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ORIGINAL ARTICLE

Reconsidering the role of selective sodium channel blockers in genetic generalized epilepsy

Emanuele Cerulli Irelli | Alessandra Morano | Martina Fanella | Biagio Orlando | Enrico M Salamone | Anna T Giallonardo | Carlo Di Bonaventura

Epilepsy Unit, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Italy

Correspondence
Carlo Di Bonaventura, Department of Human Neurosciences, "Sapienza" University of Rome, Viale dell'Università, 3000185 Rome, Italy.
Email: c_dibonaventura@yahoo.it

Objective: Selective sodium channel blockers (SSCBs) have a limited use in genetic generalized epilepsy (GGE), due to their well-known risk of seizure worsening. Although their therapeutic potential in GGE has been suggested by recent evidence, electro-clinical data supporting their prescription are lacking. We aimed to investigate SSCB safety and effectiveness in a GGE cohort.

Methods: Subjects who received SSCBs and had ≥5-year follow-up were enrolled. Lamotrigine was excluded from analysis due to its broader pharmacodynamic spectrum and its better-documented efficacy in GGE.

Results: Fifty-six patients (median follow-up 28.5 years) were included. The most used SSCB was carbamazepine in 40 subjects. At the last medical observation, only 9 subjects were still receiving SSCBs. The occurrence of generalized polyspike-wave discharges (GPSWDs) predicted reduced SSCB retention in Cox multivariate analysis. A seizure reduction ≥50% occurred in 53.5% (30/56) of subjects when considering all seizure types; however, the proportion of responders increased to 67.9% when considering only generalized tonic-clonic seizures (GTCS). GPSWDs were significantly associated with a reduced response rate, whereas GGE with GTCS only syndrome with a better outcome. The switch from SSCBs to antiseizure medications licensed for GGE improved seizure control in 65% of patients. Seizure worsening was reported in 5/56 patients; juvenile myoclonic epilepsy and a family history of epilepsy were significantly associated with seizure aggravation.

Conclusion: SSCBs appeared effective on GTCS, but epilepsy aggravation and unsatisfactory control of other seizure types were not uncommon. Our study contributes to identifying new clinical and EEG variables associated with SSCB effectiveness and safety which may help neurologists in patients' management.

KEYWORDS
antiseizure medications (ASMs), drug resistance, epilepsy aggravation, idiopathic generalized epilepsy (IGE), seizure worsening

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1 | INTRODUCTION

Genetic generalized epilepsy (GGE) represents a common form of epilepsy with a strong genetic background.[1] Although GGE has traditionally been associated with a favorable prognosis,[2,3] treatment resistance has been described in up to 40% of patients in many cohorts, including a minor percentage of subjects who never experienced any period of remission during the entire follow-up duration.[3-6] Unfortunately, fewer antiseizure medications (ASMs) can safely and effectively be used in GGE patients as compared with focal epilepsy.[7,8] Indeed, during the previous decades, many authors have highlighted the risk of epilepsy aggravation and new-onset status epilepticus when prescribing sodium channel blockers in GGE, especially in cases of juvenile myoclonic epilepsy (JME) or juvenile absence epilepsy (JAE).[9-13]

However, first-generation sodium channel blockers (carbamazepine-CBZ and phenytoin-PHT) are known for their effectiveness in GGE patients, especially in the treatment of generalized tonic-clonic seizures (GTCS).[14-16] More recently, some authors have reported the effectiveness of newer sodium channel blockers in difficult-to-treat GGE with uncontrolled GTCS.[17,18] A randomized controlled trial showing the efficacy of lacosamide (LCS) on GTCS and its relative safety on other seizure types in patients with GGE has recently been published.[19]

However, the role of sodium channel blockers in GGE treatment is still unclear since their use has been strongly discouraged due to the well-documented risk of epilepsy aggravation, also observed in animal models of absence epilepsy, in which the systemic use of sodium channel blockers has been largely associated with absence seizure worsening and spike-wave discharge prolongation on EEG.[20-23] Given the considerable number of patients with drug-resistant GGE, it is important to better understand the role of these ASMs in this type of epilepsy to potentially expand the therapeutic armamentarium, especially in patients with uncontrolled GTCS.

