Comparison of healthcare resource utilization in pediatric patients with refractory epilepsy: Vagus nerve stimulation and medical treatment cohorts

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\textbf{Abstract}

Objectives: Refractory epilepsy imposes a substantial burden on affected patients, families, and healthcare system. In terms of treating seizures in children, vagus nerve stimulation (VNS) has been proved to be comparable to that of antiepileptic drugs (AEDs). This study compared healthcare resource utilization between pediatric patients treated with AEDs only and AEDs plus VNS.

Methods: Pediatric patients diagnosed with refractory epilepsy between the 1st of January 2011 and the 31st of December 2016 were identified from the Pediatric Health Information System Database. Patients treated with AEDs only or AEDs plus VNS were included in the study and were followed up from one year before to two years after the date when defined criteria for refractory epilepsy were met. The difference-in-difference approach along with the hurdle model was used to compare the changes in healthcare resource utilization over time between patients treated with AEDs only and AEDs plus VNS.

Results: The study included 1502 patients treated with AEDs plus VNS and 4541 patients treated with AEDs only. There was a difference in post-index all-cause and epilepsy-related inpatient visits compared to the pre-index period: inpatient hospitalizations were decreased in the AEDs plus VNS cohort, and increased in the AEDs only cohort. There was no significant difference in the pre-index to post-index change for all-cause and epilepsy-related emergency department visits between the two treatment cohorts. For outpatient encounters in the initial post-index period, patients treated with AEDs plus VNS had significantly higher increase in all-cause and epilepsy-related outpatient visits compared to the AEDs only cohort.

Conclusions: Compared to those treated with AEDs only, pediatric patients with refractory epilepsy treated with AEDs plus VNS have fewer inpatient visits and more outpatient visits within a 2-year follow-up. Given the lower acuity of care in outpatient versus inpatient settings, this study can inform treatment choices for children with refractory epilepsy.

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1. Introduction

Epilepsy is a neurological disorder affecting 0.5–2.0% of the population in the United States [1] and is more common in children than adults [2]. The prevalence rate of childhood epilepsy is 10.2 per 1000 children [3]. Although many of these pediatric patients become seizure free with antiepileptic drugs (AEDs) as first-line treatment, about 1/5 –1/3 of these pediatric patients have long-term refractory epilepsy that are not controlled by multiple AEDs [4,5]. Children with poorly controlled epilepsy have more hospitalizations, emergency department visits, and outpatient visits compared to those with controlled epilepsy, defined as patients having no change in AED monotherapy or combination therapy for ≥1 year [5]. The estimated costs of treating refractory epilepsy are two- to ten-times of non-refractory epilepsy [5,6].

For lesional cases and other select candidates, cranial surgery can be a good option. Not all patients are ideal candidates for cranial epilepsy surgery [7]: some patients either continue medication therapy or receive surgery for neuromodulation modalities, the most common of which is vagus nerve stimulation (VNS).
Evidence-based clinical guidelines from American Academy of Neurology in 2013 delineate that VNS is an effective option for treating seizures in children [8]. Vagus nerve stimulation has been shown to be effective at controlling seizures with seizure burden reduction (>=50% reduction) at one year after VNS was between 51.4% and 68% [9–14]. The efficacy of VNS is thus at the very least comparable to that of new AEDs after one year [15].

Vagus nerve stimulation implantation and addition of AEDs can both be significant in terms of time, resources, and uncertainty of continued disease burden from patient, physician, payor, and policy perspectives. Hence, comparison of healthcare resource utilization associated with AEDs plus VNS and AEDs alone is warranted. To date, such information is rare for pediatric patients with refractory epilepsy. Most available publications have relatively small sample sizes or only compare the utilization before and after VNS implantation [16–19] without a comparison group. To our knowledge, this is the first study to compare resource utilization associated with AEDs only and AEDs plus VNS in pediatric patients. Here, we analyzed data from the nationwide Pediatric Health Information System (PHIS) database to compare the healthcare resource utilization between pediatric patients treated with AEDs only and AEDs plus VNS.

