, but effectively conducting trials for such a rare disease requires collaboration across multiple centers. The Pediatric Epilepsy Research Consortium (PERC) is a multicenter collaborative organization with multiple subgroups focused on different pediatric epilepsies.[17] The PERC CSWS study group is working to define the optimal treatment strategies for pediatric patients with a goal of conducting rigorous prospective comparative effectiveness research. We undertook this retrospective case series to obtain a representative picture of existing CSWS treatment practices and response to therapy across our centers to establish feasibility of a multicenter collaboration and inform sample size requirements for future prospective work .

METHODS

1. Sites & Sample Population:

This was a multicenter retrospective study, with eleven participating sites. The sites were tertiary epilepsy referral centers participating in the CSWS study group within the Pediatric Epilepsy Research Consortium. The study was approved by the Institutional Review Board at each site and informed consent was waived given the retrospective nature of the study. Children aged 2 to 18 years seen between 2014 to 2016 were included if they had a diagnosis of CSWS defined as sleep potentiated spiking causing a perceived or diagnosed clinical deficit. Each site was asked to enroll up to ten consecutive patients. A chart review for each eligible patient was completed at the patient's home institution. Study data were collected and managed using REDCap[18] electronic data capture tools hosted at University of Colorado Denver.

2. Clinical Data Collection:

Data were gathered on the following demographic and clinical variables: sex, race/ethnicity, epilepsy history (age of onset, seizure frequency, and prior ASM trials). We then collected data regarding CSWS diagnosis and management, including: age of diagnosis and age of

treatment initiation, history of developmental regression, putative etiology (e.g. structural, genetic, unknown), and EEG characteristics (initial SWI, follow-up SWI, and description of EEG characteristics). Many patients had tried more than one treatment; we gathered information for all therapies that had been initiated prior to 12/31/2016.

3. Coding of Demographic/Clinical Variables:

We coded race/ethnicity as a binary variable (White/Non-Hispanic vs. Other). We also converted several continuous variables to clinically-meaningful categories. Age of onset of epilepsy was coded as early (<3 years old) vs. late, and likewise CSWS onset was coded as early (<5 years old) or late. Three years of age is a typical cut-off used to define early life epilepsy.[19] The cut-off of five years for early onset CSWS was chosen based on prior literature[20,21] examining the impact of age of CSWS diagnosis on outcome; the cut-off was additionally motivated by statistical considerations as age five represented the 25th percentile for age at diagnosis among our patients. Prior exposure to ASMs for epilepsy was categorized as present or absent. Additionally, given concern that sodium channel blockers may provoke CSWS, we also classified prior exposure to ASMs more specifically as follows: clobazam, valproic acid, levetiracetam, sodium channel blockers (oxcarbazepine, carbamazepine, lamotrigine, lacosamide), topiramate/zonisamide, and other (ethosuximide, felbamate, perampanel, phenobarbital, runfinamide). Prior CSWS therapies were categorized by number of trials (0, 1, ≥2 trials). A delay in CSWS therapy was defined as a >6 month gap between diagnosis and treatment initiation. CSWS treatments were categorized as: (a) benzodiazepines (clobazam and oral diazepam), (b) steroids; (c) ASMs; and (d) other (including surgery, ketogenic diet, IVIG).

4. Definition and Coding of Outcomes:

Two primary outcome measures were defined a priori: (1) **clinical response to the *first* CSWS treatment**; and (2) **SWI response to the *first* CSWS treatment.** The clinical response was defined as clinical improvement in neurocognitive function, seizures, or the EEG after therapy as judged and documented in the medical record by the treating neurologist. The SWI response was defined by a 50% reduction in the sleep SWI when comparing the post- and pre-treatment EEGs. Fifteen of the 81 patients (18.5%) had their initial treatment for CSWS at a referring facility. We counted the first referring facility treatment as the “initial treatment,” to limit biasing our results with a significant proportion of known-refractory patients. We coded these patients’ first treatments as having failed from a clinical and SWI perspective as all 15 had persistent symptoms and an elevated SWI (mean 88+/−12%, range 53–100) at time of presentation to a participating epilepsy center.

Many patients underwent several sequential treatments for CSWS. To most fully capture these data, we determined: (1) **clinical response** (as judged by the evaluating neurologist); and (2) **the SWI response** (defined as a 50% reduction in the SWI between the post and pre-treatment EEGs) **to *each* individual treatment**.

5. Statistical Analysis:

Statistical analyses were performed using SAS University Edition (Cary, NC). We calculated descriptive statistics of the whole study sample as proportions. We then evaluated the

association between each demographic/clinical variable and the two outcomes (clinical and SWI response) using Fisher's exact test.

Our primary analysis focused on the association between each of the two outcomes (clinical and SWI response) and initial treatment. Specifically, we first fit a simple logistic regression to regress clinical/SWI response on the initial treatment and estimate the odds of responding to the treatment. To account for potential confounders, we conducted an additional analysis to fit a multivariable logistic model assessing treatment response, which adjusted for clinical variables associated with a poor prognosis that were identified via our analysis or review of the prior CSWS literature.[22]

Many patients went on to try additional therapies, either due to treatment failure or relapse. To fully utilize the available data, we carried out a secondary analysis to incorporate the additional measurements for more accurate point estimation and improved power. We estimated the odds of responding to a treatment by fitting a generalized estimating equation (GEE) with an exchangeable correlation matrix.[23] The GEE is a repeated-measure method that accounts for correlation within individuals who had undergone >1 CSWS treatment trial. We adjusted for the same covariates as used in the multivariable regression model and also adjusted for treatment order. Otherwise, the GEE model is consistent with our original multivariable regression model with the exception of containing additional data points.

RESULTS

1. Participation:

Eleven centers contributed data on 81 patients, with each site contributing between 2–10 patients to the database.

2. Clinical History:

Baseline information for all participants as well as for the study sample broken down by initial treatment choices is shown in Table 1. There were more males (43/81, 53%) than females (38/81, 47%) and there was a predominance of non-Hispanic Caucasian children (60/81, 76.9%) compared to other races or ethnicities (18/81, 23.1%). Demographic/clinical variables did not differ between the 15 patients initially treated at an outside institution vs. the 66 initially seen at one of the participating epilepsy centers (not shown).

