



Quantifying the burden of disease in patients with Lennox Gastaut syndrome



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ABSTRACT

Lennox-Gastaut syndrome (LGS) is a severe epileptic encephalopathy but there is limited literature characterizing the disease burden despite this being crucial for disease management strategies, and for designing and interpreting clinical trials. We searched the Vagus Nerve Stimulation (VNS) Therapy Patient Outcome Registry including over 7000 patients with drug resistant epilepsy (DRE). Propensity Score Matching (PSM) matched LGS-DRE patients and non-LGS-DRE patients and frequencies of individual seizure types were assessed. The PSM population included 705 and 1410 DRE patients with and without LGS. 40% of the LGS-DRE group had polypharmacy with 3 antiseizure medications (ASM) while 42% in non-LGS-DRE had polypharmacy with 2 ASMs. Median total monthly seizure frequency was over double in the LGS group: 90 (IQR, 28–312) versus 40 (IQR, 10–150); $p < 0.001$. This analysis suggests that seizure frequency in LGS patients who later receive VNS is more than double than in non-LGS DRE patients with mostly bilateral tonic-clonic seizures contributing to this difference. Furthermore, ASM burden with poorer seizure control may be greater in LGS patients, however data collection ceased in 2003 and therefore does not take recent ASMs approved for LGS into account. This analysis offers quantitative insight into the burden of disease in patients with LGS.

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Introduction

Lennox-Gastaut syndrome (LGS) is among the most severe epileptic and developmental encephalopathies. This form of epilepsy poses a therapeutic challenge to physicians due to the presence of multiple drug-resistant seizure types as well as behavioural and cognitive impairments which may be impacted by antiseizure medications (ASMs). LGS also substantially impacts the health-related quality of life of patients, their families, and their caregivers, and ultimately affects the physical, emotional, social, and financial health of the family [1].

As seizure freedom in LGS is rarely achieved, current disease management strategies focus on controlling the frequency and severity of the most debilitating seizure types with a combination of ASMs to balance potential side effects while attempting to pre-

serve cognitive function and foster neurodevelopment [2]. Recent clinical trials of new ASMs for LGS are evaluating a reduction in frequency of seizures that result in drops as the primary endpoint because for many patients with LGS, drops are among the most debilitating seizure type [3–5]. However, there is limited quantitative data in the published literature describing the absolute seizure and ASM burden in LGS. Such information is crucial for effective disease management strategies and is also of interest for interpreting results of randomized controlled trials of ASMs in the context of their real-world impact, as well as for designing future clinical trials in subjects with LGS.

The purpose of this post-market case-control registry-based study was to evaluate the burden of drug-resistant epilepsy (DRE) in patients with or without LGS who received vagus nerve stimulation therapy (VNS Therapy) adjunctive to anti-seizure therapies. Specifically, the study objective was to investigate the real-world characteristics and disease burden by exploring the demographics, baseline characteristics, disease history, overall seizure frequency, frequency of individual seizure types, ASM burden, and comorbidities. We therefore utilized data on patients with

Abbreviations: ASM, antiseizure medication; LGS, Lennox-Gastaut Syndrome; VNS, vagus nerve stimulation.

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LGS (and matched controls without LGS) from the VNS Therapy Patient Outcome Registry which comprises of data from more than 7000 patients treated with adjunctive VNS Therapy.

Materials and methods

This study was carried on in accordance with the STROBE statement [6] and the RECORD statement [7].

Study design and participants

This study analysed baseline patient data extracted from the VNS Therapy Patient Outcome Registry which is maintained by the manufacturer of the VNS Therapy system (Cyberonics, Inc.). The registry was established in 1999 after FDA approval of VNS Therapy for the treatment of epilepsy to systematically monitor patient outcomes. Active data collection in the registry ceased in 2003.

Data access and cleaning methods

Since 1999, registry data were prospectively and voluntarily provided by 1285 prescribing physicians from 978 centres (911 centres in the United States and Canada, and 67 centres outside of North America). Neurologists or their designated staff completed standard case report forms based on a patient's medical history or current visit and voluntarily sent these forms to Cyberonics for data entry. Active data collection ceased in 2003. Previous investigators have authenticated the integrity of the systems for collecting and processing registry data using an independent auditing agency [8].

