Research Paper

Multicenter Research Data of Epilepsy Management in Patients With Sturge-Weber Syndrome

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ABSTRACT

Background: Epilepsy in typical Sturge-Weber syndrome (SWS) is common, and many questions remain regarding the treatment outcomes. We analyzed a large multicenter database with focus on neurological drug treatment in different demographic and SWS characteristic groups.

Methods: A total of 268 patients with brain involvement and a history of seizures were selected from a research data registry generated from a multicenter cross-sectional questionnaire. We examined associations between medication use and binary variables such as sex, ethnicity, and brain, skin, and eye involvement laterality. We analyzed group differences in mean number of antiseizure medications and age at diagnosis, enrollment, and seizure onset and examined differences in median SWS neurological score patterns.

Results: The most frequently used medications were levetiracetam (48.1%), low-dose aspirin (44.8%), oxcarbazepine (39.9%), and phenobarbital (14.9%). Lamotrigine was more frequently used in adults than in children (P = 0.001). History of neurosurgery was associated with no current antiseizure medication use (P = 0.001), whereas bilateral brain involvement and family history of seizures were associated with using a higher number of antiseizure medications (P = 0.002, P = 0.027, respectively). Subjects with bilateral brain involvement and early seizure onset were associated with using a higher number of antiseizure medications (P = 0.002) and phenobarbital use (0.003).

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Introduction

Sturge-Weber syndrome (SWS) is a noninherited neurovascular disease associated with a port-wine birthmark, glaucoma, and leptomeningeal capillary venous malformation resulting in supratentorial hemisphere atrophy. The disease is caused by an activating somatic mutation in the gene \( \text{GNAQ} \), encoding the \( \text{Gq} \) subunit.1

The neurological manifestations of SWS occur with variable severity, resulting in large part from the variable extent of brain involvement with the leptomeningeal vascular malformation. The neurological consequences of this condition are often debilitating and may consist of cerebral atrophy, seizures, acquired hemiparesis, various degrees of intellectual disability, and, the most recently described, autistic behavior.2,3 Approximately from 75% to 90% of patients with SWS brain involvement develop epilepsy, mostly during the first year of life.4 Early onset of seizures and medically refractory epilepsy are indicative of a poor prognosis.5 Early recognition and aggressive management of symptoms remain the foundation of the management in this syndrome. Patients with extensive unilateral and bilateral brain involvement more frequently have drug-resistant epilepsy.6

For a subset of patients who are medically refractory, medical care remains very challenging. The goal of this study was to analyze the largest yet available multicenter database for information on the neurological management of patients with SWS with a focus on certain key groups: unilateral versus bilaterally involved patients, pediatric versus adult patients, those with early seizure onset versus later onset, surgically treated patients, and patients receiving low-dose aspirin. We aimed to identify risk factors associated with medication use for epilepsy in SWS, to describe the most commonly used antiseizure medications (ASMs), and to report the frequency of aspirin use in patients with SWS. In addition, we aimed to identify factors associated with key subgroups. We hypothesized that both early onset of seizures and bitemporal brain involvement were more likely to result in the use of multiple ASMs. With the rapidly increasing number of available ASMs, it is important to periodically review treatment options. This study utilizes the largest research database of patients with SWS and ASMs to address this important issue.

Methods

Data collection

All subjects provided written informed consent before participating. Approval for this study was obtained from the National Institutes of Health, Johns Hopkins University Institutional Review Board, and all local institutional review boards.

The data analyzed in this study were compiled from a patient/parent questionnaire administered at seven different sites (Johns Hopkins University/Kennedy Krieger Institute, Baltimore, MD; Baylor College of Medicine, Houston, Texas; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Nationwide Children's Hospital, Columbus, OH; New York University, New York, NY; Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA; Wayne State University, Detroit, MI) participating in the Brain Vascular Malformation Consortium. Data analyzed in this study were collected from August 2010 through November 2018. Only patients with SWS brain involvement demonstrated by contrast-enhanced magnetic resonance imaging were eligible to participate. Patients with neurological symptoms, including developmental delay and seizures, with a normal magnetic resonance imaging were excluded.

