



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

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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 US.

Study design This retrospective study gathered information on baseline clinical characteristics, CSWS etiology, and treatment(s) in consecutive patients seen between 2014 and 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 improvement as noted by the treating physician; and electroencephalography 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, $P = .002$) or steroids (OR 4.04, 95%CI 1.41-11.59, $P = .01$) than with ASMs and a greater odds of electroencephalography improvement after steroids (OR 3.36, 95% CI 1.09-10.33, $P = .03$) than after ASMs.

Conclusions Benzodiazepines and ASMs are the most frequent initial therapy prescribed for CSWS in the US. 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. (*J Pediatr* 2021;232:220-8).

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.^{1,2} 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-rapid eye movement 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-rapid eye movement 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 There are 4

ASM	Antiseizure medication
CSWS	Continuous spike and wave during slow wave sleep
EEG	Electroencephalography
ESES	Electrical status epilepticus of sleep
GEE	Generalized estimating equation
IVIG	Intravenous immunoglobulin
SWI	Spike wave index

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primary treatment strategies: high-dose oral benzodiazepines given before sleep, steroids, other antiseizure 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 formulations, and other immune-modulating agents including adrenocorticotrophic hormone and intravenous immunoglobulin (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

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.

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 is a multicenter collaborative organization with multiple subgroups focused on different pediatric epilepsies.¹⁷ The Pediatric Epilepsy Research Consortium 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

Sites and Sample Population

This was a multicenter retrospective study, with 11 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 age 2-18 years seen between 2014 and 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 10 consecutive patients. A chart review for each eligible patient was completed at the patient's home institution. Study data were collected and managed using research electronic data capture (REDCap)¹⁸ electronic data capture tools hosted at University of Colorado Denver.

Clinical Data Collection

Data were gathered on the following demographic and clinical variables: sex, race/ethnicity, and 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 (eg, structural, genetic, unknown), and electroencephalography (EEG) characteristics (initial SWI, follow-up SWI, and description of EEG characteristics). Many patients had tried more than 1 treatment; we gathered information for all therapies that had been initiated prior to December 31, 2016.

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 5 years of age 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 5 years represented the 25th percentile for age at diagnosis among our patients. Prior exposure to ASMs for epilepsy was categorized as present or absent. In addition, 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, perampamil, phenobarbital, runfinaamide). 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 benzodiazepines (clobazam and oral diazepam); steroids; ASMs; and other (including surgery, ketogenic diet, IVIG).

Definition and Coding of Outcomes

Two primary outcome measures were defined a priori: clinical response to the first CSWS treatment; and 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 pretreatment 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 $88 \pm 12\%$, 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 the clinical response (as judged by the evaluating neurologist); and the SWI response (defined as a 50% reduction in the SWI between the post and pretreatment EEGs) to each individual treatment.

Statistical Analyses

Statistical analyses were performed using SAS University Edition (SAS Institute Inc 2015). We calculated descriptive statistics of the whole study sample as proportions. We then evaluated the association between each demographic/clinical variable and the 2 outcomes (clinical and SWI response) using the Fisher exact test.

Our primary analysis focused on the association between each of the 2 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 because of treatment failure or relapse. To use fully 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

Clinical History

Baseline information for all 81 participants as well as for the study sample broken down by initial treatment choices is shown in **Table I**. There were more male children (43 of 81, 53%) and there was a predominance of non-Hispanic Caucasian children (60 of 81, 76.9%) compared with other

races or ethnicities (18 of 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).

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 of 67 (69%) having at least monthly seizures and 16 of 67 (24%) having daily seizures; 5 of 67 (7.5%) children had only had a single seizure. Sixty-four children had taken at least 1 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 of 81 (40%) and sodium channel blockers (including oxcarbazepine, carbamazepine, lamotrigine, and lacosamide) in 24 of 81 (30%); 3 children had tried more than one sodium channel blocker. Only 14 of 81 (17%) had tried valproic acid, 8 of 81 (9.9%) had tried topiramate/zonisamide, and 5 of 81 (6.1%) had tried clobazam. None of the other clinically available ASMs had been prescribed.