All study data were de-identified prior to analysis. Individual, de-identified data were used to construct aggregate statistics. Only aggregate data was retained and presented in any publication. Access to data was restricted to the minimum number of study investigators and accessed via encrypted security codes without further distribution prior to de-identification.

Variables and data sources

The complete registry database was queried to extract the following data for further analysis: Epilepsy syndrome (LGS or non-LGS), demographic characteristics, age at implant and at diagnosis (onset), gender, ethnicity, current number of ASMs, medical history, and seizure outcomes reported before or at VNS Therapy device implant (baseline).

The population included in the full analysis set had at least one value for analysis on overall seizure count and seizure type count. Outcome analyses were performed in the Propensity Score Matched (PSM) population: a homogeneous population derived using a PSM method.

Baseline was defined as the last non-missing observation before the VNS Therapy was implanted. Measurements collected on the day of implant, in absence of other time information, were considered baseline.

The primary endpoint of the analysis was the description of the seizure count distribution in LGS and non-LGS patients based on overall seizure frequency and frequency of individual seizure types.

Bias

Selection bias was controlled by selecting a homogeneous population through PSM method (PSM population) [9]. This method was used to match patients in the disease populations of LGS and

non-LGS. Ordinal logistic regression model was run to regress the disease population variable on age at implant, age at diagnosis, and gender. Patients were matched based on the conditional probability of belonging to a specific disease population (LGS or non-LGS) and by using an optimal matching at a 1:2 ratio, so that for each LGS patient record was matched with two non-LGS patient records.

Study sample size

The study sample size was not based on a statistical power calculation, as this is an enumerative study that will consist of all patients included in the VNS Therapy Patient Outcome Registry. A total of 7383 (808 [10.9%] and 6575 [89.1%] non-LGS) patients have been enrolled in the study.

Quantitative variables

Seizure count and other continuous variables were presented as median and interquartile range (IQR), whereas categorical variables were presented as number of non-missing observations and relevant percentage on the analysis population. In case of subcategories, the relative frequencies were calculated on the basis of the patients in the subcategory. Confidence intervals (CIs) for the medians of seizure count were provided at a two-sided 95% significance level.

Summaries on seizure count were provided as overall seizure count and by seizure types. The registry's case report form asks for frequency of the following specific seizure types according to the 1981 ILAE Classification, extended in 2010: simple partial, complex partial, generalized tonic clonic, secondary generalized, absence, drop attack, and aura. Here we refer to the seizure types according to the current International League Against Epilepsy (ILAE) seizure classification: focal aware motor (FA), focal impaired awareness motor (FIA), bilateral tonic clonic (BTC), focal to bilateral tonic clonic (FBTC), generalized-onset non-motor (GONM) with the exception of drop attack and aura, which technically should be classified as generalized-onset atonic and focal aware non-motor seizures but within the previous classification may comprise other seizure types.

Statistical methods

No statistical tests for comparison of data between LGS and non-LGS disease populations were performed and therefore, all analyses were considered descriptive and not confirmatory in nature. Patient characteristics and medical history were summarized overall (i.e., considering the entire study sample) and by disease population (LGS or non-LGS), further stratified for the subgroups of interest. Furthermore, descriptive statistics for seizures count at baseline were displayed in the following subgroups of interest: class of age at implant, duration of epilepsy, class of age at diagnosis, gender, ethnicity, number of ASMs used at implant, and prior diagnosis.

Primary analysis for this post-market case-control registry-based study was evaluated in the PSM population. Statistical analysis was performed using SAS (SAS Institute, Inc.), Version 9.4. Distribution of seizures count at baseline, including the 95% confidence intervals for the median, were summarized descriptively overall, per each seizure type and by each interested subgroup. No imputation methods were used to handle missing data.

Linkage

Not applicable.

Results

Participants

The VNS Therapy Patient Outcome Registry included a total of 7383 patients; of these 808 (10.9%) had an LGS diagnosis and 6575 (89.1%) had an alternative diagnosis. The Full Analysis Set population included a total of 7311 patients who had at least one value on overall seizure count and seizure type count: 802 (11%) were in the LGS group and 6509 (89%) were in the non-LGS group.) The PSM method selected a cohort of 2115 patients homogeneous for age at implant, age at diagnosis and gender between the LGS group (705 [33.3%]) and the non-LGS group (1410 [66.7%]).