Questionnaires were administered as described in the inaugural study of these data1; questionnaires were completed by one of the following three methods: by the participant themselves, by the participant’s parent or guardian, or by the study staff reading the questions to the participants, and their responses were transcribed directly. The questionnaire was most often completed in person, after a clinic visit, but could also be completed over the phone. All questions were answered based on patient or parent reporting; patient records were not consulted to verify responses. If the patient did not want to answer a question, or if they were unable, they could leave it blank, or mark “unknown” or “Not Applicable.” Enquiries about phrasing or questions on the questionnaire were answered by the study staff. To be included in this study, medical questions must have been answered.

Database creation

Data were uploaded into the Rare Diseases Clinical Research Network online database by the study staff at each center. Before data analysis, all entries were cleaned by the University of California San Francisco; missing data or entries with inconsistencies were addressed in cooperation with the site from which the data were collected. Changes were made only if the error was related to data entry onto the online form, or if there was an inconsistency that could be clarified based on clinic notes from that time.

Statistical methodology

All data analysis was completed in IBM SPSS Statistics 25 at the Kennedy Krieger Institute. Simple frequencies were generated to understand which ASMs were most commonly used among patients with SWS. The medications included in this study were ASMs and low-dose aspirin. All analyses were run only among patients with a history of seizures. A \( p \) value less than or equal to 0.05 was used to determine significance.

Two-tailed chi-square or Fisher’s exact tests were done to determine if using a medication was associated with another binary variable (sex, ethnicity, laterality of brain involvement, presence/absence of port-wine birthmark and glaucoma, history of brain surgery, concatenate use with another medication) or race, or if a specific SWS characteristic was associated with a medication.

Two-tailed \( t \) tests were done to determine if using a medication was associated with a difference in the mean number of ASMs at the time of enrollment, age at diagnosis, enrollment, or seizure onset. Mann-Whitney \( U \) tests were used to determine if there was a significant difference in median seizure, hemiparesis, visual field

Conclusions: Levetiracetam, low-dose aspirin, and oxcarbazepine were the most frequently used medications. More severely affected patients were frequently on a greater number of antiseizure medications. Surgery for epilepsy was associated with the ability to discontinue antiseizure medication. Longitudinal studies are needed to further investigate medication use in patients with SWS.

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cut, cognitive function, or total neuroscores. The SWS neuroscore, previously validated through neuropsychological testing, quantitatively electroencephalography, and perfusion imaging, is a 15-point scale used to assess seizure frequency (0 to 4), hemiparesis severity (0 to 4), visual field cut extent (0 to 2), and cognitive function (0 to 5), where higher scores indicate poorer outcomes. In all reported analyses, patients using the medication were compared with those who were not.

Data analysis

Having a history of seizures, but not using ASMs at the time the questionnaire was completed, was considered to be an indicator of seizure freedom. To understand SWS, demographic, or medication variables related to eventual "seizure freedom," patients with a history of seizures not using ASMs were compared with those using ASMs. These analyses were repeated in adults (18 years at enrollment, based on rounded age) and patients with a history of brain surgery. History of seizures was defined by the responses to two questions: "Has the participant ever experienced any of the following conditions: Epilepsy?" or "Does the subject have a history of seizures?" If either question was answered as "yes," the patient was considered to have a history of seizures. A patient did not have a history of seizures if both questions were answered "no," or if one question was answered as "no" and the other was left blank. If both questions were left as blank or unknown, the subject was excluded.

To understand how demographics and SWS outcomes were related to medications used, patients with variables of interest (bilateral brain involvement, family history of seizures, patients younger than two years, adults, patients with seizure onset before age one year) were compared with the rest of the group. An additional analysis focused on patients using aspirin, levetiracetam, oxcarbazepine, phenobarbital, lamotrigine, lacosamide, and gabapentin and associated SWS and demographic factors.