2. Material and methods

2.1. Data sources

Data from the Children’s Hospital Association’s Pediatric Health Information System (PHIS) database, which represents 13.3% of the national volume of all hospitalized pediatric patients, was used to conduct this retrospective observational study. PHIS contains inpatient, emergency department, ambulatory, and observation encounter level data from more than 44 children’s hospitals in the United States since 2007. This database includes treatment details as well as all charged items/services billed to the patient, pharmacy, imaging/radiology, lab, clinical, supplies, and other charges that allow us to examine healthcare resource utilization and hospitalization costs among pediatric patients receiving epilepsy treatment. All encounter-level data are de-identified. This study received exempt status as non-human subjects research with the Institutional Review Board at Ann and Robert H Lurie Children’s Hospital of Chicago.

2.2. Study design and population

The study cohort (Fig. 1) was assembled in a 4-step process. First, we performed a retrospective query from PHIS using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code and 10th Revision, Clinical Modification (ICD-10-CM) codes. We extracted the data on pediatric patients (ages 0 and 17 years) discharged between 1/1/2011 and 12/31/2018 based on available data at the time of analysis, with primary diagnosis codes of epilepsy (ICD-9-CM code 345.XX and ICD-10-CM code G40.XXX) or seizure (ICD-9-CM code 780.3X and ICD-10-CM code R56.X or R56.XX). Patients were included in this step if they had at least two visits and met any of the following published algorithms that have been used to identify epilepsy [20–24]: (1) at least 2 encounters with diagnosis code 345.XX or G40.XXX on separate dates in any visit (including inpatient, emergency department, or ambulatory care); (2) at least 1 encounter with diagnosis code 345.XX or G40.XXX and at least 1 separate encounter on a different date with diagnosis code 780.3X or R56.X or R56.XX; (3) a primary diagnosis code 345.XX or G40.XXX and a therapeutic category code indicating antiepileptic medication; (4) at least 2 encounters with diagnosis code 780.3X or R56.X or R56.XX and code(s) for antiepileptic medication; (5) an inpatient or emergency department visit with a primary diagnosis code 345.XX or G40.XXX. Second, we selected patients with refractory epilepsy from the epilepsy cohort using the diagnosis codes listed in Supplementary Table 1. Third, patients with refractory epilepsy were assigned to the AEDs only cohort if they received at least three types of AEDs or to the AEDs plus VNS cohort if they received VNS in addition to their existing medications. For the AEDs only cohort, the first encounter date of the third type of AEDs was defined as the index date for the purpose of study tracking. The first encounter date for VNS implantation was defined as the index date for the AEDs plus VNS cohort. Finally, we included patients whose index admission date was between 1/1/2011 and 12/31/2016, whose age at index date was between 0 and 17 and who had treatment information available for at least one year before and two years after the index date. Patients were excluded if they had any cranial surgery for epilepsy before and within two years following index date or had missing values on key variables.

2.3. Dependent variables

2.3.1. Healthcare resource utilization

Healthcare resource utilization that can be extracted from the PHIS database includes inpatient encounters, outpatient encounters, and emergency department visits. Treatment information was extracted one year before the index date (pre-index period) and was followed up two years after the index date (post-index period). Encounters occurring at the index date were counted as utilization in the post-index period. All-cause and epilepsy-related healthcare resource utilization were measured as average annual utilization during the pre-index and post-index periods, which included counts of inpatient admissions, outpatient visits and emergency department visits. Epilepsy-related utilization were identified from records that had 345.XX, G40.XXX, 780.3X, R56.X or R56.XX as the diagnosis code. In this rubric, “epilepsy-related” refers to primary diagnosis codes that are related to epilepsy and seizures for those encounters. Patients with epilepsy can present with injuries that are a direct consequence of their seizures, such as fractures or lacerations: such scenarios would be captured in “all-cause” groupings rather than “epilepsy-related” groupings in this study as causation cannot be inferred in PHIS coding.