In this paper, we aimed to review the safety and effectiveness of selective sodium channel blockers (SSCBs) in the treatment of GGE and to investigate the clinical and EEG variables associated with SSCB effectiveness and retention. We specifically focused on ASMs mainly acting as sodium channel blockers and with a less proven effectiveness in GGE. In this view, lamotrigine (LTG) was excluded from the analysis, given its broader pharmacodynamic spectrum and its more documented efficacy in GGE.[24,25]

2 | METHODS

This study was conducted according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies and approved by the local ethics committee. We reviewed medical charts and a computerized database of patients followed at the Policlinico Umberto I epilepsy outpatient clinic from 1980 to 2019. Subjects were enrolled according to the following inclusion criteria: 1) diagnosis of GGE; 2) use of an SSCB, defined as CBZ, PHT, LCS, oxcarbazepine (OXC), eslicarbazepine (ESL), or rufinamide (RUF); 3) availability of complete clinical documentation in order to properly evaluate treatment response and side effects at each outpatient visit; and 4) at least 5 years of follow-up after SSCB introduction.

Even if other mechanism of actions cannot be excluded for some of the analyzed ASMs (ie, ESL and LCS),[26,27] we purposefully included them given their prominent action as sodium channel blockers and their less proven efficacy on GGE. Conversely, LTG was excluded from the analysis considering its broader pharmacodynamic spectrum and its better-documented efficacy in GGE.[24,25]

The diagnosis of GGE was made by two expert epileptologists (ECI, ATG) according to commonly accepted criteria defined in a previous paper by our group.[4] The GGE syndromes defined in the latest International League Against Epilepsy (ILAE) classification were included in the analysis: childhood absence epilepsy (CAE), JAE, JME, and GGE with GTCS only (GGE-GTCS).[28]

For each patient, clinical charts were reviewed by two trained epileptologists (ECI, ATG) in order to obtain demographic data and baseline clinical characteristics at epilepsy onset: age of epilepsy onset, family history of epilepsy, type of seizures, epilepsy syndrome, history of febrile and photosensitive seizures, and intellectual abilities. Treatment response and ASM regimen changes were assessed at each follow-up visit.

A pre-treatment standard EEG was carefully reviewed by two trained epileptologists (ECI, ATG) blinded to outcome measures. For each patient, the following EEG characteristics were analyzed: frequency and distribution of generalized spike-and-wave discharges/generalized polyspike-and-wave discharges (GSWD/GPSWD), occurrence of focal epileptiform abnormalities and/or asymmetric/asynchronous representation of GSWD/GPSWD, presence of eye closure sensitivity, and photoparoxysmal response.

The primary outcome of our study was to evaluate SSCB safety and effectiveness in a cohort of patients with GGE. The secondary aim of our study was to evaluate clinical and EEG variables potentially associated with treatment response, retention, and safety. The main outcome measures considered in the analysis were the following: 1) treatment response, defined as a seizure reduction ≥50% at 12 months after the introduction of an SSCB; 2) treatment retention, defined as the probability of SSCB retention at different time points; and 3) safety, defined as the occurrence of epilepsy aggravation and/or status epilepticus after SSCB introduction.

2.1 | Statistical analysis

Data were tested for normal distribution using data visualization methods and the Shapiro-Wilk test. Data were presented as mean or median according to their normal or non-normal distribution, and comparison across groups was performed with Student's t test or Mann-Whitney U test/Wilcoxon test, respectively. Categorical variables were presented as counts and compared using the chi-square test or Fisher exact test. Different clinical and EEG variables were

compared across groups by stratifying patients according to the presence or absence of treatment response and epilepsy aggravation with SSCBs. P values <0.05 were considered statistically significant. The variable "focal abnormalities" was defined as both the occurrence of focal epileptiform abnormalities and/or asymmetric/asynchronous GSWDs/GPSWDs.