2.1 Epilepsy History: Sixty-seven of 81 (83%) children had a pre-existing diagnosis of epilepsy with onset at a median of 3.0 years of age (IQR 1–5 years; range 0–10 years). The majority of children with epilepsy had frequent seizures, with 46/67 (69%) having at least monthly seizures and 16/67 (24%) having daily seizures; 5/67 (7.5%) children had only had a single seizure. Sixty-four children had taken at least one ASM prior to CSWS diagnosis, with a median of 1 (IQR 1–2) medications per treated patient. The most commonly prescribed ASMs prior to the CSWS diagnosis were levetiracetam in 32/81 (40%) and sodium channel blockers (including oxcarbazepine, carbamazepine, lamotrigine, and lacosamide) in 24/81 (30%); 3 children had tried more than one sodium channel blocker. Only 14/81 (17%) had tried valproic acid, 8/81 (9.9%) had tried topiramate/zonisamide,

and 5/81 (6.1%) had tried clobazam. None of the other clinically-available ASMs had been prescribed.

2.2 CSWS Diagnosis: The median age of diagnosis of CSWS was 6 years (IQR 5–7 years; range 2–13 years), on average 3 years after the first epilepsy diagnosis. Most patients had focal spikes (53/81; 65%) though 28/81 (35%) had generalized or a mixture of focal and generalized spikes on the diagnostic EEG. An approximately equal number of EEGs showed spikes with a left (33/81; 41%) or right (30/81; 37%) predominance, with 18/81 (22%) showing bilateral discharges. The SWI upon initial evaluation at the epilepsy center ranged from 33–100% with a median of 90% (IQR 85–95%), and 61/81 (75%) patients had a SWI >85% at presentation. Etiology of ESES was structural in 36/81 (44%) cases, genetic in 16/81 (20%), or unknown in 29/81 (36%). Structural causes included: stroke (7), hypoxic ischemic injury (7), polymicrogyria (4), prematurity/periventricular leukomalacia (3), thalamic injury (3), double cortex (2), temporal lobe abnormalities (mesial temporal sclerosis, volume loss) (2), dysplasia (2), meningoencephalitis (2), hydrocephalus (1), periventricular nodular heterotopia (1), and no specific cause recorded (2). Only 20/81 (25%) had baseline neurocognitive testing done as part of the diagnostic process.

3. Initial CSWS Treatment

3.1 Prescribing Practices and Timing: Most children (50/81; 62%) received a benzodiazepine as their first agent for CSWS while 22/81 (27%) received an ASM; only 5/81 (6.2%) received steroids and 4/81 (4.9%) underwent other treatments. Of the benzodiazepines, diazepam (36/50) was used more frequently than clobazam (14/50). Among the ASMs, children most often received valproic acid (8/22) or levetiracetam (6/22). Please see Table 2 (online) for a detailed break-down of initial treatment choice. There were no significant demographic or baseline clinical differences between children who received benzodiazepines, steroids, ASMs, or other treatments as their initial CSWS therapy (Table 1). Though not depicted in Table 1, initial CSWS treatment also did not differ depending on prior exposure to any specific ASM ($p>0.46$ for all ASMs). Sixty-four of 81 (79%) children began treatment for CSWS the same year as they were diagnosed, but initial treatment was delayed by 0.5–5 years for 17/81 patients (21%).

3.2 Factors Associated with Clinical Response: Fifty nine percent (48/81) of patients achieved a clinical response to the first treatment. Table 3 shows the relationship of baseline variables with clinical response. No demographic or clinical variables were significantly associated with clinical response. Though not depicted in Table 3, clinical response also did not differ depending on prior exposure to any specific ASM ($p>0.19$ for all comparisons).

3.3 Factors Associated with SWI Response: Only 35% (28/81) achieved an SWI response. As shown in Table 3, patients with a structural etiology of their CSWS were half as likely to have an SWI response (8/36; 22%) compared to those with a genetic or unknown cause (20/45; 44%) ($p=0.04$). Though not depicted in Table 3, those who had received valproic acid prior to the CSWS diagnosis showed a substantially lower SWI response: none of the 14 patients who had previously been treated with valproic acid achieved an

SWI response compared with 28/67 (42%) of patients who had not tried the medication (p=0.002). No other baseline variables were associated with SWI response.

3.4 Efficacy of Initial Treatment: Table 4 shows the unadjusted and adjusted logistic regression analyses modeling odds of a clinical or SWI response to the initial CSWS therapy. We adjusted for factors previously reported to be associated with a poor prognosis, including history of epilepsy, age of CSWS onset, delay in CSWS treatment, and etiology.[22] In both the unadjusted and adjusted models, medication choice was significantly associated with clinical response. Children initially prescribed benzodiazepines had a higher odds of clinical improvement than those prescribed ASMs (OR 6.10, 95%CI 2.04–18.27, p=0.001), and the odds of clinical response increased after adjusting for the aforementioned clinical factors (OR 9.11, 95%CI 2.61–31.83, p=0.0005). The odds of responding to steroids was over four times that of responding to other ASMs, but as so few children had tried steroids initially, this estimation was imprecise and the result was not statistically significant (adjusted OR 4.24, 95%CI 0.47–38.17, p=0.41). Response to other treatments (adjusted OR 0.87, 95%CI 0.06–11.74, p=0.98) did not differ from response to other ASMs. There was no significant association between any treatment choice and SWI response (p>0.38 for unadjusted and p>0.20 for adjusted comparisons).

4. All CSWS Treatments

4.1 Prescribing Practices: Across the 81 participants, clinical response data were available for 152 individual treatments trials while SWI response data were available for 153. Children underwent a median of 2.0 treatments (IQR 1–3 treatments, range 1–5 treatments); this excludes prior ASM used specifically for epilepsy but not for CSWS. By the end of the study, 68/81 (84%) of children had tried a benzodiazepine, 25/81 (32%) had tried a steroid, 45/81 (56%) had tried an ASM, and 14/81 (17%) had tried another treatment (such as surgery or the ketogenic diet). Table 2 (online) reviews the treatments used by this cohort and the response to these therapies.