Demographics and baseline clinical characteristics

As the PSM population is aged matched, comparisons of age at VNS implant must be made in the Full Analysis Set (FAS) population, defined as all patients enrolled in the registry having at least one value on overall seizure count and seizure type count. At the time of VNS implant, LGS patients were comparatively younger with a median age of 14 years (IQR, 9–23) years compared with 28 years (IQR, 15–41) in the non-LGS group. Furthermore, the median age of LGS patients at disease onset was younger 1 year (IQR, 0.5–3) compared with 5 years (IQR, 1–12.5) in the non-LGS population. Therefore, the median latency from disease onset to VNS implant was 13 years (IQR, 8.5–21) in the LGS group compared with 23 years (IQR, 14–28.5) in the non-LGS group, potentially indicating a more rapid escalation of seizure burden in the LGS group.

Seizure type

Fig. 1 summarizes the distribution by seizure type of the subjects matched with the PSM method. Most patients in the LGS group experienced BTCs (51.3%) and “drop attacks” (38.7%). In the non-LGS group, most patients experienced FIAs (55.9%).

Outcome results

Overall, LGS patients showed a greater median monthly seizure count (90; 95% CI 83–105) compared with the non-LGS patients (40; 95% CI 34–45). This difference was not reflected within seizure type; however, a trend toward a higher count of monthly BTC was observed in the LGS versus non-LGS group (12 [95% CI 10–16] vs 10 [95% 8–10]) as presented in Fig. 2.

In the age groups younger than 12 years at disease onset, higher monthly seizure count was observed at VNS implant in the LGS patients versus non-LGS patients, with overall monthly seizure counts being more than twice as high in groups < 1 year, 1–2 years, and 3–12 years of age. Baseline characteristics associated with higher monthly seizure count in the LGS group were developmental delay, psychosocial/psychiatric disorders, behavioural problems, mental retardation, chronic illness, neurological defects, and chronic illness (Table 2).

At the time of implant 40.0% and 34.% of LGS patients were receiving 3 ASM and 2 ASM therapies respectively, whereas 32.1% and 41.7% of patients in the non-LGS group were receiving 3 ASM and 2 ASM therapies respectively (Table 1; Fig. 3). Higher monthly seizure counts were observed in LGS patients versus non-LGS patients irrespective of whether they were receiving 1, 2, 3, or more than 3 ASMs. Interestingly, within both the LGS and non-LGS groups median monthly seizure count was similar regardless of how many ASMs were being taken, however 95%CI s were widest in the LGS groups with 0 and more than 3 ASMs. (Fig. 4).

Discussion

This analysis suggests that seizure frequency in LGS patients who later undergo VNS implant is more than double than that in non-LGS patients with DRE. The difference was in part due to a trend towards a higher frequency of bilateral tonic clonic seizures in the LGS population, which together with “drop attacks” are often considered as being among the most debilitating seizure types. Furthermore, ASM burden with poorer seizure control could be considered to be greater in LGS patients and appeared to be associated with factors in patients’ medical history considered to be