SSCB retention was calculated as the probability of remaining on SSCBs during follow-up and was analyzed with Kaplan-Meier survival analysis. A survival analysis was also performed in relation to different clinical (sex, age at epilepsy diagnosis, years from epilepsy onset to SSCB prescription, previous failure of other ASMs, seizure type, and epilepsy syndrome) and EEG variables (focal abnormalities, photoparoxysmal response, occurrence of polyspike, and eye closure sensitivity). Survival curves were compared using log-rank test. A multivariate Cox model was also elaborated, and independent variables were chosen according to log-rank test results (ie, variables showing a p value ≤0.2). Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

3 | RESULTS

3.1 | General characteristics of the patient population

A total of 401 subjects with GGE were identified; 56 of whom were enrolled in the study according to the inclusion criteria (51.8% female, n=29). The median age of seizure onset was 13.5 years (interquartile range (IQR) 11–17), and the median follow-up after SSCB introduction was 28.5 years (IQR 18–33, range 5–39). The main clinical characteristics of the patient population are summarized in Table 1.

TABLE 1 Demographic and clinical characteristics.

Age of epilepsy onset, years, median (IQR)	13.5 (11–17)
Sex, female, n (%)	29 (51.8)
Follow-up duration, years, median (IQR)	28.5 (18–33)
Time from disease onset to SSCB prescription, years, mean (SD)	5.6 (8.76)
Left handedness, n (%)	4 (7.1)
History of febrile seizures, n (%)	6 (10.7)
Family history of epilepsy in 1st or 2nd degree relatives, n (%)	23 (41.1)
Psychiatric comorbidity, n (%)	10 (17.9)
Borderline IQ or mild cognitive impairment, n (%)	3 (5.4)
Type of epilepsy	
Childhood absence epilepsy, n (%)	5 (8.9)
Juvenile absence epilepsy, n (%)	10 (17.8)
Juvenile myoclonic epilepsy, n (%)	24 (42.9)
GGE with generalized tonic-clonic seizures only, n (%)	17 (30.4)
Seizure type at onset	
Absence seizures, n (%)	10 (17.9)
Myoclonic seizures/myoclonia, n (%)	6 (10.7)
Generalized tonic-clonic seizures, n (%)	40 (71.4)

Abbreviations: IQ, intelligence quotient; IQR, interquartile range; SD, standard deviation; SSCB, selective sodium channel blocker.

3.2 | EEG characteristics

GSWDs/GPSWDs were recorded in all patients during follow-up. The median maximum GSWD/GPSWD frequency was 4 (IQR 3–4), and the median minimum frequency was 3 (IQR 3–3). GPSWDs occurred in 36 patients (64.3%). Photoparoxysmal response during intermittent photic stimulation was recorded in 12 subjects (21.4%), and eye closure sensitivity was recorded in 2 (3.6%). Focal epileptiform abnormalities were found during follow-up in 9 patients (16.1%), whereas GSWD/GPSWD asymmetry/asynchrony was found in 13 (23.2%).

3.3 | SSCB prescribing pattern at first observation and during follow-up

SSCBs were used at the first observation in 17/56 (30.4%) patients (14 CBZ and 3 PHT). When SSCBs were used during follow-up, the mean number of years from seizure onset to SSCB prescription was 5.6 (SD ±8.76). The mean number of ASMs used prior to SSCB prescription was 2.1 (SD ±2.3), and 16/56 (28.6%) subjects tried at least 4 ASMs prior to SSCB introduction. The use of different SSCBs at the first observation and during follow-up is illustrated in Figure 1. SSCBs were used in a polytherapy regimen in 38/56 patients (67.9%). The most common ASMs used in association with SSCBs were valproate (VPA) in 18/38 patients and phenobarbital (PB) in 12/38 patients.