4.2 Factors Associated with Clinical Response: Fifty one percent (77/152) of all treatment trials led to a clinical response. There were no significant associations between the baseline variables and clinical response.

4.3 Factors Associated with SWI Response: Thirty three percent (51/153) of treatment trials produced an SWI response. Several baseline variables were associated with an SWI response (Table 5; online). Structural etiology was associated with a lower odds of SWI response (OR 0.27, 95%CI 0.12–0.63, p=0.002), as was a prior history of epilepsy (OR 0.33, 95%CI 0.14–0.77, p=0.01). Children were also more likely to have an SWI response to the second vs. first CSWS treatment (OR 2.01, 95% CI 1.13–3.56, p=0.02).

4.4 Efficacy of All Treatments: Table 6 shows the unadjusted and adjusted logistic regression analyses modeling the odds of clinical and SWI response to treatment when considering all treatments. We adjusted for the same clinical variables as in Table 4 (history of epilepsy, age of CSWS onset, delay in CSWS treatment, and etiology) and additionally adjusted for treatment order. In both the unadjusted and adjusted models, treatment choice

was associated with clinical response, with benzodiazepines associated with a significantly higher odds of response than treatment with ASMs (adjusted OR 3.32, 95%CI 1.57–7.04, p=0.002). Similar to the model of initial treatment response, this model showed that the odds of clinical response to steroids was four times that of response to ASMs, but with the larger sample size, the difference was now statistically significant (adjusted OR 4.04, 95%CI 1.41–11.59, p=0.01). Additionally, this model demonstrated a greater odds of SWI response with steroids than with ASMs (adjusted OR 3.36, 95%CI 1.09–10.33, p=0.03).

DISCUSSION

This retrospective multicenter study of consecutively treated CSWS patients was undertaken to determine current treatment practices across a variety of pediatric epilepsy centers in the United States in order to evaluate the feasibility of a larger prospective comparative effectiveness study. The demographic and clinical characteristics (including age of onset, CSWS etiology, and history of epilepsy) of our cohort are in line with what has previously been reported[8,22,24], suggesting that our sample is fairly representative of the CSWS population. We identify that there is a relative consensus among treatment choices. While the majority of patients first receive a benzodiazepine, a sizeable minority receive one of several ASMs and very few first receive steroids. Choice of treatment was not obviously driven by patients' demographic or clinical variables, which suggests that initial therapy may reflect provider preference or experience rather than specific patient characteristics. In agreement with prior literature,[8,24,25] we find that benzodiazepines and steroids are more effective against CSWS than ASMs. Though we restricted enrollment from some of the largest centers, it is still notable that there were only 81 subjects over a two year window, supporting that CSWS is a rare condition. Taken together, these results suggest that adequately powered comparative effectiveness studies will require multicenter collaboration in which participating centers first standardize their benzodiazepine, ASM and steroids treatment regimens (defining a specific agent, dose, and duration of treatment). Furthermore, we must address the hesitancy to prescribe steroids as the initial treatment. If participating sites can not agree to randomize among the three regimens, than study design must account for the fact that steroids are typically prescribed after failure of the first agent. In contrast to the relatively uniform treatment preferences that currently exist across our centers, there is lack of consistency in how treatment response is measured. To conduct meaningful prospective research and improve outcomes, the pediatric epilepsy community also needs to develop and uniformly adopt consensus guidelines regarding the diagnosis and evaluation of outcomes for children with CSWS.

The treatments prescribed in our cohort are in keeping with survey results from a group of predominantly North American physicians; 205 of the 219 respondents practiced in the United States or Canada.[3] In our cohort, slightly more patients were initially prescribed benzodiazepines than suggested by the survey (62% vs. 47%) and fewer were prescribed ASMs (23% vs. 38%) and steroids (6% vs. 15%). In contrast, preferences for initial CSWS therapy appear to differ elsewhere in the world. A consecutive case series of 47 patients treated in the Netherlands showed that while benzodiazepines were still the most frequently prescribed (45%), children were more likely to receive steroids (30%) and less like to receive ASMs (21%).[24] Multicenter consecutive case series from Brazil and

Chile reported that ASMs are typically first line therapy for CSWS[26] and Landau-Kleffner Syndrome[27] in South America. These regional differences in prescribing practices could create the opportunity for a "natural experiment" of treatment effects if baseline clinical variables could be reliably measured and adjusted for across patients and if reliable outcome measurements could be gathered across sites to enable a robust observational comparative effectiveness design.

Our study highlights a need for better defined methods to assess the impact of treatment on CSWS. Controversy remains as to whether treatment response should be measured as a function of neurocognitive/behavioral improvement, electrographic improvement, or both. Children in our cohort were more likely to achieve a clinical than SWI response. This clinical-electrographic discrepancy may be due to the fact that outcome variables were dichotomized and the SWI response criteria may be more stringent than the clinical response criteria. While our SWI response criteria of 50% reduction was based on prior literature[28,29] and allowed us to account for variability in SWI at diagnosis, it is not clear what change in SWI is necessary for clinical improvement (or if this is consistent across patients). A second explanation is that clinical response was based on subjective, unblinded assessments, and therefore was prone to bias that may differ across therapies, providers, or study sites. While ideally we would have used standardized neurocognitive testing, only 25% of children had such baseline testing. Several challenges interfere with obtaining more rigorous clinical assessments. First, it is not logistically or financially feasible to obtain full neurocognitive testing before initiation of therapy, nor to assess each therapy with a full battery. Tailored assessments would improve feasibility, but it is not clear which neuropsychometric assessments best capture the impact of CSWS on cognition and behavior as patients can be affected in multiple domains.[30] Domain-specific assessments will likely be needed to truly capture improvements. Prospective treatment trials will require close collaboration with multi-stakeholder teams that include parents, neuropsychologists, and epileptologists to identify and validate robust clinical outcome measures relevant to CSWS and to determine if such measures fluctuate with SWI.