Results

Sample demographics

A total of 312 patients completed the database questionnaire: 268 patients with a history of seizures (55.2% female, 86.2% younger than 18 years at enrollment, 78.4% white, 6.3% black, 6.3% Asian, 4.9% multiracial, 3.4% unknown, 0.4% Native Hawaiian Pacific Islander, and 0.4% American Indian/Alaskan Native; Table 1) were included in this study. In the 268 patients with seizures, the most frequently used ASMs were levetiracetam (48.1%), oxcarbazepine (39.9%), and phenobarbital (44.8%). One hundred and twenty (44.8%) were using aspirin; medication frequencies for patients with seizures can be seen in Table 2. One hundred and one patients (37.7%) were using one ASM, 91 (34.0%) were using two ASMs, 38 (14.2%) were using three ASMs, and 10 (3.7%) were using four or more ASMs. In subjects who were using two ASMs (n = 91), not including aspirin, levetiracetam, and oxcarbazepine was the most frequent combination of seizure medications (34.1%). In subjects using three ASMs (n = 38), not including aspirin, the most frequent combination of seizure medications was levetiracetam, oxcarbazepine, and lacosamide (10.5%) or phenobarbital (10.5%).

For brevity and clarity, only significant values of clinical relevance are reported. All P values can be found in Tables 3-5.

History of brain surgery

Twenty-eight participants had a history of brain surgery. Among patients who continued ASM therapy (n = 18, 64%), levetiracetam (N = 7) and oxcarbazepine (N = 7) were the most frequently used ASMs and six subjects were using low-dose aspirin. Only one subject with a history of brain surgery also had bilateral brain involvement. This subject, female and aged four years at the time of enrollment, continued to use phenobarbital.

Patients not using ASMs

All patients

Of the N = 268 patients with a history of seizures, N = 28 patients were not using ASMs at the time the questionnaire was completed. A history of brain surgery (n = 10 of 28, 36% not on ASM) was associated with being off of seizure medications at the time the questionnaire was administered (P = 0.001). Of the subjects not using an ASM with no history of neurosurgery (n = 15 with full data available, mean age = 11.4 years, range from 0 to 32 years), 13 had unilateral brain involvement and seven were using aspirin.

Adults

Of the N = 37 adults with history of seizures, six (16.2%) were not using ASMs at the time the questionnaire was administered. Of the adults who were not using ASMs, one subject, a 31-year-old female with unilateral brain involvement, had history of brain surgery. Not using ASMs as an adult was significantly associated with female sex (P = 0.022) and a unilateral port-wine birthmark (P = 0.020, among patients with port-wine birthmarks only).

| TABLE 1. Demographics and Medications Used in N = 268 Respondents With Seizures |
|-----------------------------|---------------------------------|
| Population or SWS           | Respondents With History of Seizures (N = 268) |
| Sex                         |                                  |
| Female                      | 148 (55.2%)                      |
| Male                        | 120 (44.8%)                      |
| Adult versus child          |                                  |
| Child                       | 231 (86.2%)                      |
| Adult                       | 37 (13.8%)                       |
| Ethnicity                   |                                  |
| Hispanic/Latino origin      | 27 (10.1%)                       |
| Not Hispanic/Latino origin  | 227 (84.7%)                      |
| Unknown                     | 14 (5.2%)                        |
| Race                        |                                  |
| American Indian/Alaskan Native | 1 (0.4%)                  |
| Asian                       | 17 (6.3%)                        |
| Black                       | 17 (6.3%)                        |
| Native Hawaiian Pacific Islander | 1 (0.4%)             |
| White                       | 210 (78.4%)                      |
| Multiracial                 | 13 (4.9%)                        |
| Unknown                     | 9 (3.4%)                         |
| Brain involvement           |                                  |
| Unilateral                  | 216 (80.6%)                      |
| Bilateral                   | 52 (19.4%)                       |
| Port-wine birthmark         |                                  |
| Not present                 | 38 (14.2%)                       |
| Unilateral                  | 126 (47.0%)                      |
| Bilateral                   | 104 (38.8%)                      |
| Glaucoma                    |                                  |
| Not present                 | 128 (47.8%)                      |
| Unilateral                  | 103 (38.4%)                      |
| Bilateral                   | 32 (11.9%)                       |
| Unknown                     | 5 (1.9%)                         |
| Using an antiseizure medication |                          |
| Yes                         | 240 (89.6%)                      |
| No                          | 28 (10.4%)                       |
| Using aspirin               |                                  |
| Yes                         | 120 (44.8%)                      |
| No                          | 148 (55.2%)                      |