During follow-up, 47/56 (83.9%) patients switched to other ASMs or withdrew from treatment. The most common reason was unsatisfactory seizure control in 26/47 subjects (55.3%), adverse effects in 9 (19.2%), drug substitution due to epilepsy syndrome redefinition despite adequate seizure control in 5 (10.6%), and drug withdrawal during intervals of seizure freedom in 7 (14.9%). Among the patients who switched to different ASMs, VPA and levetiracetam (LEV) were the most frequent alternatives (VPA in 23/40—57.5%—and LEV in 9/40—22.5%). Seizure outcomes after SSCB substitution with ASMs licensed for GGE were complete remission in 13/40 subjects (32.5%), >50% seizure reduction in 13 (32.5%), and unchanged in 14 (35%).

At the last medical observation, SSCBs were still used by 9 patients (16.1%), all of whom were on a polytherapy regimen. When considering epilepsy syndromes, JME was associated with a lower rate of SSCB retention at last observation (2/24—8.3%—vs 7/32—21.9%, p=0.27).

During the whole duration of the follow-up, SSCB retention was 89.3% at 6 months, 78.6% at 12 months, 73.2% at 2 years,

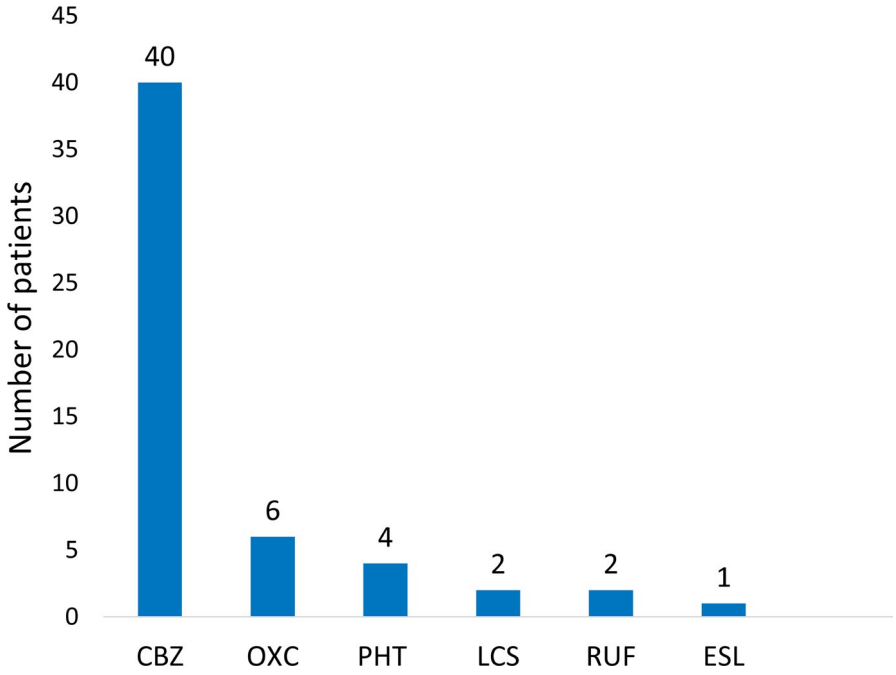

FIGURE 1 Selective sodium channel blocker use in our cohort. The number of patients using different selective sodium channel blockers is expressed above the bars. CBZ, Carbamazepine; ESL, Eslicarbazepine; LCS, Lacosamide; OXC, Oxcarbazepine; PHT, Phenytoin; RUF, Rufinamide.