We additionally find that ASMs are less effective than benzodiazepines for achieving a clinical response and less effective than steroids for achieving a clinical or SWI response. Outcomes after benzodiazepines and steroid therapy did not significantly differ. Two other studies have directly compared the efficacy of CSWS treatments. A meta-analysis analyzing 950 treatments in 575 patients found that benzodiazepines, steroids, and surgery were all more effective than ASMs in achieving "any improvement" (improvement in EEG and/or cognition).[8] Steroids (75%) and surgery (93%) were also more effective than benzodiazepines (59%). A single European epilepsy center also reported their experience with 147 treatments in 47 patients seen over 11 years[24] and found that steroids were superior to other therapies (benzodiazepines, ASMs, surgery, IVIG) in achieving cognitive improvement. Our findings that ASMs are less effective align with these prior results, but we do not find strong evidence for superiority of steroids over benzodiazepines. This discrepancy could be explained by selection bias due to differential prescribing patterns in the United States and Europe; it is possible that patients who are most likely to recover respond to whichever treatment they receive first. Arguing against this, however, is the fact that our patients were not more likely to respond to their initial therapy. A second possibility

is that efficacy depends on specific steroid protocol: in our cohort, all but two patients received oral prednisone or prednisolone, whereas the majority of patients in the European study[24] received intravenous, pulse-dose methylprednisolone.

While we did not identify any baseline variables that predict clinical response, we did find that structural etiology, history of epilepsy, and prior use of valproic acid are associated with a reduced odds of SWI response (Table 3 and Table 5; online). Other authors have identified structural etiology as a risk factor for worse outcomes. One study[31] found that only 20% of children with a structural etiology vs. 66% in the idiopathic group (defined as atypical Rolandic or Landau-Kleffner Syndrome) returned to pre-CSWS cognitive levels. A second study[26] reported generally more favorable cognitive outcomes but still found a discrepancy between those with a structural etiology (with 75% returning to baseline) vs. those with a genetic or unknown etiology (100% returning to baseline). Importantly, only 4 of the 36 patients with structural etiology in our cohort underwent epilepsy surgery and 3 of these had *both* a clinical and SWI response. In comparison, 53% of the structural group as a whole achieved a clinical response and only 22% achieved an SWI response. Our data support recommendations made by prior authors that epilepsy surgery evaluation should be considered for children with CSWS caused by unilateral brain lesions amenable to resection.[32] We additionally considered whether prior treatment with specific ASMs would be related to treatment outcome, as there have been multiple reports[33–35] of sodium channel blockers inducing CSWS. We did not find improved outcomes in those with prior exposure to sodium channel blockers, as might be expected if CSWS was truly drug-induced and reversible, but did find that none of the children with prior exposure to valproic acid achieved an SWI response. We speculate that this may be due to the fact that valproic acid typically suppresses spikes[36] and hence diagnosis of CSWS even while taking this medication is prognostic of refractory disease. Alternatively, this may indicate that valproic acid is not as effective for CSWS as it is for generalized epilepsies.

Though our study provides important results from a multicenter consortium of US pediatric epilepsy centers, some limitations merit consideration. The CSWS etiologies were classified coarsely as structural or genetic/unknown. A range of structural lesions – including cortical malformations, vascular insults, and thalamic injury – have been associated with CSWS.[9] Genetic causes are also increasingly identified but we did not mandate a specific protocol for genetic testing in this cohort of patients. In addition to the well-described association with GRIN2A mutations, more than 20 other genetic variants have now been associated with the CSWS phenotype.[37] Categorizing our cohort into structural vs. genetic/unknown etiologies therefore obscures subtleties that may influence treatment response. Additionally, given the retrospective nature of this study, we could not pre-specify treatment dose, treatment duration, or the time between treatment initiation and follow-up assessment. Such factors may influence assessment of treatment efficacy, especially since CSWS can be a relapsing-remitting condition. Finally, the fact that sample size is a limitation even in our multicenter cohort highlights that prospective and sustained collaboration between sites will be necessary to adequately study this rare disorder. This is in line with compelling recent arguments for national and international registries to advance pediatric epilepsy care.[38]

CONCLUSIONS

CSWS is a complex epilepsy syndrome with multiple etiologies and variable clinical manifestations. Little agreement exists about diagnosis, treatment, or objective outcome measures. We find that patients in the United States epilepsy centers typically received either benzodiazepines or ASMs as the initial treatment for CSWS and were rarely prescribed steroids or other therapies. As has been suggested previously[8,24], ASMs seem to be inferior to benzodiazepines and steroids. We conclude that to develop evidence-based treatment protocols for children with CSWS, we must first work to standardize initial assessments (especially of baseline cognitive function), treatment protocols, and clinically-relevant outcome measures. Development of national guidelines addressing these issues would allow for robust comparison across treatments and would set the stage for much-needed prospective treatment trials.

ACKNOWLEDGEMENTS

We would like to acknowledge the following physicians and research assistants who also contributed patient data to this study: Tobias Loddenkemper, MD of Boston Children's Hospital and Aliza L. Khuhro of the Ohio State University. TL discloses that he serves on the Council of the American Clinical Neurophysiology Society, as founder and consortium PI of the pediatric status epilepticus research group (pSERG), as an Associate Editor for Wyllie's Treatment of Epilepsy 6th edition and 7th editions (Wolters Kluwer), and as a member of the NORSE Institute, and CCEMRC. He served as Associate Editor of Seizure (Elsevier), and served on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, and American Board of Clinical Neurophysiology in the past. He has several patent applications for detection and prediction of clinical outcomes and seizures and is a co-inventor of the TriVox Health technology, for which he may be compensated in the future. He received research support from the Epilepsy Research Fund, NIH, CIMIT/DoD, PCORI, the Epilepsy Foundation of America, the American Epilepsy Society, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, the Danny Did Foundation, Cure, the HHV6 Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sunovion, Sage, Empatica, Acorda, and Pfizer, including past device donations from various companies, including Empatica, SmartWatch, and Neuro-electrics. In the past, he served as a consultant for Eisai, Lundbeck, UCB, Amzell, Sunovion, Upsher Smith and Zogenix. He has received speaker honorariums/Grand Round travel support from national/international societies and national/international academic centers and several trainees received salary support from international foundations/societies and academic centers while working in his laboratory.