2.4. Independent variables

The analyses had three independent variables of interest. The first was a binary pre-post variable, with “post” capturing the periods before and after index date, and coded as 1 for post-index period and as 0 for pre-index period. The second was a binary variable “VNS” indicating the treatment patients received, and coded as 1 for AEDs plus VNS cohort and as 0 for AEDs only cohort. The third was the interaction between post and VNS. Other variables controlled for in the analyses were patient level sociodemographic and clinical characteristics. Sociodemographic characteristics included age at index date (<4, 4–11, and 12–17 yr); gender (female, male); race (Non-Hispanic white, Non-Hispanic black, Hispanic, and others); insurance (Medicaid, private insurance, and others); geographic region (Midwest, Northeast, South, and West). Clinical characteristics included patient type at index date (inpatient, outpatient), epilepsy diagnosis (focal/partial epilepsy, generalized epilepsy, and others); pediatric complex chronic conditions (P-CCCs) (Yes, No). P-CCCs was calculated using one year of records in the pre-index period.
2.5. Statistical analysis

Bivariate comparisons of baseline characteristics between two cohorts were conducted using Pearson’s chi-square tests for categorical variables and t tests for continuous variable. Pre-index and post-index healthcare resource utilization were compared using Wilcoxon signed-rank test. The difference in changes of healthcare resource utilization between AEDs plus VNS cohort and AEDs only cohort were compared using Mann–Whitney U test.

A difference-in-differences framework (DID) was used to estimate the effect of VNS on healthcare resource utilization of patients treated with VNS, relative to patients treated with AEDs. The DID framework is a quasi-experimental design that can estimate the effect of treatment by comparing the changes in outcomes overtime between patients who received additional treatment (VNS) and patients without the treatment (AEDs). Difference-in-differences framework is often used to study causal relationships in public heath settings where randomized controlled trials are infeasible [25]. Additionally, since healthcare resource utilization have skewed distributions with a large proportion of zero, hurdle model was conducted to analyze resource utilization [26]. To analyze the counts of all-cause and epilepsy-related inpatient, outpatient and emergency department visits, six hurdle models were conducted. The first part of hurdle model was a logistic regression analyzing the binary dependent variable of whether there was any resource utilization, while the second part was a negative binomial model evaluating the annual visits of inpatient, outpatient, and emergency department for patients having any resource utilization. In addition to reporting the odds ratios and percentage changes of continuous dependent variables, overall marginal effects combining the marginal effects from both parts of hurdle models were also reported [27]. Analysis was done using Statistical software SAS® 9.4 (SAS Institute Inc. 2013. Cary, North Carolina) and Stata 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas). The significance level was set at \( p < 0.05 \).

3. Results

3.1. Baseline characteristics of participants

This study included 6043 pediatric patients with refractory epilepsy, with 1502 patients receiving AEDs plus VNS and 4541 patients receiving AEDs only. Significant variations in age, geographic region, race and ethnicity, patient type at index date, PCCCs, primary diagnosis and insurance were identified between AEDs plus VNS cohort and AEDs only cohort \( (p < 0.05) \). The AEDs
plus VNS cohort was older (mean age = 9.74 yr, SD = 4.23) and had a higher proportion of patients who were living in Midwest (28.63%) and South (40.88%), were non-Hispanic White (66.05%), had outpatient visits at index date (75.17%), had P-CCCs (94.27%), had primary diagnosis of focal/partial epilepsy (18.11%), and had private insurance (41.34%), as compared with the AEDs only cohort (Table 1). These baseline differences in patient characteristics are accounted for in the DID methodology in further analysis.