Abbreviation: SWS — Sturge-Weber syndrome
Brain involvement (unilateral versus bilateral) was significantly greater in those with bilateral (19.4%) versus unilateral brain involvement, respectively. Extent of brain involvement (unilateral versus bilateral) was significantly associated with extent of eye involvement ($P < 0.001$) and extent of skin involvement ($P < 0.001$).

**Eye involvement**

One hundred and thirty-six subjects had glaucoma. One hundred and three had unilateral and 32 had bilateral involvement. Presence of glaucoma was associated with use of carbamazepine ($P = 0.011$) and phenytoin ($P = 0.001$). Subjects with glaucoma also used a greater number of ASMs compared with subjects without glaucoma ($P = 0.036$; mean $= 1.88 \pm 1.1$ versus $1.5 \pm 0.9$). Bilateral glaucoma was associated with use of carbamazepine ($P = 0.008$), phenytoin ($P = 0.001$), and phenobarbital ($P = 0.023$).

**Family history of seizures**

Sixty-four participants had a family history of seizures. A family history of seizures was associated with using levetiracetam ($P < 0.001$) and having more extensive (bilateral) port-wine birthmark ($P = 0.003$). Those with bilateral brain involvement and seizure onset before age one year were associated with using lamotrigine ($P = 0.001$) and aspirin ($P = 0.001$; 113 of 231 children versus seven of 37 adults), whereas others with a history of seizures did not answer the family history of seizures question. A family history of seizures was associated with using a significantly greater number of ASMs overall ($P = 0.027$; mean $= 1.9 \pm 1.0$ versus $1.6 \pm 1.0$ in patients with and without a family history of seizures, respectively).

**Adults**

Thirty-seven participants were adults. Levetiracetam (40.5%) and lamotrigine (24.3%) were the most frequently used ASMs in adults. Adult status was associated with using lamotrigine ($P = 0.001$; nine of 37 adults versus 13 of 231 children), whereas child status was associated with using oxcarbazepine ($P < 0.001$; 102 of 231 children versus five of 37 adults), phenobarbital ($P = 0.004$; 40 of 231 children versus zero of 37 adults), and aspirin ($P = 0.001$; 113 of 231 children versus seven of 37 adults).

**Patients younger than two years**

Seventy-one patients were two years of age or younger at the time of enrollment. Using levetiracetam ($P < 0.001$) and phenobarbital ($P < 0.001$) was associated with the two years and younger group, whereas using carbamazepine ($P = 0.031$) and lamotrigine ($P = 0.004$) was associated with the three years and older group.

**Seizure onset before age one year**

One hundred and ninety-six patients had seizure onset at or before age 12 months. Seizure onset at or before age 12 months was associated with using phenobarbital ($P = 0.003$).

**Bilateral brain involvement and seizure onset before age one year**

Forty-two patients had bilateral brain involvement and seizure onset at or before age 12 months. This group of interest was associated with using a greater number of ASMs as opposed to all other subjects with a history of seizures ($P = 0.002$; mean $= 2.1 \pm 1.1$ versus $1.6 \pm 1.0$). Phenobarbital was more frequently used ($P = 0.003$). Those with bilateral brain involvement and seizure onset at or before 12 months were more frequently associated with having a more extensive (bilateral) port-wine birthmark ($P < 0.001$) and having more extensive (bilateral) glaucoma ($P < 0.001$). This group was also associated with more severe hemiparesis scores ($P = 0.049$; median $= 3$ versus 1 in those with bilateral brain involvement and seizures at or before 12 months [n = 9] versus all others with a history of seizures). Cognitive impairment scores were also worse ($P = 0.044$; median $= 2$ versus 1) in those with bilateral brain involvement and seizures at or before 12 months.