Funding:

The authors are supported by the National Institutes of Health (1K23NS116110 to FMB; R21NS109669, R01DC016902, & U54HD090257 to WBG; RO1HL147261 & RO1NS111166 to RAS), the National Science Foundation (1532061 to WBG), the Pediatric Epilepsy Research Foundation (to WBG, APO, and RAS), PCORI (to RAS), PCORnet (to WBG), and the University of Michigan (to RAS). Dr. Shellhaas serves as a consultant for the Epilepsy Study Consortium, receives honoraria from UpToDate, and is Associate Editor for *Neurology*. Dr. Gaillard is the current president of the American Epilepsy Society.

REFERENCES

1. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. Neurology. 1957 Aug;7:523–30. [PubMed: 13451887]
2. Patry G, Lyagoubi S, Tassinari CA. Subclinical "Electrical Status Epilepticus" Induced by Sleep in Children: A Clinical and Electroencephalographic Study of Six Cases. Arch Neurol. 1971 Mar;24:242–52. [PubMed: 5101616]
3. Fernández IS, Chapman KE, Peters JM, Kothare SV, Nordli DR, Jensen FE, et al. 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. 2013 Apr;54:741–50. [PubMed: 23163318]

4. Tassinari CA, Rubboli G. Encephalopathy related to Status Epilepticus during slow Sleep: current concepts and future directions. Epileptic Disord. 2019 Jun 1;21:82–7. [PubMed: 31180330]
5. Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: From a single spike to electrical status epilepticus during sleep. Epilepsia. 2006 Nov;47:40–3. [PubMed: 17105458]
6. Kotagal P Current status of treatments for children with electrical status in slow-wave sleep (ESES/CSWS). Epilepsy Curr. 2017 Jul 1;17:214–6. [PubMed: 29225521]
7. Jansen FE, Nikanorova M, Peltola M. Current treatment options for Encephalopathy related to Status Epilepticus during slow Sleep. Epileptic Disord. 2019 Jun 1;21:S76–81.
8. van den Munckhof B, van Dee V, Sagi L, Caraballo RH, Veggiotti P, Liukkonen E, et al. Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases. Epilepsia. 2015 Nov 1;56:1738–46. [PubMed: 26337159]
9. Sánchez Fernández I, Loddenkemper T, Peters JM, Kothare SV. Electrical status epilepticus in sleep: clinical presentation and pathophysiology. Pediatr Neurol. 2012 Dec;47:390–410. [PubMed: 23127259]
10. Fine AL, Wirrell EC, Wong-Kisiel LC, Nickels KC. Acetazolamide for electrical status epilepticus in slow-wave sleep. Epilepsia. 2015 Sep 1;56:e134–8. [PubMed: 26230617]
11. Wilson RB, Eliyan Y, Sankar R, Hussain SA. Amantadine: A new treatment for refractory electrical status epilepticus in sleep. Epilepsy Behav. 2018 Jul 1;84:74–8. [PubMed: 29754107]
12. Vrielynck P, Marique P, Ghariani S, Lienard F, de Borchgrave V, van Rijckevorsel K, et al. Topiramate in childhood epileptic encephalopathy with continuous spike-waves during sleep: A retrospective study of 21 cases. Eur J Paediatr Neurol. 2017 Mar 1;21:305–11. [PubMed: 27641809]
13. Loddenkemper T, Cosmo G, Kotagal P, Haut J, Klaas P, Gupta A, et al. Epilepsy Surgery in Children with Electrical Status Epilepticus in Sleep. Neurosurgery. 2009 Feb;64:328–37. [PubMed: 19190460]
14. Downes M, Greenaway R, Clark M, Helen Cross J, Jolleff N, Harkness W, et al. Outcome following multiple subpial transection in Landau-Kleffner syndrome and related regression. Epilepsia. 2015 Nov;56:1760–6. [PubMed: 26337264]
15. Kelley SA, Kossoff EH. How effective is the ketogenic diet for electrical status epilepticus of sleep? Epilepsy Research. 2016 Nov; 127: 339–43. [PubMed: 27710878]
16. Moeller F, Moehring J, Ick I, Steinmann E, Wolff S, Jansen O, et al. EEG-fMRI in atypical benign partial epilepsy. Epilepsia. 2013 Aug;54:e103–8. [PubMed: 23758518]
17. Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015 Apr;56:617–25. [PubMed: 25779538]
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42:377–81. [PubMed: 18929686]
19. Berg AT, Wusthoff C, Shellhaas RA, Loddenkemper T, Grinspan ZM, Saneto RP, et al. Immediate outcomes in early life epilepsy: A contemporary account. Epilepsy Behav. 2019 Aug 1;97:44–50. [PubMed: 31181428]
20. Bishop DVM. Age of Onset and Outcome in “Acquired Aphasia with Convulsive Disorder” (Landau-Kleffner Syndrome). Dev Med Child Neurol. 1985 Dec;27:705–12. [PubMed: 2419188]
21. Scholtes FBJ, Hendriks MPH, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. Epilepsy Behav. 2005 Mar 1;6:167–73. [PubMed: 15710299]
22. Nickels K, Wirrell E. Electrical status epilepticus in sleep. Semin Pediatr Neurol. 2008 Jun;15:50–60. [PubMed: 18555191]
23. Zeger S, Liang K. Longitudinal Data Analysis for Discrete and Continuous Outcomes. Biometrics. 1986 Mar;42:121–30. [PubMed: 3719049]
24. van den Munckhof B, Alderweireld C, Davelaar S, van Teeseling HC, Nikolakopoulos S, Braun KPJ, et al. Treatment of electrical status epilepticus in sleep: Clinical and EEG characteristics and response to 147 treatments in 47 patients. Eur J Paediatr Neurol. 2018 Jan 1;22:64–71. [PubMed: 29128194]