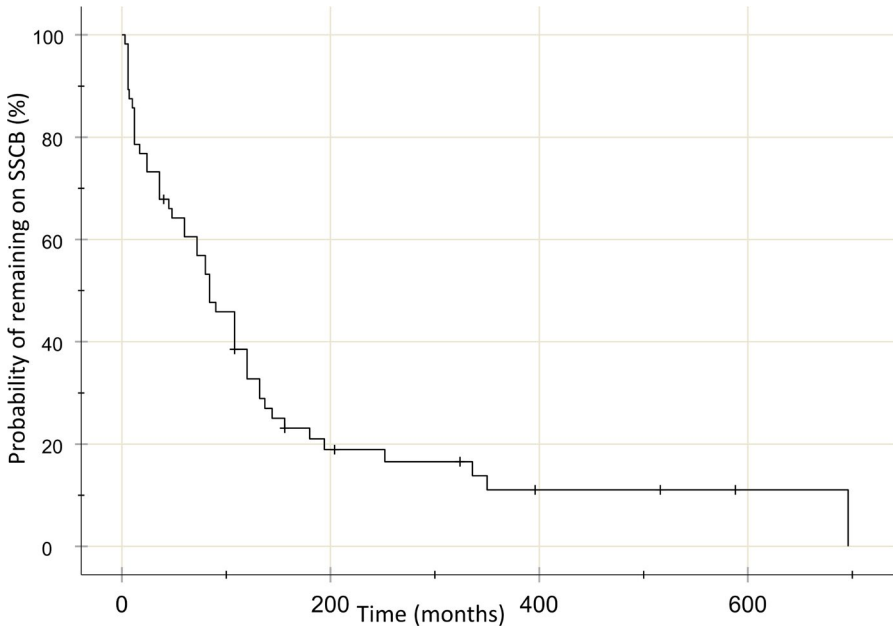

FIGURE 2 Kaplan-Meier survival estimates. Probability of remaining on a selective sodium channel blocker. Censored patients are indicated by crosses. SSCBs =selective sodium channel blockers.

58.9% at 5 years, and 30.4% at 10 years (Figure 2). The probability of SSCB retention during follow-up was significantly lower in patients exhibiting GPSWDs on EEG (log-rank test p=0.001) (Figure 3), while no other significant differences between groups were found according to log-rank test, including the number of ASMs tried prior to SSCB introduction (for a detailed description of survival estimates see Table S1). Cox multivariate regression analysis showed that GPSWD occurrence on EEG was the only variable significantly associated with a reduced probability of SSCB retention over time (HR: 0.32 95% CI 0.17–0.62, p=0.001) (see supplementary Table S2).

3.4 | Seizure outcome with SSCBs and clinical characteristics associated with drug response

A seizure reduction ≥50% occurred in 30/56 (53.6%) subjects when considering all seizure types and in 38 (67.9%) when considering only GTCS. Freedom from GTCS was obtained in 14/56 (25%) patients.

GPSWD occurrence on EEG was negatively associated with a ≥50% reduction in all seizure types (GPSWD 13/36 vs. GSWD only 17/20, p=0.001). A statistically significant seizure reduction of ≥50% was also found according to epilepsy syndrome (GGE-GTCS 13/17 vs. other syndromes 17/39, p=0.04). A detailed description of