**TABLE 3.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Using Levetiracetam</th>
<th>Using Oxcarbazepine</th>
<th>Using Phenytoin</th>
<th>Unilateral Versus Bilateral B.I.</th>
<th>Bilateral B.I. and Early Sz Onset</th>
<th>Fam Hx of Sz</th>
<th>Adult Versus Child Status</th>
<th>Under Versus Over 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>1.000</td>
<td>0.134</td>
<td>1.000</td>
<td>0.163</td>
<td>0.176</td>
<td>0.561</td>
<td>0.001*</td>
<td>0.579</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.037</td>
<td>0.000</td>
<td>0.033*</td>
<td>1.000*</td>
<td>0.389*</td>
<td>0.807</td>
<td>0.060*</td>
<td>0.031</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1.000</td>
<td>0.112</td>
<td>0.317*</td>
<td>0.396*</td>
<td>0.362*</td>
<td>0.427</td>
<td>0.001*</td>
<td>0.004</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>---</td>
<td>0.173</td>
<td>0.025</td>
<td>0.440</td>
<td>0.402</td>
<td>0.006</td>
<td>0.377</td>
<td>0.000</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0.173</td>
<td>---</td>
<td>0.053</td>
<td>0.753</td>
<td>0.305</td>
<td>0.556</td>
<td>0.000</td>
<td>0.324</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.025</td>
<td>0.053</td>
<td>---</td>
<td>0.003</td>
<td>0.003</td>
<td>0.687</td>
<td>0.004</td>
<td>0.000</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>0.259</td>
<td>0.573</td>
<td>0.420*</td>
<td>0.140*</td>
<td>0.104*</td>
<td>0.042*</td>
<td>1.000*</td>
<td>0.524*</td>
</tr>
</tbody>
</table>

Abbreviations:

B.I. – Brain involvement

Fam – Family

Hx – History

SWS – Sturge-Weber syndrome

Sz – Seizure

Bold face denotes a significant P value.

*Fisher’s exact test.

---

**TABLE 2.**

Antiseizure Medications Used in Patients With Seizures

<table>
<thead>
<tr>
<th>ASM</th>
<th>Number of Subjects Using</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ASM</td>
<td>240 (89.6%)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>129 (48.1%)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>107 (39.9%)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>40 (14.5%)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>33 (12.3%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>25 (9.3%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>22 (8.2%)</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>21 (7.8%)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>16 (6.0%)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>“Other” ASM</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>11 (4.1%)</td>
</tr>
<tr>
<td>Clozolam</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>5 (1.9%)</td>
</tr>
</tbody>
</table>

Abbreviation:

ASM – Antiseizure medication

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**Analysis by Sturge-Weber syndrome characteristics**

**Bilateral brain involvement**

Fifty-two patients had bilateral brain involvement (19.4%). Bilateral brain involvement was associated with using phenobarbital ($P = 0.003$) and using a greater number of ASMs overall ($P = 0.002$; mean $= 2.0 \pm 1.1$ versus $1.6 \pm 1.0$ in patients with bilateral and unilateral brain involvement, respectively). Extent of brain involvement (unilateral versus bilateral) was significantly associated with extent of eye involvement ($P < 0.001$) and extent of skin involvement ($P < 0.001$).
One hundred and twenty patients (44.8%) were using aspirin. Aspirin use was associated with a significantly younger age at enrollment ($P < 0.001; \text{mean} = 7.18 \pm 6.68$ years versus $11.76 \pm 12.69$ years in patients using and not using aspirin, respectively).