25. Wiwattanadittakul N, Depositario-Cabacar D, Zelleke TG. Electrical status epilepticus in sleep (ESES) — Treatment pattern and EEG outcome in children with very high spike–wave index. Epilepsy Behav. 2020 Apr 1;105.
26. Caraballo RH, Veggiotti P, Kaltenmeier MC, Piazza E, Gamboni B, Lopez Avaria MF, et al. 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. 2013 Jul;105:164–73. [PubMed: 23507330]
27. Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau–Kleffner syndrome: A study of 29 patients. Seizure. 2014 Feb;23:98–104. [PubMed: 24315829]
28. De Negri M, Baglietto MG, Battaglia FM, Gaggero R, Pessagno A, Recanati L. Treatment of electrical status epilepticus by short diazepam (DZP) cycles after DZP rectal bolus test. Brain Dev. 1995 Sept-Oct;17:330–3. [PubMed: 8579219]
29. Francois D, Roberts J, Hess S, Probst L, Eksioglu Y. Medical management with diazepam for electrical status epilepticus during slow wave sleep in children. Pediatr Neurol. 2014 Mar;50:238–42. [PubMed: 24393416]
30. Raha S, Shah U, Udani V. Neurocognitive and neurobehavioral disabilities in Epilepsy with Electrical Status Epilepticus in slow sleep (ESES) and related syndromes. Epilepsy Behav. 2012 Nov;25:381–5. [PubMed: 23103314]
31. Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granström ML, et al. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. Epilepsia. 2010 Oct;51:2023–32. [PubMed: 20477851]
32. Loddenkemper T, Fernández IS, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. J Clin Neurophysiol. 2011 Apr;28:154–64. [PubMed: 21399511]
33. Marescaux C, Hirsch E, Finck S, Maquet P, Schlumberger E, Sellal F, et al. Landau-Kleffner Syndrome: A Pharmacologic Study of Five Cases. Epilepsia. 1990 Nov-Dec;31:768–77. [PubMed: 1700953]
34. Cerminara C, Montanaro ML, Curatolo P, Seri S. Lamotrigine-induced seizure aggravation and negative myoclonus in indiopathic rolandic epilepsy. Neurology. 2004 Jul 27;63:373–5. [PubMed: 15277643]
35. Pavlidis E, Rubboli G, Nikanorova M, Kölmel M, Gardella E. Encephalopathy with status epilepticus during sleep (ESES) induced by oxcarbazepine in idiopathic focal epilepsy in childhood. Funct Neurol. 2015 Apr-Jun;30:139–41. [PubMed: 26415787]
36. Duncan JS. Antiepileptic Drugs and the Electroencephalogram. Epilepsia. 1987 May-Jun;28:259–66. [PubMed: 2884097]
37. Kessi M, Peng J, Yang L, Xiong J, Duan H, Pang N, et al. Genetic etiologies of the electrical status epilepticus during slow wave sleep: Systematic review. BMC Genet. 2018 Jul 6;19:40. [PubMed: 29976148]
38. Berg AT, Goldman S. Getting serious about the early-life epilepsies: Lessons from the world of pediatric oncology. Neurology. 2018 May1;90:842–8. [PubMed: 29618625]

J Pediatr. Author manuscript; available in PMC 2022 May 01.

Table 1:

Demographic and Clinical Variables and Relationship with Initial Medication Choice

Patient Factors	Total (n=81) n (%)	ASM (n=22) n (%)	Benzos (n=50) n (%)	Steroids (n=5) n (%)	Other (n=4) n (%)	p
DEMOGRAPHIC						
Gender						0.59
Male	43 (53)	10 (46)	27 (54)	4 (80)	2 (50)	
Female	38 (47)	12 (55)	23 (46)	1 (20)	2 (50)	
Race/Ethnicity						0.34
White/Non-Hispanic	60 (77)	14 (64)	39 (81)	4 (80)	3 (75)	
Other	18 (23)	8 (36)	9 (19)	1 (20)	0 (0)	
EPILEPSY HISTORY						
Prior History of Epilepsy						0.32
Yes	67 (83)	17 (77)	43 (86)	3 (60)	4 (100)	
No	14 (17)	5 (23)	7 (14)	2 (40)	0 (0)	
Age of Epilepsy Onset *						0.12
< 3 years	29 (43)	11 (65)	15 (36)	2 (67)	1 (25)	
≥ 3 years	38 (57)	6 (35)	28 (65)	1 (33)	3 (75)	
Seizure Frequency *						0.74
Rare (<Monthly)	21 (31)	4 (24)	14 (33)	1 (33)	2 (50)	
Frequent (>Monthly)	46 (69)	13 (77)	29 (67)	2 (67)	2 (50)	
Prior ASM Use						0.40
No	17 (21)	6 (27)	9 (18)	2 (40)	0 (0)	
Yes	64 (79)	16 (72)	41 (82)	3 (60)	4 (100)	
CSWS CLINICAL HISTORY						
Age of CSWS Onset						0.51
< 5 years	18 (22)	5 (22)	10 (20)	1 (20)	2 (50)	
≥ 5 years	63 (78)	17 (77)	40 (80)	4 (80)	2 (50)	
Developmental Regression						0.85
Yes	50 (65)	14 (70)	30 (61)	4 (80)	2 (67)	
No	27 (35)	6 (30)	19 (39)	1 (20)	1 (33)	

Patient Factors	Total (n=81) n (%)	ASM (n=22) n (%)	Benzos (n=50) n (%)	Steroids (n=5) n (%)	Other (n=4) n (%)	p
CSWS Etiology						0.26
Unknown/Genetic	45 (56)	16 (73)	25 (50)	2 (40)	2 (50)	
Structural	36 (44)	6 (27)	25 (50)	3 (60)	2 (50)	
Time to Initial Treatment						0.78
< 6 months	64 (79)	19 (86)	38 (76)	4 (80)	3 (75)	
> 6 months	17 (21)	3 (14)	12 (24)	1 (20)	1 (25)	
CSWS EEG DATA						
SWI at Diagnosis [#]						0.16
< 85%	20 (25)	3 (14)	15 (30)	0 (0)	2 (50)	
> 85%	61 (75)	19 (86)	35 (70)	5 (100)	2 (50)	
CSWS Spike Type						0.84
Focal	53 (65)	15 (68)	32 (64)	4 (80)	2 (50)	
Generalized	7 (8.6)	3 (14)	4 (8.0)	0 (0)	0 (0)	
Both	21 (26)	4 (18)	14 (28)	1 (20)	2 (50)	
CSWS Spike Laterality						0.10
Left	33 (41)	7 (32)	25 (50)	1 (20)	0 (0)	
Right	30 (37)	8 (36)	15 (30)	4 (8.0)	3 (75)	
Bilateral	18 (22)	7 (32)	10 (20)	0 (0)	1 (25)	

Benzos = Benzodiazepines. Missing Data (n): Race/Ethnicity (3); Developmental Regression (4).