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 of 81; 65%) though 28 of 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 of 81; 41%) or right (30 of 81; 37%) predominance, with 18 of 81 (22%) showing bilateral discharges. The SWI upon initial evaluation at the epilepsy center ranged from 33% to 100% with a median of 90% (IQR 85%-95%), and 61 of 81 (75%) patients had a SWI >85% at presentation. Etiology of ESES was structural in 36 of 81 (44%) cases, genetic in 16 of 81 (20%), or unknown in 29 of 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 of 81 (25%) had baseline neurocognitive testing done as part of the diagnostic process.

Initial CSWS Treatment

Prescribing Practices and Timing. Most children (50 of 81; 62%) received a benzodiazepine as their first agent for CSWS and 22 of 81 (27%) received an ASM; only 5 of 81 (6.2%) received steroids and 4 of 81 (4.9%) underwent other treatments. Of the benzodiazepines, diazepam (36 of 50) was used more frequently than clobazam (14 of 50). Among the ASMs, children most often received valproic acid (8 of 22) or levetiracetam (6 of 22). **Table II** (available at www.jpeds.com) details the breakdown of initial treatment choice.

Table I. Demographic and clinical variables and relationship with initial medication choice

Patient factors	Total (n = 81) n (%)	ASM (n = 22) n (%)	Benzodiazepines (n = 50) n (%)	Steroids (n = 5) n (%)	Other (n = 4) n (%)	P
Demographic						
Sex						.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						.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						.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*						.12
<3 y	29 (43)	11 (65)	15 (36)	2 (67)	1 (25)	
≥3 y	38 (57)	6 (35)	28 (65)	1 (33)	3 (75)	
Seizure frequency*						.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						.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						.51
<5 y	18 (22)	5 (22)	10 (20)	1 (20)	2 (50)	
≥5 y	63 (78)	17 (77)	40 (80)	4 (80)	2 (50)	
Developmental regression						.85
Yes	50 (65)	14 (70)	30 (61)	4 (80)	2 (67)	
No	27 (35)	6 (30)	19 (39)	1 (20)	1 (33)	
CSWS etiology						.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						.78
<6 mo	64 (79)	19 (86)	38 (76)	4 (80)	3 (75)	
>6 mo	17 (21)	3 (14)	12 (24)	1 (20)	1 (25)	
CSWS EEG data						
SWI at diagnosis [†]						.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						.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						.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)	

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 ($P = .59$).

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 I). Though not depicted in Table I, initial CSWS treatment also did not differ depending on prior exposure to any specific ASM ($P > .46$ 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 of 81 patients (21%).

Factors Associated with Clinical Response. Fifty nine percent (48 of 81) of patients achieved a clinical response to the first treatment (Table III). No demographic or clinical variables were significantly associated with clinical

response. Though not depicted in Table III, clinical response also did not differ depending on prior exposure to any specific ASM ($P > .19$ for all comparisons).

Factors Associated with SWI Response. Only 35% (28 of 81) achieved an SWI response. As shown in Table III, patients with a structural etiology of their CSWS were one-half as likely to have an SWI response (8 of 36; 22%) compared with those with a genetic or unknown cause (20 of 45; 44%) ($P = .04$). Though not depicted in Table III, 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

Table III. Baseline characteristics associated with response to initial treatment

Variables	Clinical response			SWI response		
	Response (n = 48) n (%)	Nonresponse (n = 33) n (%)	P	Response (n = 28) n (%)	Nonresponse (n = 53) n (%)	P
Demographic						
Sex			.50			.69
Male	24 (56)	19 (44)		14 (33)	29 (67)	
Female	24 (63)	14 (37)		14 (37)	24 (63)	
Race/ethnicity			.15			.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			.31			.47
Yes	38 (57)	29 (43)		22 (33)	45 (67)	
No	10 (71)	4 (29)		6 (43)	8 (57)	
Age of epilepsy onset*			.22			.80
<3 y	14 (48)	15 (52)		10 (35)	19 (66)	
≥3 y	24 (63)	14 (37)		12 (32)	26 (68)	
Seizure frequency *			.31			.62
Rare (<monthly)	10 (48)	11 (52)		6 (29)	15 (71)	
Frequent (>monthly)	28 (61)	18 (39)		16 (35)	30 (65)	
Prior ASM use			.61			.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			.47			.32
<5 y	12 (67)	6 (33)		8 (44)	10 (56)	
≥5 y	36 (57)	27 (43)		20 (32)	43 (68)	
Developmental regression			.68			.28
Yes	32 (64)	18 (36)		16 (32)	34 (68)	
No	16 (59)	11 (41)		12 (44)	15 (56)	
CSWS etiology			.29			.04
Unknown/genetic	29 (64)	16 (36)		20 (44)	25 (56)	
Structural	19 (53)	17 (47)		8 (22)	28 (78)	
Time to initial treatment			.61			.52
<6 mo	37 (58)	27 (42)		21 (33)	43 (67)	
>6 mo	11 (65)	6 (35)		7 (41)	10 (59)	
CSWS EEG data						
SWI at diagnosis†			.55			.96
<85%	13 (65)	7 (35)		7 (35)	13 (65)	
>85%	35 (57)	26 (47)		21 (34)	40 (66)	
CSWS spike type			.68			.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			.48			.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)	