Levetiracetam

One hundred and twenty-nine (48.1%) patients were using levetiracetam. Using levetiracetam was associated with younger age of seizure onset ($P = 0.015; \text{mean} = 14.05 \pm 23.32$ months versus $28.17 \pm 61.18$ months in patients using and not using levetiracetam, respectively), younger mean age at diagnosis ($P = 0.021; \text{mean} = 12.1 \pm 25.5$ months versus $26.7 \pm 67.7$ months for patients using and not using levetiracetam, respectively), and younger mean age at enrollment ($P = 0.023; \text{mean} = 8.18 \pm 11.6$ years versus $11.13 \pm 9.57$ years for patients using levetiracetam and not using levetiracetam, respectively). Patients using levetiracetam were likely neither to have a history of epilepsy surgery ($P = 0.004$) nor to be using carbamazepine ($P = 0.037$). Patients on levetiracetam were more frequently using phenobarbital compared with patients who were not using levetiracetam ($P = 0.025$).

Oxcarbazepine

One hundred and seven (39.9%) patients with seizures used oxcarbazepine. Using oxcarbazepine was associated with a significantly younger age at enrollment, ($P < 0.001; \text{mean} = 6.54 \pm 5.63$ years versus $11.81 \pm 12.55$ years for patients using and not using oxcarbazepine, respectively).

Phenobarbital

Forty (14.9%) patients with seizures were using phenobarbital. Patients using phenobarbital had a younger mean age at enrollment ($P < 0.001; \text{mean} = 3.48 \pm 3.6$ years versus $10.80 \pm 11.1$ years for patients using phenobarbital and not using phenobarbital, respectively), younger mean age at diagnosis ($P < 0.001; \text{mean} = 4.05 \pm 4.8$ months versus $22.4 \pm 56.1$ months for patients using and not using phenobarbital, respectively), and younger age at seizure onset ($P < 0.001; \text{mean} = 7.18 \pm 11.67$ months versus $23.88 \pm 50.7$ months in patients using phenobarbital and not using phenobarbital, respectively). Phenobarbital was associated with a greater hemiparesis neuroscore ($P = 0.002$; median = 3 versus 1 in those using and not using phenobarbital, respectively) and greater total neuroscore ($P = 0.013$; median = 6 versus 4 in those using [n = 14] versus not using phenobarbital [n = 62], respectively). Bilateral brain involvement and bilateral glaucoma were associated with using phenobarbital ($P = 0.003$ and $P = 0.023$, respectively). Phenobarbital was likely to be used with levetiracetam ($P = 0.025$); it was unlikely to be used with oxcarbazepine ($P = 0.053$) or carbamazepine ($P = 0.033$).

Other ASMs

Lamotrigine

Twenty-two (8.2%) patients with history of seizures were using lamotrigine. Patients who were using lamotrigine were associated with using a greater number of ASMs ($P = 0.001; \text{mean} = 2.5 \pm 1.1$ versus $1.6 \pm 1.0$). Patients using lamotrigine were also associated with higher age at enrollment ($P < 0.001; \text{mean} = 18.7 \pm 15.2$ years versus $8.9 \pm 9.7$ years in those using and not using lamotrigine, respectively).

Lacosamide

Twenty-one (7.8%) patients with seizures were using lacosamide. Patients who were using lacosamide were associated with using a greater number of ASMs ($P < 0.001; \text{mean} = 2.7 \pm 1.0$ versus $1.6 \pm 1.0$ in patients using and not using lacosamide, respectively).

Clobazam

Seven (2.6%) patients with seizures were using clobazam. Those who were using clobazam were associated with using a greater number of ASMs ($P < 0.001; \text{mean} = 3.0 \pm 0.6$ versus $1.6 \pm 1.0$ in patients using and not using clobazam, respectively).

ASMs as monotherapy

One hundred and one (37.7%) patients with seizures were using one ASM. Oxcarbazepine (34.7%), levetiracetam (32.7%), and carbamazepine (11.5%) were the most frequently used ASMs for monotherapy. Fifty (49.5%) subjects on ASM monotherapy were also using low-dose aspirin.

**Discussion**

We present the results of the largest multicenter registry, and here we provide the evidences that levetiracetam and...
### TABLE 5.