3.2. Healthcare resource utilization

All-cause and epilepsy-related annual inpatient, outpatient, and emergency department visits were measured for the AEDs plus VNS and AEDs only cohorts in the pre-index and post-index periods (Table 2). For both cohorts, statistically significant differences between pre-index period and post-index period were observed in all-cause and epilepsy-related inpatient, outpatient and emergency department visits ($P < 0.0001$). For the AEDs plus VNS cohort, the average unadjusted epilepsy-related annual inpatient visits per patient per year were decreased by 0.26 and epilepsy-related annual emergency department visits decreased by 0.16 after VNS implantation. The average unadjusted epilepsy-related annual outpatient visits increased from 0.36 in the pre-index period to 0.66 in the post-index period (Fig. 2). For the AEDs only cohort, the average unadjusted epilepsy-related annual inpatient and outpatient visits increased by 0.65 and 0.09 after the index date, respectively. The average unadjusted epilepsy-related annual emergency department visits decreased from 1.20 in the pre-index period to 1.03 in the post-index period. The average unadjusted changes for all-cause and epilepsy-related inpatient and outpatient visits were significantly different between AEDs plus VNS and AEDs only cohorts ($P < 0.0001$), while the average unadjusted changes for all-cause and epilepsy-related emergency department visits were similar between the two cohorts (all-cause: $P = 0.41$, epilepsy-related: $P = 0.32$).

To analyze the association between treatment cohort and healthcare resource utilization, DID analyses were also conducted using six sets of hurdle models (Table 3). The average adjusted all-cause and epilepsy-related annual inpatient visits of the AEDs plus VNS cohort decreased in the post-index period, while the inpatient visits increased in the AEDs only cohort ($P < 0.05$). For AEDs plus VNS cohort, the average adjusted epilepsy-related annual inpatient visits decreased by 0.44 (95% CI: −0.60 to −0.28) after the surgical index date; while average adjusted epilepsy-related annual inpatient visits of AEDs only cohort increased by 0.66 (95% CI: 0.58–0.74). Statistically significant differences between the AEDs plus VNS cohort and AEDs only cohort were observed in the adjusted all-cause and epilepsy-related changes for the odds of having outpatient visits (all-cause: OR: 5.76, 95% CI: 4.67–7.11; epilepsy-related: OR: 6.77, 95% CI: 5.49–8.34) and in the adjusted epilepsy-related change for the incidence rate ratio (IRR) among patients with outpatient visits (epilepsy-related: IRR: 0.81, 95% CI: 0.68–0.97). The average adjusted all-cause and epilepsy-related annual outpatient visits