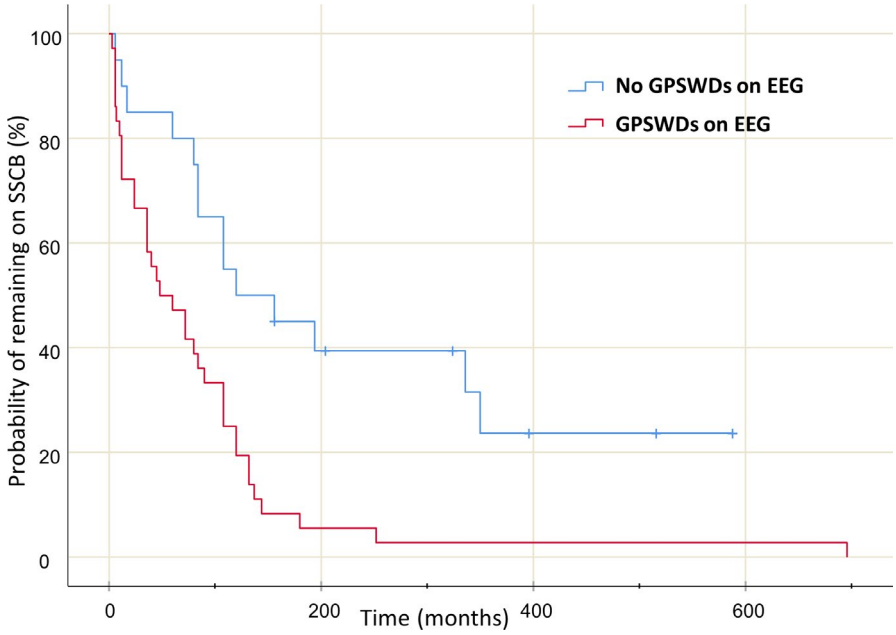

FIGURE 3 Kaplan-Meier survival estimates. Probability of remaining on a selective sodium channel blocker according to the presence or absence of generalized polyspike-wave discharges on EEG. Log-rank test was used to test significance, and censored patients are indicated by crosses. GPSWDs, generalized polyspike-wave discharges; SSCBs, selective sodium channel blockers.

all clinical and EEG variables stratified according to the occurrence of a ≥50% treatment response is presented in Table 3.

3.5 | Seizure and epilepsy aggravation after SSCB prescription

Considering the overall population, 5/56 (8.9%) patients displayed seizure worsening and epilepsy aggravation after SSCB introduction (CBZ in 4/5 and OXC in 1/5), and all were diagnosed with JME. When focusing on JME syndrome alone, epilepsy aggravation after SSCB introduction occurred in 5/24 patients (20.1%). All subjects experienced myoclonic seizure worsening (two of whom also showed absence seizure worsening), and one patient developed a myoclonic status epilepticus (see Table 2 for a detailed description of patient characteristics at the moment of epilepsy aggravation). Seizure worsening occurred with a median delay of 2 months from SSCB introduction (range 1–3 months).

A statistically significant difference in the rate of epilepsy aggravation was found for the following clinical variables: JME syndrome (5/24 vs. 0/32, p=0.01), family history of epilepsy (5/23 vs. 0/33, p=0.009), and history of myoclonic seizures (5/24 vs. 0/32, p=0.01). No other clinical or EEG variables were found to be significantly associated with seizure worsening and/or epilepsy aggravation, including SSCB maximal dose.

4 | DISCUSSION

The results of our study conducted in adult and adolescent GGE patients with long-term follow-up revealed some interesting findings: 1) SSCBs were used in a surprisingly high number of patients with GGE and were confirmed to be effective, especially in GTCS; 2) a few clinical, EEG, and syndromic variables were found to be associated with epilepsy aggravation and treatment response; and 3) the switch from SSCBs to ASMs licensed for GGE was often associated with improved seizure control during follow-up.

As previously mentioned, we found that a surprisingly high number of patients were prescribed SSCBs during their clinical history. This finding could be partially explained by the very long study timespan implying a limited number of available ASMs during the first years of the study period. Moreover, a considerable number of patients could have been erroneously considered as suffering from focal epilepsy at the time of diagnosis. A misdiagnosis between focal and generalized epilepsy syndromes has been frequently described in the literature and is known to potentially determine drug pseudoresistance and epilepsy aggravation in GGE patients,[29,30] especially in JME and JAE syndromes.[31,32] In spite of the reason for SSCB prescription, this gave us the opportunity to evaluate the effectiveness and safety of SSCBs in a considerable number of GGE patients during long-term follow-up.