Values for Difference in Median Neuroscore for SWS Characteristics Related to ASM Use

<table>
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</thead>
<tbody>
<tr>
<td>Subcortical</td>
<td>0.237 (2.15)</td>
<td>0.911 (1.5, 2)</td>
<td>0.002</td>
<td>0.081</td>
<td>0.686</td>
<td>0.096</td>
<td>0.766</td>
<td>0.313</td>
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<tr>
<td>Lacosamide</td>
<td>0.663 (2.0)</td>
<td>1.000 (0, 0)</td>
<td>1.000</td>
<td>0.132</td>
<td>0.570</td>
<td>0.002</td>
<td>0.914</td>
<td>0.690</td>
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<tr>
<td>Levetiracetam</td>
<td>0.962 (3.3)</td>
<td>0.606 (0.5, 1)</td>
<td>0.244</td>
<td>0.766</td>
<td>0.966</td>
<td>0.968</td>
<td>0.968</td>
<td>0.933</td>
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<tr>
<td>Oxcarbazepine</td>
<td>0.680 (3.0)</td>
<td>1.000 (0, 0)</td>
<td>0.244</td>
<td>0.517</td>
<td>0.629</td>
<td>0.966</td>
<td>0.517</td>
<td>0.573</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.967 (1.5)</td>
<td>1.000 (0, 0)</td>
<td>0.244</td>
<td>0.946</td>
<td>0.667</td>
<td>0.966</td>
<td>0.946</td>
<td>0.771</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0.967 (1.5)</td>
<td>1.000 (0, 0)</td>
<td>0.244</td>
<td>0.706</td>
<td>0.667</td>
<td>0.966</td>
<td>0.706</td>
<td>0.573</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- ASM: Antiseizure medication
- Lacos: Lacosamide
- Levt: Levetiracetam
- Oxcarb: Oxcarbazepine
- Phenob: Phenobarbital
- Lamotr: Lamotrigine
- Hx: History

The epilepsy in SWS is often associated with focal seizures. The goal of the treatment is to seizure freedom and low risk of adverse effects of treatment. Based on evidence for efficacy and effectiveness as initial monotherapy for seizures with focal mnemonic of onset, levetiracetam and oxcarbazepine are often the first choices. These ASMs are the most frequently used ones in this observational study. The results of a previous study suggest that carbamazepine and oxcarbazepine should be preferred as the initial therapy, given better seizure control when compared with levetiracetam.

SWS results in lesional epilepsy. The early mechanisms for epileptogenesis are certainly different in the mature brain, and the abnormal neuronal excitability may stabilize as the patient ages. However, the low threshold for seizures remains and therefore long-term treatment with ASMs is likely necessary. Lamotrigine can be considered as monotherapy in adults, and in our study levetiracetam and lamotrigine were the most common ASMs used by adults. More studies with longitudinal data in natural history are necessary.

Phenobarbital is a highly effective broad-spectrum ASM and has a significant role as adjuvant therapy in medically resistant epilepsy; however, because of its sedative and cognitive effects, it is rarely a drug of first choice. In this study, phenobarbital was associated with bilateral SWS brain involvement and younger age at enrollment. The frequent use of phenobarbital in SWS is likely due to the refractory nature of seizures in SWS, where phenobarbital is used as a second- or third-line ASM as an attempt to gain control of seizures. Extent of glaucoma was associated with carbamazepine, phenytoin, and phenobarbital use; however, the relationship between these ASMs and glaucoma is uncertain given that the extent of brain involvement is significantly related to the extent of both the birthmark and glaucoma.

Lacosamide, approved as monotherapy for focal epilepsy, was commonly reported in combination with levetiracetam and oxcarbazepine. Clobazam, a US Food and Drug Administration-approved ASM for adjuvant treatment of drug-resistant epilepsies, was found to be typically used in combination with a greater number of ASMs in this cohort, suggesting that it is often used early on in treatment and was chosen after failing medications more specifically indicated for focal seizures.

One of the hallmarks of SWS in the central nervous system is abnormalities in the medullary and subependymal veins as well as deep venous structures associated with impaired venous outflow. Because venous congestion, stasis, and thrombosis predispose...
patients with SWS to ischemia-related progressive brain injury, low-dose aspirin has been considered for management of seizures and stroke-like episodes. Retrospective case series and case reports have reported the potential benefits of aspirin in SWS.\(^9,10\) In addition, there is a hypothesis that aspirin could be used in pre-symptomatic patients.\(^9\) Prospective randomized studies will be necessary to establish the full spectrum of benefits of aspirin use in patients with SWS.