[*] Proportions for Age of Epilepsy Onset and Seizure Frequency are taken from 67 subjects diagnosed with epilepsy rather than 81 subjects in cohort.

[#] SWI is calculated from the first EEG from a participating epilepsy center. Sensitivity analysis considering only the 66 subjects first diagnosed at a participating epilepsy center also shows no significant difference across treatment groups (p=0.59).

Table 2:

Use and Success of Specific CSWS Treatments

Treatment	First CSWS Treatment			All CSWS Treatments		
	1st Treatment (n,%)	Clinical Response (n, %)	SWI Response (n, %)	Ever Tried (n,%)	Clinical Response (n, %)	SWI Response (n, %)
Antiepileptic Drugs (all)	**22 (27)**	**7 (32)**	**6 (27)**	**45 (56)**	**11 (24)**	**9 (20)**
Levetiracetam	6 (7.4)	2 (33)	2 (33)	8 (8.9)	2 (25)	2 (25)
Valproic Acid	8 (9.9)	3 (38)	3 (38)	16 (20)	6 (38)	4 (25)
Topiramate or Zonisamide	2 (2.5)	0 (0)	0 (0)	4 (4.9)	0 (0)	0 (0)
Sodium Channel Blockers	2 (2.5)	2 (100)	1 (50)	7 (8.6)	2 (29)	2 (29)
Other	4 (4.9)	0 (0)	0 (0)	10 (12)	1 (10)	1 (10)
Benzodiazepines (all)	**50 (62)**	**37 (74)**	**19 (38)**	**68 (84)**	**44 (65)**	**24 (35)**
Diazepam	36 (44)	25 (69)	15 (42)	42 (52)	30 (71)	18 (43)
Clobazam	14 (17)	12 (86)	4 (29)	26 (32)	14 (54)	6 (23)
Steroids	**5 (6.2)**	**3 (60)**	**2 (40)**	**25 (32)**	**14 (56)**	**6 (24)**
Other Treatments (all)	**4 (4.9)**	**1 (1.2)**	**1 (1.2)**	**14 (17)**	**5 (36)**	**3 (21)**
Epilepsy Surgery	1 (1.2)	1 (100)	1 (100)	4 (4.9)	3 (75)	3 (75)
Other Treatments	3 (3.7)	0 (0)	0 (0)	5 (6.2)	1 (20)	0 (0)
Ketogenic Diet	0	n/a	n/a	4 (4.9)	1 (25)	0 (0)

The percent who initially or ever tried a treatment is based on the percent of all 81 patients in the sample. The Clinical and SWI Response percentages are derived from the total number of patients who tried a given treatment.

Table 3:

Baseline Characteristics Associated with Response to Initial Treatment

Variable	Clinical Response			SWI Response		
	Response (n=48) n (%)	Non-response (n=33) n (%)	p	Response (n=28) n (%)	Non-response (n=53) n (%)	p
DEMOGRAPHIC						
Gender			0.50			0.69
Male	24 (56)	19 (44)		14 (33)	29 (67)	
Female	24 (63)	14 (37)		14 (37)	24 (63)	
Race/Ethnicity			0.15			0.48
White/Non-Hispanic	38 (63)	22 (37)		18 (30)	42 (70)	
Other	8 (44)	10 (56)		7 (39)	11 (61)	
EPILEPSY HISTORY						
Prior History of Epilepsy			0.31			0.47
Yes	38 (57)	29 (43)		22 (33)	45 (67)	
No	10 (71)	4 (29)		6 (43)	8 (57)	
Age of Epilepsy Onset *			0.22			0.80
< 3 years	14 (48)	15 (52)		10 (35)	19 (66)	
≥ 3 years	24 (63)	14 (37)		12 (32)	26 (68)	
Seizure Frequency *			0.31			0.62
Rare (<Monthly)	10 (48)	11 (52)		6 (29)	15 (71)	
Frequent (>Monthly)	28 (61)	18 (39)		16 (35)	30 (65)	
Prior ASM Use			0.61			0.94
No	11 (65)	6 (35)		6 (35)	11 (65)	
Yes	37 (58)	27 (42)		22 (34)	42 (66)	
CSWS CLINICAL HISTORY						
Age of CSWS Onset			0.47			0.32
< 5 years	12 (67)	6 (33)		8 (44)	10 (56)	
≥ 5 years	36 (57)	27 (43)		20 (32)	43 (68)	
Developmental Regression			0.68			0.28
Yes	32 (64)	18 (36)		16 (32)	34 (68)	

J Pediatr. Author manuscript; available in PMC 2022 May 01.

Variable	Clinical Response			SWI Response		
	Response (n=48) n (%)	Non-response (n=33) n (%)	p	Response (n=28) n (%)	Non-response (n=53) n (%)	p
No	16 (59)	11 (41)		12 (44)	15 (56)	
CSWS Etiology			0.29			0.04
Unknown/Genetic	29 (64)	16 (36)		20 (44)	25 (56)	
Structural	19 (53)	17 (47)		8 (22)	28 (78)	
Time to Initial Treatment			0.61			0.52
< 6 months	37 (58)	27 (42)		21 (33)	43 (67)	
> 6 months	11 (65)	6 (35)		7 (41)	10 (59)	
CSWS EEG DATA						
SWI at Diagnosis [#]			0.55			0.96
< 85%	13 (65)	7 (35)		7 (35)	13 (65)	
> 85%	35 (57)	26 (47)		21 (34)	40 (66)	
CSWS Spike Type			0.68			0.47
Focal	32 (60)	21 (40)		20 (38)	33 (62)	
Generalized	5 (71)	2 (29)		1 (14)	6 (86)	
Both	11 (52)	10 (48)		7 (33)	14 (67)	
CSWS Spike Laterality			0.48			0.46
Left	22 (67)	11 (33)		14 (42)	19 (58)	
Right	17 (57)	13 (43)		9 (30)	21 (70)	
Bilateral	9 (50)	9 (50)		5 (28)	13 (72)	

Missing Data (n): Race/Ethnicity (3); Developmental Regression (4).