As regards treatment effectiveness, we found that treatment response occurred in about half of patients when taking into account all seizure types and in almost 70% when considering only GTCS. When considering possible differences among different epilepsy syndromes, patients diagnosed with GGE-GTCS only were found to respond more frequently to SSCBs as compared with other GGE syndromes. SSCB effectiveness in this syndrome could be explained by the exclusive presence of GTCS and the absence of other seizure types (namely absence and myoclonic seizures) that are usually less responsive and more prone to worsening with SSCBs.[9] The interpretation of this result could be affected by the possible erroneous inclusion of patients suffering from focal epilepsies, considering the challenges in classifying epilepsy type in cases with GTCS only and atypical EEG findings.[33]

TABLE 2 Clinical characteristics of patients experiencing seizure worsening with SSCBs.

	PPR	Family history of epilepsy	SSCB	Years from onset to SSCB use	N of ASMs used prior to SSCB	ASMs used with SSCB	Type of worsened seizure	GTCS control	ASM used in place of SSCB	Seizure control after SSCB switch
Pt 1	No	Yes	CBZ	1	1	VPA	Myoclonic/ absence/GTCS	Worsening	LEV	>50%
Pt 2	Yes	Yes	OXC	23	6	CNZ, PB	Myoclonic (MSE)	<50%	LEV	>90%
Pt 3	No	Yes	CBZ	1	2	None	Myoclonic	Unchanged	VPA	>50%
Pt 4	No	Yes	CBZ	0	0	None	Myoclonic	<50	VPA	SF
Pt 5	No	Yes	CBZ	0	0	None	Myoclonic/absence	SF	VPA	SF

Abbreviations: ASM, antiseizure medications; CBZ, Carbamazepine; CNZ, Clonazepam; GTCS, generalized tonic-clonic seizures; LEV, Levetiracetam; PB, Phenobarbital; PPR, photoparoxysmal response; Pt, patient; SF, seizure freedom; SSCB, selective sodium channel blockers; VPA, Valproate.

Moreover, in contrast to what we usually observe with ASMs commonly prescribed in refractory GGE patients,[34] SSCB effectiveness did not appear to be influenced by the number of previous ASM failures. This observation could be related to the different mechanisms of action between SSCBs and other ASMs typically used in GGE patients.[35]

When considering the EEG variables influencing treatment response, we found that GPSWD occurrence was significantly associated with reduced effectiveness. The significance of this finding was also corroborated by survival analysis, which highlighted that GPSWD occurrence was the only variable significantly associated at multivariate analysis with an increased risk of reduced SSCB retention during follow-up. This observation may support the use of GPSWD as a potential EEG biomarker for the prediction of SSCB ineffectiveness, regardless of seizure type or epilepsy syndrome. When considering epilepsy syndromes, JME was associated with reduced SSCB retention at univariate analysis.

In terms of SSCB safety, we did not find any patients with absence epilepsies reporting seizure worsening, a result that contrasts with that of previous studies.[10,31] This discrepancy was probably related to the reduced sample size of our study. However, we confirmed a high rate of epilepsy aggravation among JME patients who were prescribed SSCBs, further confirming that SSCBs should be preferably avoided in patients with a history of myoclonic seizures.[30] Such observation was also suggested by our data about SSCB retention at last observation, at which a difference between JME and other GGE syndromes emerged. Interestingly, we also found a significant association between a family history of epilepsy and epilepsy aggravation in our cohort. Since systematic genetic testing was not performed, we cannot exclude an underlying sodium channelopathy in patients displaying seizure worsening.[36,37]

When reviewing the treatment regimen of patients experiencing seizure worsening in our cohort, we found that 3/5 patients were taking SSCBs as a monotherapy. This observation, although anecdotal, potentially suggests that the concomitant use of ASMs with a marked antiabsence/antimyoclonic effect may be considered to prevent SSCB-related worsening in patients with uncontrolled GTCS requiring an SSCB trial.