Epilepsy surgery in SWS offers the best option for the majority of the refractory epilepsy cases. Surgical modalities include lesionectionomy, selected disconnection, callosotomy, and hemispherectomy.\(^23\) Despite the well-documented effectiveness of surgery in SWS, optimal timing and patient selection remain controversial. The decision for surgery is often easier when patients with intractable epilepsy also present significant hemiparesis and developmental delay. However, determining the optimal timing for surgical intervention is more difficult for patients with relatively mild deficits. According to the database, patients who had epilepsy surgery were likely to come off ASMs.

Although the development of new medications and surgical options have helped seizure control in SWS, future considerations in management of neurological symptoms in SWS is necessary. Cannabidiol (CBD), a cannabinoid with nonpsychotropic action available in drug-resistant epilepsies, recently received US Food and Drug Administration approval in tuberous sclerosis complex (TSC) where focal seizures are most common, similar to SWS.\(^23\) Kaplan et al. published the first series of patients with SWS treated with CBD. Based on the limited report, it seems that this is a safe choice for patients with SWS and intractable epilepsy.\(^22\) Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been implicated in the treatment of SWS\(^23\) for cognitive impairments, particularly in those with history of stroke-like episodes or impaired processing speed.\(^24\)

Despite advances in the discovery of new ASMs and alternative epilepsy treatment, prevention of epilepsy remains one of the most important goals in individuals with SWS because seizures can increase the risk of stroke and brain injury. Early seizure onset has been associated with lower cognitive function neuroquality of life.\(^29\) We therefore postulate that children with controlled seizures will have better prognosis. Animal studies have found that epilepsy can be prevented or modified before seizure onset.\(^26\) From laboratory to clinical trials, disease-modifying treatments for epilepsy or use of ASMs have been considered in other diseases such as tuberous sclerosis.\(^27\) A successful multicenter trial concluded that preventative ASM treatment of infants with TSC and high risk of epilepsy markedly improves their neurodevelopmental outcome and reduces the incidence of drug-resistant seizures.\(^28\) Patients with TSC who will develop infantile spasms/epilepsy can be identified by electroencephalography during infancy. This reliable biomarker allows early and effective interventions in this population.\(^29\) There are insufficient data to provide guidance on presymptomatic treatment for patients with SWS. However, SWS is a good disease model to develop presymptomatic approach given the opportunity to triage the high-risk patients by the port-wine stain characteristics. The symptoms typically occur after the neonatal period, providing a window for intervention. Work is underway to identify the mechanisms that enable the prevention or modification of epileptogenesis before seizure onset. Previous studies have used phenobarbital,\(^30\) valproic acid, ocarbazepine, and levetiracetam as well as low-dose aspirin in pre-symptomatic cases.\(^15\) The most effective intervention is yet to be determined, but steps should be taken to modify or prevent epileptogenesis in SWS.

We acknowledge that there are limitations to our study, including that it was retrospective and included patient/parent-reported data. There is an unmet need to understand the natural history in SWS with neurological symptoms. This study design was not appropriate to evaluate the longitudinal aspects of SWS, to draw conclusions on long-term use of ASMs.

Conclusion

In patients with SWS, bilateral brain involvement and early onset of seizures were predictive factors for multiple ASM use. Levetiracetam, oxcarbazepine, and low-dose aspirin were the most commonly used medications. However, new options such as lacosamide, clobazam, and CBD might be considered.\(^25\) Lamotrigine and levetiracetam were the most frequently used ASMs in adults. Epilepsy surgery was associated with ASM discontinuation. This is a questionnaire-based study, and it will be necessary to have a multicenter longitudinal study design to allow definite conclusions regarding long-term use of ASM and presymptomatic treatment in SWS.

Acknowledgments

We thank the participants and their families for their willingness to contribute to this research.

References