EEG, Electroencephalography.

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 ($P = .30$) and SWI response ($P = .90$).

of 67 (42%) of patients who had not tried the medication ($P = .002$). No other baseline variables were associated with SWI response.

Efficacy of Initial Treatment. Table IV 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, $P = .001$), and the odds of clinical response increased after adjusting for the aforementioned clinical factors (OR 9.11, 95% CI 2.61-31.83, $P = .0005$). The odds of responding to steroids was over 4 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 (aOR 4.24, 95% CI 0.47-38.17, $P = .41$). Response to other treatments (aOR 0.87, 95% CI 0.06-11.74, $P = .98$) did not differ from response to other ASMs. There was no

Table IV. Odds of response to initial treatment

Type of treatment response based on treatment	Unadjusted ORs		aOR*	
	OR (95% CI)	P value	OR (95% CI)	P value
Clinical response				
CSWS treatment				
ASM	Reference	–	Reference	
Benzodiazepines	6.10 (2.04-18.27)	.001	9.11 (2.61-31.83)	.0005
Steroids	3.21 (0.43-23.79)	.25	4.24 (0.47-38.17)	.20
Other	0.71 (0.06-8.15)	.79	0.87 (0.06-11.74)	.92
SWI response				
ASM	Reference	–	Reference	
Benzodiazepines	1.63 (0.55-4.90)	.38	2.13 (0.66-6.86)	.20
Steroids	1.78 (0.24-13.40)	.58	2.52 (0.28-23.14)	.41
Other	0.89 (0.08-10.30)	.93	0.97 (0.07-13.67)	.98

Significant *P* values <.01 are indicated in bold.

*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).

significant association between any treatment choice and SWI response ($P > .38$ for unadjusted and $P > .20$ for adjusted comparisons).

All CSWS Treatments

Prescribing Practices. Across the 81 participants, clinical response data were available for 152 individual treatments trials and 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 of 81 (84%) of children had tried a benzodiazepine, 25 of 81 (32%) had tried a steroid, 45 of 81 (56%) had tried an ASM, and 14 of 81 (17%) had tried another treatment (such as surgery or the ketogenic diet). **Table II** reviews the treatments used by this cohort and the response to these therapies.

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

Factors Associated with SWI Response. Thirty-three percent (51 of 153) of treatment trials produced an SWI response. Several baseline variables were associated with an SWI response (**Table V**; available at www.jpeds.com). Structural etiology was associated with a lower odds of SWI response (OR 0.27, 95% CI 0.12-0.63, $P = .002$), as was a prior history of epilepsy (OR 0.33, 95% CI 0.14-0.77, $P = .01$). 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, $P = .02$).

Efficacy of All Treatments. **Table VI** 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 IV** (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 (aOR 3.32, 95% CI 1.57-7.04,

Table VI. Odds of response to all treatments

Variables	Unadjusted ORs		aOR*	
	OR (95% CI)	P value	OR (95% CI)	P value
Clinical response				
CSWS treatment				
ASM	Reference	–	Reference	–
Benzodiazepines	2.81 (1.35-5.82)	.006	3.32 (1.57-7.04)	.002
Steroids	3.49 (1.25-9.80)	.02	4.04 (1.41-11.59)	.01
Other	2.30 (0.68-7.81)	.18	2.68 (0.71-10.12)	.15
SWI response				
CSWS treatment				
ASM	Reference	–	Reference	–
Benzodiazepines	1.33 (0.72-2.47)	.37	1.77 (0.87-3.58)	.11
Steroids	2.64 (1.06-6.55)	.04	3.36 (1.09-10.33)	.03
Other	0.99 (0.37-2.69)	.99	1.26 (0.27-5.88)	.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, $P = .004$), after adjusting for the other clinical variables and treatment choice.