| Characteristics                  | Total | AEDs plus VNS cohort N = 1502 | AEDs only cohort N = 4541 | P value |
|----------------------------------|-------|--------------------------------|---------------------------|---------|
|                                   | Mean  | SD                             | Mean                      | SD      |         |
| Age in yr                         | 8.45  | 4.47                           | 9.74                      | 4.23    | <0.0001 |
|                                   | N     | %                             | N                         | %       |         |
| Age in yr <4                      | 1174  | 19.43                         | 130                       | 8.66    | 1044    | 22.99   | <0.0001 |
| 4–11                             | 3337  | 55.22                         | 866                       | 57.66   | 2471    | 54.42   |
| 12–17                            | 1532  | 25.35                         | 506                       | 33.68   | 1026    | 22.59   |
| Gender                           |       |                                |                           |         |         |
| Male                             | 3225  | 53.37                         | 835                       | 55.59   | 2390    | 52.63   | 0.05    |
| Female                           | 2818  | 46.63                         | 667                       | 44.41   | 2151    | 47.37   |
| Geographic region                |       |                                |                           |         |         |
| Midwest                          | 1624  | 26.87                         | 430                       | 28.63   | 1194    | 26.29   | <0.0001 |
| Northeast                        | 828   | 13.70                         | 157                       | 10.45   | 671     | 14.78   |
| South                            | 2226  | 36.84                         | 614                       | 40.88   | 1612    | 35.50   |
| West                             | 1365  | 22.59                         | 301                       | 20.04   | 1064    | 23.42   |
| Race and ethnicity               |       |                                |                           |         |         |
| Non-Hispanic white               | 3390  | 56.10                         | 992                       | 66.05   | 2398    | 52.81   | <0.0001 |
| Non-Hispanic black               | 869   | 14.38                         | 156                       | 10.39   | 713     | 15.70   |
| Hispanic                         | 1310  | 21.68                         | 291                       | 17.58   | 1046    | 23.03   |
| Others                           | 474   | 7.84                          | 90                        | 5.99    | 384     | 8.46    |
| Patient type at index date       |       |                                |                           |         |         |
| Inpatient                        | 4261  | 70.51                         | 373                       | 24.83   | 3888    | 85.62   | <0.0001 |
| Outpatient                       | 1782  | 29.49                         | 1129                      | 75.17   | 653     | 14.38   |
| Comorbidity with P-CCCs          |       |                                |                           |         |         |
| No                               | 1244  | 20.59                         | 86                        | 5.73    | 1158    | 25.50   | <0.0001 |
| Yes                              | 4799  | 79.41                         | 1416                      | 94.27   | 3383    | 74.50   |
| Primary diagnosis                |       |                                |                           |         |         |
| Focal/Partial                    | 778   | 12.87                         | 272                       | 18.11   | 506     | 11.14   | <0.0001 |
| Generalized                      | 619   | 10.24                         | 198                       | 13.18   | 421     | 9.27    |
| Others                           | 4646  | 76.88                         | 1032                      | 68.71   | 3614    | 79.59   |
| Insurance                        |       |                                |                           |         |         |
| Medicaid                         | 3404  | 56.33                         | 774                       | 51.53   | 2630    | 57.92   | <0.0001 |
| Private insurance                | 2221  | 36.75                         | 621                       | 41.34   | 1600    | 35.23   |
| Others                           | 418   | 6.92                          | 107                       | 7.12    | 311     | 6.85    |
of the AEDs plus VNS cohort increased more than those of AEDs only cohort. The average adjusted epilepsy-related annual outpatient visits increased by 0.32 (95% CI: 0.26–0.39) for the AEDs plus VNS cohort and 0.05 (95% CI: 0.006 to 0.11) for the AEDs only cohort, the increase of average adjusted epilepsy-related annual outpatient visits in AEDs only cohort was not significant. The average adjusted all-cause annual outpatient visits increased by 0.36 (95% CI: 0.28–0.43) for the AEDs plus VNS cohort and 0.06 (95% CI: 0.005–0.12) for the AEDs only cohort. It is important to note that for over 3/4 of VNS patients, the VNS implantation surgery was attributed to outpatient utilization at the index date, which was included in the post-index period. Vagus nerve stimulation and Medication therapy both had reduced the emergency department utilization in the post-index period: the average adjusted epilepsy-related annual emergency department visits decreased by 0.19 (95% CI: 0.31 to 0.06) for the AEDs plus VNS cohort and 0.16 (95% CI: 0.24 to –0.08) for the AEDs only cohort. There was no significant difference in the adjusted pre-index to post-index change in all-cause and epilepsy-related emergency department visits between the two cohorts (P > 0.05).

4. Discussion

To our knowledge, this is the first study to compare the healthcare resource utilization associated with AEDs plus VNS and AEDs only in a large sample of 6043 pediatric patients in the US. For inpatient hospitalizations, we found that the average annual all-cause and epilepsy-related inpatient visits decreased (from pre-index to post-index period) among pediatric patients receiving VNS. Among the AEDs only cohort, inpatient encounters were increased in the post-index period. For a chronic disease with known exacerbations and setbacks such as epilepsy, a marker of accountable disease management is stable outpatient management rather than inpatient and ED encounters, which may be a marker of episodes of higher disease severity requiring higher acuity care. Thus, the finding of decreased inpatient encounters in the AEDs plus VNS cohort is encouraging as it suggests a treatment strategy that may offer better disease control than the AEDs only cohort.