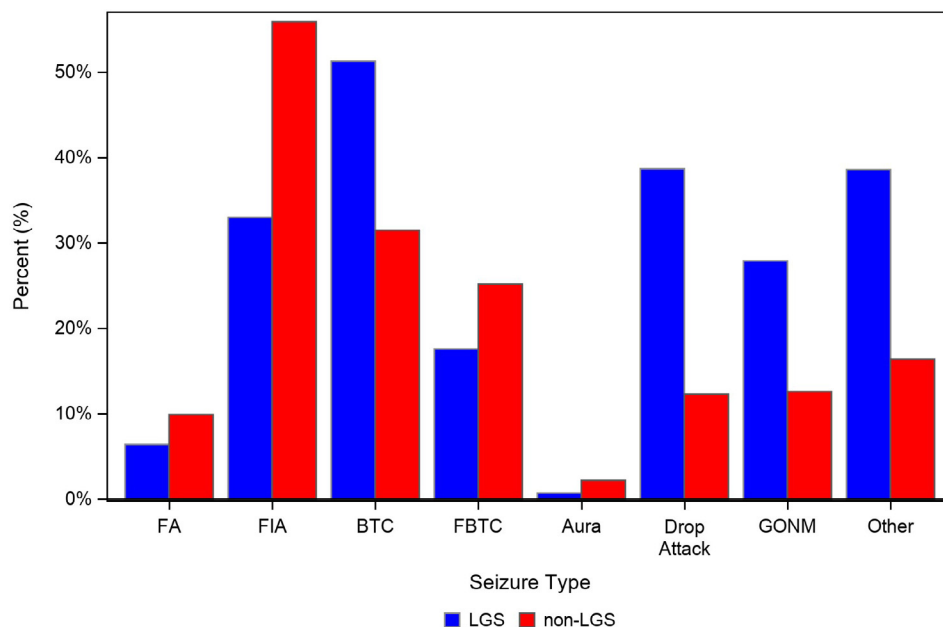


Fig. 1. Prevalence of seizure types in patients with DRE with and without Lennox-Gastaut syndrome in the PSM population. Most patients in the LGS group experienced BTCs (51.3%) and “drop attacks” (38.7%). In the non-LGS group, most patients experienced FIAs (55.9%).

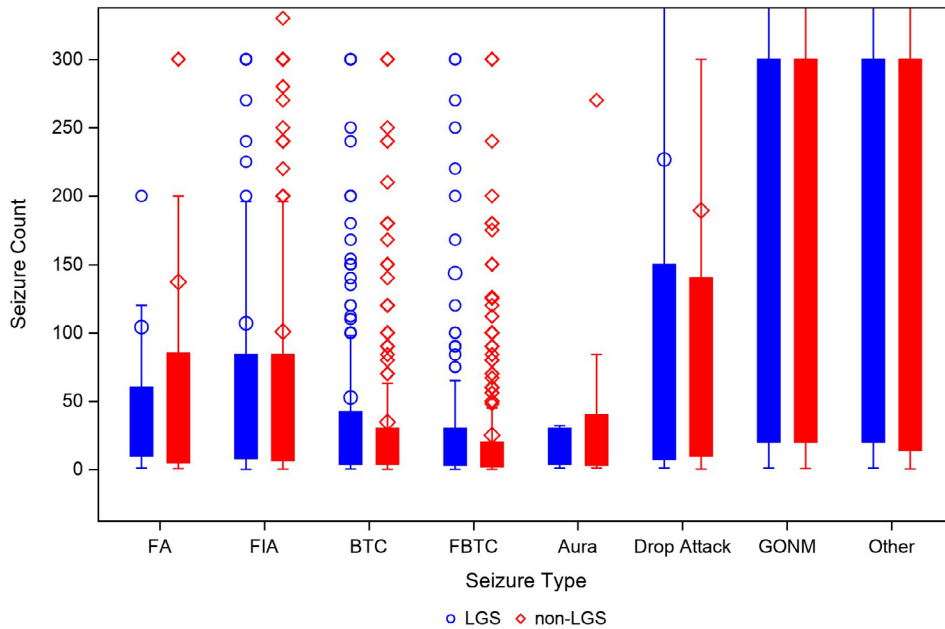


Fig. 2. Monthly seizure count in patients with DRE with and without Lennox-Gastaut syndrome in the PSM population. Variable interquartile range (IQR) are represented through boxes in which the middle line fits the distribution median and the first-third quartiles (q1-q3) are represented by the lower and first edges of the box. The lower fence is defined as the q1-1.5(IQR). The upper fence is defined as the q3 + 1.5(IQR). Observations outside the fences are identified as extreme outliers.

Table 1
Demographics and characteristics of patients with or without Lennox-Gastaut syndrome in the PSM population.