[*] Proportions for Age of Epilepsy Onset and Seizure Frequency are taken from 67 subjects diagnosed with epilepsy rather than 81 subjects in cohort.

[#] SWI is calculated from the first EEG from a participating epilepsy center. Sensitivity analysis considering only the 66 subjects first diagnosed at a participating epilepsy center show no significant association between baseline SWI and clinical (p=0.30) and SWI response (p=0.90).

Table 4:

Odds of Response to Initial Treatment

	Unadjusted Odds Ratios		Adjusted Odds Ratios*	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
CLINICAL RESPONSE				
CSWS Treatment				
ASM	Reference	--	Reference	
Benzodiazepines	6.10 (2.04–18.27)	**0.001**	9.11 (2.61–31.83)	**0.0005**
Steroids	3.21 (0.43–23.79)	0.25	4.24 (0.47–38.17)	0.20
Other	0.71 (0.06–8.15)	0.79	0.87 (0.06–11.74)	0.92
SWI RESPONSE				
ASM	Reference	--	Reference	
Benzodiazepines	1.63 (0.55–4.90)	0.38	2.13 (0.66–6.86)	0.20
Steroids	1.78 (0.24–13.40)	0.58	2.52 (0.28–23.14)	0.41
Other	0.89 (0.08–10.30)	0.93	0.97 (0.07–13.67)	0.98

*Adjusted for history of epilepsy, age of CSWS onset (greater or less than 5 years), delay in CSWS treatment (>6 months), and CSWS etiology (structural vs. other).

Table 5:

Characteristics Associated with Response to All Treatments

Variable	Odds of Clinical Response		Odds of SWI Response	
	OR (95% CI)	p-value	OR (95% CI)	p-value
DEMOGRAPHIC				
Gender		0.79		0.95
Male	Reference		Reference	
Female	1.12 (0.51–2.43)		0.98 (0.45–2.13)	
Race/Ethnicity		0.50		0.78
White/Non-Hispanic	Reference		Reference	
Other	0.73 (0.30–1.80)		1.14 (0.45–2.89)	
EPILEPSY HISTORY				
Prior History of Epilepsy		0.12		**0.01**
No	Reference		Reference	
Yes	0.44 (0.15–1.24)		0.33 (0.14–0.77)	
Age of Epilepsy Onset		0.38		0.63
< 3 years	Reference		Reference	
≥ 3 years	1.51 (0.60–3.78)		1.28 (0.46–3.56)	
Seizure Frequency		0.08		0.33
Rare (<Monthly)	Reference		Reference	
Frequent (>Monthly)	2.31 (0.91–5.84)		1.68 (0.59–4.76)	
Prior ASM Use				
No	Reference	-	Reference	-
Yes	0.93 (0.37–2.35)	0.88	0.80 (0.32–2.01)	0.63
CSWS CLINICAL HISTORY				
Age of CSWS Onset		0.84		0.24
< 5 years	Reference		Reference	
≥ 5 years	1.10 (0.44–2.78)		0.58 (0.24–1.44)	
Developmental Regression		0.57		0.91
No	Reference		Reference	
Yes	1.30 (0.53–3.17)		0.95 (0.40–2.28)	

Variable	Odds of Clinical Response		Odds of SWI Response	
	OR (95% CI)	p-value	OR (95% CI)	p-value
CSWS Etiology		0.18		**0.002**
Unknown/Genetic	Reference		Reference	
Structural	0.58 (0.27–1.28)		0.27 (0.12–0.63)	
Time to Initial Treatment		0.84		0.98
< 6 months	Reference		Reference	
> 6 months	1.10 (0.42–2.94)		0.99 (0.38–2.60)	
Prior Number of CSWS Trials				
None	Reference	--	Reference	
One	1.27 (0.62–2.60)	0.51	**2.01 (1.13–3.56)**	**0.02**
≥ Two	1.38 (0.64–3.00)	0.82	1.59 (0.78–3.21)	0.20
CSWS EEG DATA				
SWI at Diagnosis		0.05		0.99
< 85%	Reference		Reference	
> 85%	1.95 (1.00–3.80)		1.00 (0.56–1.77)	
CSWS Spike Type				
Focal	Reference	-	Reference	-
Generalized	1.56 (0.38–6.46)	0.54	0.36 (0.07–1.74)	0.20
Both	1.02 (0.42–2.50)	0.96	1.13 (0.49–2.63)	0.77
CSWS Spike Laterality				
Left	Reference	-	Reference	-
Right	0.91 (0.37–2.23)	0.91	1.07 (0.45–2.54)	0.88
Bilateral	0.60 (0.21–1.67)	0.32	0.51 (0.17–1.55)	0.24

Missing data (n): Race (3); Developmental Regression (4).

Table 6:

Odds of Response to All Treatments

Variable	Unadjusted Odds Ratios		Adjusted Odds Ratios*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
CLINICAL RESPONSE				
CSWS Treatment				
ASM	Reference	--	Reference	--
Benzodiazepines	2.81 (1.35–5.82)	**0.006**	3.32 (1.57–7.04)	**0.002**
Steroids	3.49 (1.25–9.80)	**0.02**	4.04 (1.41–11.59)	**0.01**
Other	2.30 (0.68–7.81)	0.18	2.68 (0.71–10.12)	0.15
SWI RESPONSE				
CSWS Treatment				
ASM	Reference	--	Reference	--
Benzodiazepines	1.33 (0.72–2.47)	0.37	1.77 (0.87–3.58)	0.11
Steroids	2.64 (1.06–6.55)	**0.04**	3.36 (1.09–10.33)	**0.03**
Other	0.99 (0.37–2.69)	0.99	1.26 (0.27–5.88)	0.77

*Adjusted for history of epilepsy, age of CSWS onset (greater or less than 5 years), delay in CSWS treatment (>6 months), CSWS etiology (structural vs. other), and number of prior CSWS treatments (0, 1, ≥2). Structural etiology is associated with a reduced odds of an SWI response (OR 0.27, 95%CI 0.11–0.66, p=0.004), after adjusting for the other clinical variables and treatment choice.