$P = .002$). Similar to the model of initial treatment response, this model showed that the odds of clinical response to steroids was 4 times that of response to ASMs, but with the larger sample size, the difference was now statistically significant (aOR 4.04, 95% CI 1.41-11.59, $P = .01$). In addition, this model demonstrated a greater odds of SWI response with steroids than with ASMs (aOR 3.36, 95% CI 1.09-10.33, $P = .03$).

Discussion

This retrospective multicenter study of consecutively treated patients with CSWS was undertaken to determine current treatment practices across a variety of pediatric epilepsy centers in the US 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. Although the majority of patients first receive a benzodiazepine, a sizeable minority receives one of several ASMs and 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 2-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 cannot agree to randomize among the 3 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 US 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, prefer-

ences for initial CSWS therapy appear to differ elsewhere in the world. A consecutive case series of 47 patients treated in the Netherlands showed that although 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 CSWS²⁶ and Landau-Kleffner Syndrome²⁷ 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 because outcome variables were dichotomized and the SWI response criteria may be more stringent than the clinical response criteria. Although 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. Although 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 multistakeholder 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 years²⁴ 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 US 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 2 patients received oral prednisone or prednisolone, whereas the majority of patients in the European study²⁴ received intravenous, pulse-dose methylprednisolone.

Although 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 III and Table V). Other authors have identified structural etiology as a risk factor for worse outcomes. One study³¹ 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 study²⁶ 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 reports³³⁻³⁵ 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.

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 obscure subtleties that may influence treatment response. In addition, given the retrospective nature of this study, we could not prespecify treatment dose, treatment duration, or the time between treatment initiation and follow-up assessment. Such factors may influence assessment of treatment efficacy, especially because 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

We find that patients in the US epilepsy centers typically received either benzodiazepines or ASMs as the initial treatment for CSWS and were rarely prescribed steroids or other therapies. 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. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Conflicts of Interest Disclosures

T.L. 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

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Table II. Use and success of specific CSWS treatments

Treatments	First CSWS treatment			All CSWS treatments		
	First 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 V. Characteristics associated with response to all treatments

Variables	Odds of clinical response		Odds of SWI response	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographic				
Sex		.79		.95
Male	Reference		Reference	
Female	1.12 (0.51-2.43)		0.98 (0.45-2.13)	
Race/ethnicity		.50		.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		.12		.01
No	Reference		Reference	
Yes	0.44 (0.15-1.24)		0.33 (0.14-0.77)	
Age of epilepsy onset		.38		.63
<3 y	Reference		Reference	
≥3 y	1.51 (0.60-3.78)		1.28 (0.46-3.56)	
Seizure frequency		.08		.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)	.88	0.80 (0.32-2.01)	.63
CSWS clinical history				
Age of CSWS onset		.84		.24
<5 y	Reference		Reference	
≥5 y	1.10 (0.44-2.78)		0.58 (0.24-1.44)	
Developmental regression		.57		.91
No	Reference		Reference	
Yes	1.30 (0.53-3.17)		0.95 (0.40-2.28)	
CSWS etiology		.18		.002
Unknown/genetic	Reference		Reference	
Structural	0.58 (0.27-1.28)		0.27 (0.12-0.63)	
Time to initial treatment		.84		.98
<6 mo	Reference		Reference	
>6 mo	1.10 (0.42-2.94)		0.99 (0.38-2.60)	
Prior number of CSWS Trials				
None	Reference	-	Reference	
1	1.27 (0.62-2.60)	.51	2.01 (1.13-3.56)	.02
≥2	1.38 (0.64-3.00)	.82	1.59 (0.78-3.21)	.20
CSWS EEG data				
SWI at diagnosis		.05		.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)	.54	0.36 (0.07-1.74)	.20
Both	1.02 (0.42-2.50)	.96	1.13 (0.49-2.63)	.77
CSWS spike laterality				
Left	Reference	-	Reference	-
Right	0.91 (0.37-2.23)	.91	1.07 (0.45-2.54)	.88
Bilateral	0.60 (0.21-1.67)	.32	0.51 (0.17-1.55)	.24

Missing data (n): Race (3); Developmental Regression (4).
Significant P values <.01 are indicated in bold.