	LGS (N = 705)	non-LGS (N = 1410)	Total (N = 2115)
Age at implant (years), median (IQR)	14 (9–23)	14 (8–24)	14 (8–23)
Age of onset (years), median (IQR)	1 (0.5–3)	1 (0.4–3)	0.4 (0–3)
Male, n (%)	463 (57.7)	3370 (51.8)	3833 (52.4)
<i>Ethnicity, n (%)</i>			
Caucasian	571 (81.0)	1179 (83.6)	1750 (82.7)
African American	31 (4.4)	64 (4.5)	95 (4.5)
Hispanic	50 (7.1)	98 (7.0)	148 (7.0)
Asian	10 (1.4)	7 (0.5)	17 (0.8)
Other/Unknown/Not Checked	43 (6.1)	62 (4.4)	105 (5.0)
<i>Current ASM therapies, n (%)</i>			
0	5 (0.7)	16 (1.1)	21 (1.0)
1	60 (8.5)	191 (13.5)	251 (11.9)
2	242 (34.3)	588 (41.7)	830 (39.2)
3	282 (40.0)	453 (32.1)	735 (34.8)
>3	116 (16.5)	162 (11.5)	278 (13.1)
<i>Medical history, n (%)</i>			
Patients with at least one previous disease *	675 (95.7)	1344 (95.3)	2019 (95.5)
Congenital brain malformation	70 (10.4)	239 (17.8)	309 (15.3)
Meningitis/encephalitis	60 (8.9)	128 (9.5)	188 (9.3)
Vascular brain malformation	6 (0.9)	26 (1.9)	32 (1.6)
Evaluated for epilepsy surgery/intracranial surgery	298 (44.1)	655 (48.7)	953 (47.2)
Previous callosotomy for epilepsy	69 (10.2)	52 (3.9)	121 (6.0)
Previous lobectomy for epilepsy	3 (0.4)	90 (6.7)	93 (4.6)
Other for epilepsy	5 (0.7)	60 (4.5)	65 (3.2)
Other for any IC Surgery	3 (0.4)	62 (4.6)	65 (3.2)
Brain Tumour	4 (0.6)	49 (3.6)	53 (2.6)
Head Injury	33 (4.9)	104 (7.7)	137 (6.8)
Febrile Seizures	59 (8.7)	191 (14.2)	250 (12.4)
Psychosocial/Psychiatric Disorder	120 (17.8)	269 (20.0)	389 (16.3)
Depression	21 (3.1)	114 (8.5)	135 (6.7)
Behavioural Problems	224 (33.2)	393 (29.2)	617 (30.6)
Neurological Defect	354 (52.4)	574 (42.7)	928 (46.0)
Mental Retardation	482 (71.4)	655 (48.7)	1137 (56.3)
Development Delay	434 (64.3)	735 (54.7)	1169 (57.9)
Cerebral Palsy	131 (19.4)	197 (14.7)	328 (16.2)
Autism	48 (7.1)	83 (6.2)	131 (6.5)
Rett Syndrome	5 (0.7)	10 (0.7)	15 (0.7)
Tuberous Sclerosis	24 (3.6)	61 (4.5)	85 (4.2)
Major Surgical Procedures	74 (11.0)	184 (13.7)	258 (12.8)
Chronic Illness	73 (10.8)	158 (11.8)	231 (11.4)
Other	133 (19.70)	264 (19.6)	397 (19.7)

IQR: Interquartile Range

Percentage denominator is the overall number of patients included in the overall PAS population.

Patients may be counted in more than one previous disease term.

* In case of subcategories, the relative frequencies are calculated on the patients in the subcategory.

characteristic of LGS such as behavioural problems and developmental delay.

Although LGS is well known to be associated with drug resistance and frequent seizures of different types, little data is available quantifying the magnitude thereof. The results of this analysis suggest that in investigations of therapies for DRE, LGS

patients be evaluated separately and by using potentially different methodology. The majority of clinical studies evaluating the efficacy of treatments for DRE populations define a reduction in overall seizure frequency of 50% as response. This may be adequate for certain DRE populations, however may be too vague for evaluating treatment effects in patients with LGS, who suffer from multiple

Table 2

Summary of median seizure counts per month (95% confidence intervals) experienced by patients with or without Lennox–Gastaut syndrome in the PSM population.