In spite of these encouraging observations, the most frequent reason for SSCB switch/withdrawal was unsatisfactory seizure control. Indeed, even though the treatment response rate was substantially high in our cohort, the lack of complete seizure remission probably justified drug substitution in favor of more conventional ASMs. The switch from SSCBs to ASMs licensed for GGE (mainly VPA and LEV) was found to determine improved seizure control in the majority of patients, confirming previous findings reported in the literature.[30-32]

Our study has several limitations, including: 1) its small sample size and retrospective design, the latter of which may be susceptible to recall and selection bias; 2) the long study timespan implying a reduced ASM armamentarium at baseline for many patients, which may have affected SSCB retention rate; 3) the lack of a systematic quantification of seizure frequency, which may have resulted in

TABLE 3 Demographic and clinical characteristics stratified according to the occurrence of ≥50% treatment response.

	≥50% all seizure reduction (30 pts)	<50% all seizure reduction (26 pts)	p value
Age of epilepsy onset, years, mean (SD)	13.5 (5.4)	13.2 (4.7)	0.9
Sex, female, n (%)	16 (53.3)	13 (50)	1
Time from disease onset to SSCB prescription, years, mean (SD)	5.4 (8.4)	6 (9.2)	0.8
Number of ASMs used prior to SSCB prescription, n, mean (SD)	2.1 (2.1)	2.1 (2.5)	1
History of febrile seizures, n, %	4 (13.3)	2 (7.7)	0.7
Family history of epilepsy in a 1st or 2nd degree relative, n (%)	11 (36.7)	12 (46.2)	0.5
Psychiatric comorbidity, n (%)	6 (20)	4 (15.4)	0.7
Borderline IQ or mild cognitive impairment, n (%)	2 (6.7)	1 (3.8)	1
Type of epilepsy			
Childhood absence epilepsy, n (%)	2 (6.7)	3 (11.5)	0.7
Juvenile absence epilepsy, n (%)	2 (6.7)	6 (23.1)	0.1
Juvenile myoclonic epilepsy, n (%)	12 (40)	12 (46.2)	0.6
GGE with generalized tonic-clonic seizures only, n (%)	13 (43.3)	4 (15.4)	0.04*
Myoclonic seizures, n (%)	12 (40)	12 (46.2)	0.6
GPSWDs on EEG, n (%)	13 (43.3)	23 (88.5)	0.001*
Focal abnormalities on EEG, n (%)	14 (46.7)	9 (34.6)	0.4
Photoparoxysmal response, n (%)	9 (30)	3 (11.5)	0.2

Abbreviations: ASMs, antiseizure medications; GGE, genetic generalized epilepsy; GPWSDs, generalized polyspike-wave discharges; IQ, intelligence quotient; SD, standard deviation.

The asterisks indicate statistically significant variables ($p < 0.05$).

inaccuracies in assessing treatment response and epilepsy aggravation; and 4) the prominent use of CBZ in our cohort, which may reduce the generalizability of our findings on the safety and effectiveness of newer SSCBs (eg, LCS and RUF). Finally, since SSCBs were mainly used in association with other ASMs, we cannot exclude the potential role of drug-drug interaction in treatment effectiveness and seizure aggravation (especially for inducers like PHT and CBZ).

In conclusion, our study contributes to clarifying the controversial topic of SSCB use in GGE patients. In particular, it provided new clinical and EEG variables associated with treatment effectiveness and epilepsy aggravation which may help neurologists in selecting the syndromic contexts in which the use of SSCBs may be more helpful. Based on our findings, SSCBs could be tried in GGE patients with uncontrolled GTCS seizures despite previous pharmacological trials, in association with more conventional broad-spectrum ASMs active on myoclonic/absence seizures. Nevertheless, particular caution should be used in JME patients, whom we confirmed to be more prone to SSCB-related epilepsy aggravation and reduced SSCB retention.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to disclose.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

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

ORCID

Carlo Di Bonaventura https://orcid.org/0000-0003-1890-5409

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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