The average annual all-cause and epilepsy-related outpatient visits increased in both cohorts, and the increase in outpatient visits was greater in the AEDs plus VNS cohort than the AEDs only cohort. This finding may be explained by 2 contributing factors. First, 75.17% of VNS implantation surgery encounters were classified as outpatient at the index date. Thus the VNS surgical encounters for those patients receiving VNS implantation are attributed as outpatient encounters in the post-index period in our study design.
Table 3
Difference-in-difference models of healthcare resource utilization.

| Variables          | Inpatient visits |          | Outpatient visits |          | Emergency department visits |          |
|--------------------|------------------|----------|-------------------|----------|----------------------------|----------|
|                    | First part OR (95%CI) | IRR (95%CI) | Second part OR (95%CI) | IRR (95%CI) | First part OR (95%CI) | IRR (95%CI) | Second part OR (95%CI) | IRR (95%CI) |
| All-cause          |                  |          |                   |          |                           |          |                   |          |
| VNS                | 4.08* (3.46, 4.81) | 1.18* (1.06, 1.32) | 0.42* (0.36, 0.49) | 0.93   | 0.67* (0.58, 0.77) | 1.12   |
| Post               | 24.87* (21.36, 28.97) | 0.90* (0.84, 0.96) | 2.87* (2.62, 3.14) | 0.69* | 1.69* (1.55, 1.85) | 0.69* |
| VNS'Post           | 0.054* (0.043, 0.07) | 0.75* (0.65, 0.86) | 5.76* (4.67, 7.11) | 0.89   | 0.93* (0.78, 1.10) | 0.91   |
| Average marginal effect | Pre vs. Post |          |                   |          |                           |          |                   |          |
| VNS                | −0.45* (−0.63, −0.28) | 0.36* (0.28, 0.43) | −0.22* (−0.37, −0.07) |          |
| AEDs               | 0.66* (0.58, 0.73) |          | 0.06* (0.0005, 0.12) |          | −0.16* (−0.25, −0.08) |          |
| Epilepsy-related   |                  |          |                   |          |                           |          |                   |          |
| VNS                | 3.36* (2.86, 3.95) | 1.07 | 0.25* (0.21, 0.30) | 0.89   | 0.48* (0.41, 0.55) | 0.99   |
| Post               | 24.54* (21.09, 28.57) | 0.90* (0.85, 0.96) | 2.89* (2.63, 3.16) | 0.69* | 1.69* (1.55, 1.85) | 0.69* |
| VNS'Post           | 0.05* (0.04, 0.06) | 0.72* (0.63, 0.84) | 6.77* (5.49, 8.34) | 0.81* | 0.84 (0.70, 1.004) | 0.88   |
| Average marginal effect | Pre vs. Post |          |                   |          |                           |          |                   |          |
| VNS                | −0.44* (−0.60, −0.28) | 0.32* (0.26, 0.39) | −0.19* (−0.31, −0.06) |          |
| AEDs               | 0.66* (0.58, 0.74) |          | 0.05 (−0.006, 0.11) |          | −0.16* (−0.24, −0.08) |          |

Denotes p < 0.05; First part denotes first part of hurdle model; Second part denotes second part of hurdle model; IRR: incidence rate ratio.