	LGS (N = 705)	non-LGS (N = 1410)	Total (N = 2115)
Overall median seizure count per month (95% CI)*	90 (83–105)	40 (34–45)	55 (48–60)
<i>Seizure type</i>			
Focal aware motor (FA)	28 (20–40)	20 (12–30)	20 (19–30)
Focal impaired awareness motor (FIA)	30 (20–30)	20 (20–28)	24 (20–30)
Bilateral tonic clonic (BTC)**	12 (10–16)	10 (8–10)	10 (10–12)
Focal to bilateral tonic clonic (FBTC)	10 (8–15)	8 (6–10)	8 (6–10)
Aura	10 (1–32)	20 (4–30)	17.5 (5–30)
Drop attack	40 (30–60)	40 (30–60)	40 (30–60)
Generalized-onset non-motor	67 (45–98)	60 (35–100)	63.5 (50–90)
Other	89.5 (60–100)	90 (60–100)	90 (60–100)
<i>Age at implant, year</i>			
<1 year	—	—	—
1–2 years	200 (66–930)	200 (14–330)	200 (140–300)
3–12 years*	180 (132–240)	71 (60–90)	98 (88–120)
13–17 years*	100 (90–136)	50 (38–63)	64.5 (56–86)
≥18 years*	41 (35–60)	20 (16–23)	26 (22–30)
<i>Age at onset, year</i>			
<1 year*	120 (90–150)	55 (45–60)	68 (60–84)
1–2 years*	76 (60–105)	30.5 (28–41)	42 (35–52)
3–12 years*	64.5 (45–90)	30 (27–36)	35 (30–50)
13–17 years	7.5 (3–3015)	34 (7–150)	32 (7–92)
≥18 years	136 (23–2620)	7 (3–30)	22 (4–136)
<i>Gender</i>			
Male*	100 (90–120)	38 (31–45)	55 (45–60)
Female*	80 (60–101)	41 (34–53)	56 (45–60.3)
<i>Ethnicity</i>			
Caucasian*	92 (84–115)	40 (34–45)	56 (48–60)
Afro-American	46 (24–200)	22 (14–53)	30 (18–53)
Hispanic	88.5 (60–120)	45 (30–64)	60 (40–68)
Asian	40.5 (12–660)	170 (20–1100)	110 (33–448)
<i>Current ASM therapies</i>			
0	160 (1–4950)	37 (12–600)	80 (12–272)
1*	122 (60–215)*	36 (25–56)	51.3 (35–70)
2*	91.8 (74–122)*	32 (30–40)	45 (38–60)
3*	79 (61–98)*	45 (38–60)	60 (46–65)
>3*	107.5 (80–200)*	50 (36–65)	73.5 (50–91)
<i>Medical history</i>			
Congenital brain malformation	90 (43–181)	65 (56–100)	74 (60–100)
Meningitis or encephalitis	81.5 (45–130)	39 (28–56)	46.8 (32–68)
Vascular brain malformation	275 (32–694)	26 (4–80)	38 (8–102)
Evaluated for epilepsy surgery or intracranial surgery*	104 (90–135)	35 (30–41)	50 (42–60)
Previous callosotomy for epilepsy	83 (40–154)	49 (31–86)	65 (42–96)
Previous lobectomy for epilepsy	110 (2–300)	31 (23–49)	32 (24–50)
Other medical history related to epilepsy	160 (10–300)	32 (17–92)	50 (20–94)
Other medical history related to interstitial cystitis surgery	30 (8–1503)	35.5 (20–84)	35 (20–64)
Brain tumour	257.5 (36–630)	40 (30–61)	45 (32–64)
Head injury	22 (10–39)	30 (20–41)	28 (20–35)
Febrile seizures	40 (21–180)	24 (19–30)	26.5 (20–36)
Psychosocial or psychiatric disorder*	86.3 (60–115)	26 (20–33)	40 (30–50)
Depression	40 (18–87.5)	12 (10–20)	18 (12–28)
Behavioural problems*	90 (72–124)	48 (40–60)	60 (52–76)
Neurological defect*	132 (98–170)	52 (44–62)	72.5 (60–90)
Mental retardation*	85.8 (65–100)	50 (40–60)	60 (56–70)
Development delay*	90 (73.6–105)	60 (48–70)	66 (60–83)
Cerebral palsy	150 (103–220)	84 (50–120)	113.5 (76–150)
Autism	138 (72–300)	52 (35–89)	75 (52–110)
Rett syndrome	392 (65–693)	33.5 (8–310)	65 (15–392)
Tuberous sclerosis	100 (46–250)	84 (60–120)	90 (65–121.5)
Major surgical procedures	98 (60–210)	40 (30–80)	60.5 (39.8–91)
Chronic illness*	181 (80–360)	40 (30–70)	63 (40–102)
Other*	120 (83–160)	56.5 (38–60)	62 (56–89)

* Median (95% CI) in LGS group is significantly greater than median (95% CI) in non-LGS group.

** Trend towards difference in LGS versus non-LGS median 95% CIs (lower limit in LGS group is equal to upper limit in non-LGS group).

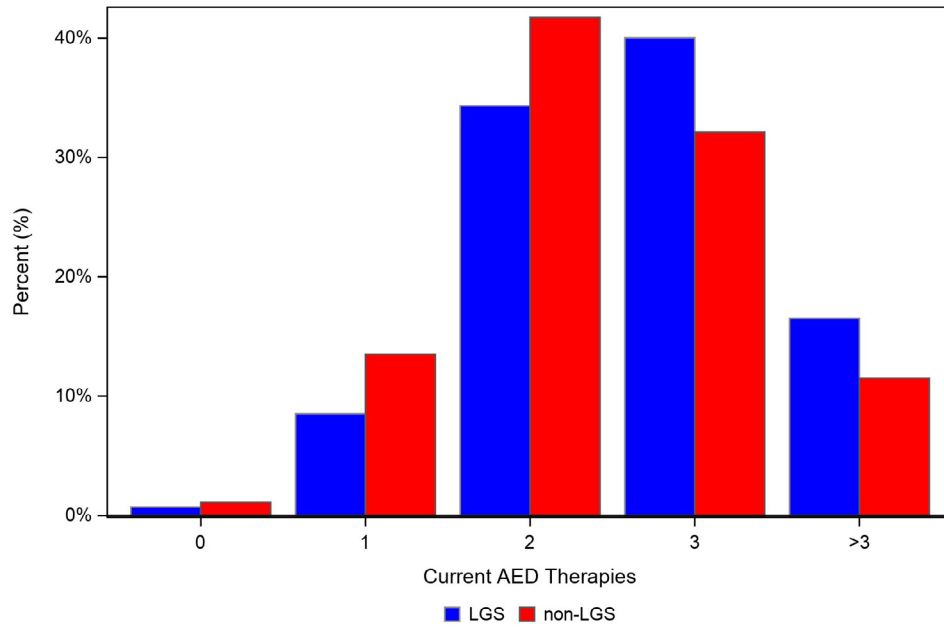


Fig. 3. At the time of implant, 40.0% of LGS patients were receiving 3 ASM therapies, whereas 41.7% of patients in the non-LGS group were receiving only 2 ASM therapies.