Second, VNS patients often require more frequent outpatient visits in the period after device implantation for titration of VNS parameters to patient response. Optimizing VNS parameters is patient-specific and physician dependent, and may last from a few months up to 2 years. It is possible that the incremental increase in outpatient encounters in the postsurgical period after VNS implantation would taper off to a low rate of outpatient visit usage over time. In our data, the unadjusted all-cause and epilepsy-related outpatient visits per patient per month increased by 0.01 and the number of ED visits decreased by 0.02 per patient per month, while the changes in outpatient and ED visits were not significant [17]. Ben-Menachem et al. also reported a decrease in total number of emergency department visits of 43 patients after VNS implantation [28], with pre-implantation total ED visits of 26 and post-implantation total ED visits of 17 in the 18 months before and 18 months after surgery. Helmers et al. compared the visits per patient-quarter for children (age 1–11 years) and adolescents (age 12–17 years) and found a different result that the average quarterly outpatient visits were reduced during the post-VNS period compared to the pre-VNS period [16]: the adjusted incidence rate ratios for children and adolescents were 0.95 (95% CI: 0.93–0.97) and 0.80 (95% CI: 0.78–0.82). The reason for this immediate decline in outpatient encounters may be inherent to the patient population or the comparison time frame chosen. Helmers et al. compared the outpatient visits between 6 months pre-VNS period and up to 36 months post-VNS period. The health status of patients eventually undergoing VNS surgery in the 6 months leading up to the implantation of VNS may have been worse than average for many patients. If this trajectory of clinical deterioration may be changed by VNS surgery, it is possible that the number of outpatient visits may have been decreasing by comparison in the 36 months included in the post-VNS period when seizures were gradually being controlled with VNS programming and ramp-up. Our current study included a timeframe of 12 months pre-index date, and 24 months post-index date, which may account for some of the differences between our results and previously reports. In addition, our study includes a comparison group of pediatric patients treated with AEDs only, which adds important information to the literature.

This study has limitations. There are inherent limitations to using administrative data for studying epilepsy due to limits of reliability in coding and documentation. There is a lack of nuance in coding for epilepsy in ICD-9 and ICD-10 data. Clinical granularity is not discernable. Decision-making and treatment rationale are not known. Unobserved factors cannot be adjusted for in the analysis. The PHIS program has procedures to uphold data fidelity with quarterly verifications and data quality management which mitigates concerns about administrative data sources. The limitations in coding are fixed. In this study, we used previously published algorithms for identification of refractory epilepsy, since these algorithms were verified by other author groups and had also undergone peer review. We recognize that the underlying
mechanisms and etiologies for refractory drug-resistant epilepsy are heterogeneous and multifactorial in this cohort. We also note that there are many treatment strategies in the armamentarium for pediatric epilepsy, including medications, ketogenic diet, and surgeries including resections, disconnections, and neurostimulation among others. This study design only represents continued medication therapy and addition of VNS, which are common strategies that are available at most centers across the country. Nevertheless, a national look at pediatric epilepsy is an important endeavor, especially given the high disease burden and the high resource utilization, as well as the sustained impact on patients, families, communities, and the healthcare system. There are baseline differences demonstrated between the 2 cohorts: the Difference-in-Difference methodology controls for these differences in our analyses, as a statistical technique in quantitative research intended to mitigate the effects of extraneous factors and selection bias. While some studies apply both DID and propensity score matching [29,30], other studies apply one [31,32], as we did in using the DID here. While the current study cannot substitute for clinical studies, it can already provide a larger sample size and provide data to motivate future clinical study designs or contribute to data to build the basis for future clinical trials.

5. Conclusions

We conducted an analysis of the PHIS database estimating the healthcare resource utilization of pediatric patients with refractory epilepsy treated with AEDs plus VNS and AEDs only. We demonstrated that VNS reduces the number of inpatient visits compared with AEDs. Given the efficacy of VNS is reported in the literature to be at least comparable to that of AEDs, our study suggests expanding VNS therapy for more favorable decreases in healthcare utilization.

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Conflict of interest

Joyce Y Wu reports grant support from Greenwich Biosciences, and has served on advisory boards and speaker bureaus for Greenwich Biosciences and Novartis. Sandi K Lam reports an investigator initiated study award from LivaNova to study patterns of care in pediatric epilepsy using independent national datasets, and has served on advisory boards of Aesculap, LivaNova, and Encoded Therapeutics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108281.

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