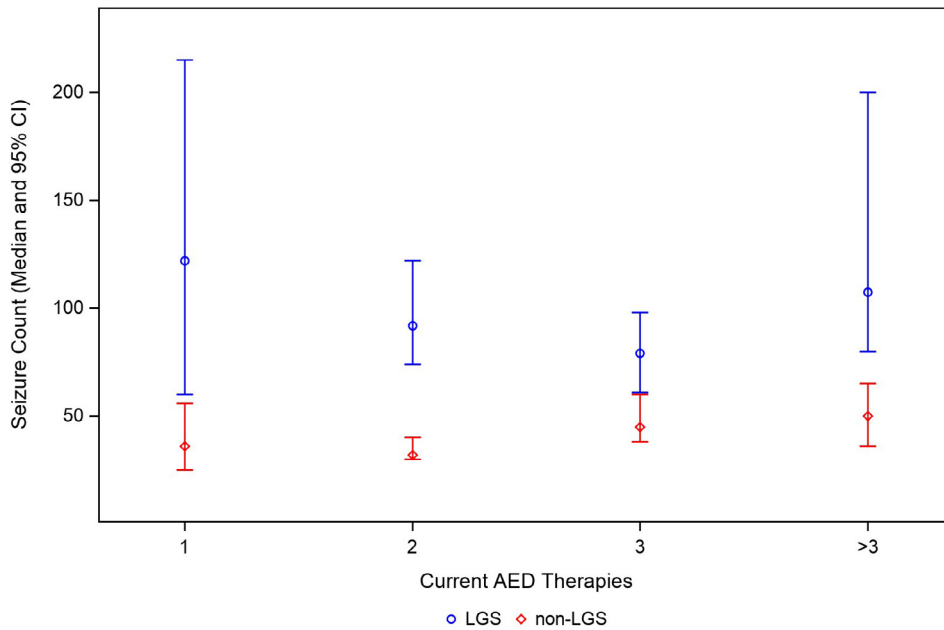


Fig. 4. Seizure count by ASM therapy in patients with DRE with and without Lennox-Gastaut syndrome in the PSM population. Higher monthly seizure counts were observed in LGS patients versus non-LGS patients irrespective of whether they were receiving 1, 2, 3, or more than 3 ASMs.

seizure types occurring at different frequencies as shown in this analysis. Considering the pronounced differences in seizure and medication burden in LGS patients found by this analysis, one may hypothesize that a 50% reduction in seizure frequency – the definition of response in the majority of trials of antiepileptic therapies - may hold a different importance for LGS patients and their families than for non-LGS patients with DRE. Therefore, establishing outcome measures more tailored to the LGS population may be of value in better evaluating the clinical meaningfulness of treatments in LGS patients. For example, outcome measures may focus on an intervention’s ability to reduce bilateral tonic clonic seizures or reduce the number of concomitant ASMs and their side-effects while not aggravating behavioural problems or neurodevelopment.

Such an outcomes strategy may be more meaningful and achievable in the LGS population. Furthermore, the early onset and rapid escalation of seizure burden in LGS call for therapies suitable in a paediatric population and that are accessible without a long delay. Additionally, establishing standard reporting criteria for LGS treatments may be useful and may include a commitment to reporting on the treatments effect on all seizure types experienced by the patient in absolute numbers (even if the treatment is only being evaluated for one seizure type) and specific clinical tools for assessing daily functioning. Lastly, with the presentation of LGS being diverse, and there often being a delay between first symptoms and the emergence of the full clinical syndrome, identifying early predictors of LGS may allow for investigation of an interventions

ability to prevent the escalation of disease described in this analysis. Future studies may focus on quantifying the relative degree of seizure control (change in seizure frequency, in seizure severity and in seizure clustering of individual seizure types) necessary to achieve meaningful quality of life improvements in patients with LGS and evaluate treatments in this context.

Several limitations must be taken into consideration when interpreting the results of this analysis. Most importantly, the fact that this analysis only includes patients who later received VNS Therapy inserts a selection bias into the study population, which may also include bias from the fact that VNS Therapy is FDA approved for drug-resistant focal-onset seizures potentially affecting patient selection/referral for VNS in the LGS group differently. Furthermore, although the data in the VNS Therapy Patient Outcomes Registry was collected prospectively, the current analysis was retrospective in nature and therefore, all inherent bias of retrospective analyses apply. Further limitations arise from the fact that the data was collected observationally and voluntarily by neurologists and their designated staff between 1999 and 2003 potentially affecting accuracy and consistency of the classification of seizure types and the diagnosis of LGS, resulting in variability in the combination of ASMs and in stimulation parameters and leading to inconsideration of the three newer ASMs approved for LGS in the United States.

Conclusions

Taken together, the results from this analysis offer quantitative insight into the burden of disease in patients with LGS and may inform more LGS-specific trial designs and interpretation of trials results in LGS patients in the future.

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Disclosures

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of LivaNova PLC. JKHS has received a research grant from LivaNova PLC. MAK has received consulting fees from the Deutsche Krebsgesellschaft.

Compliance with Ethical Standards

Not applicable.

Conflicts of Interest

MD, TG, and SF are employees of LivaNova PLC, the manufacturer of VNS Therapy System and MD holds stock options. JS has received a research grant from LivaNova PLC. MAK has received consultation fees from Deutsche Krebsgesellschaft.

Accessibility of protocol and raw data: The identified participant's data for the VNS Therapy Patient Outcome Registry will not be shared. Please contact the corresponding author for data requests.

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