reprints from

Epilepsy & Behavior

Epilepsy & Behavior
Volume 22, Issue 2, October 2011, Pages 370-375

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Elsevier
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The Netherlands
Tel: +31 (0)20 485 3440
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Epilepsy & Behavior 22 (2011) 370–375

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy ☆

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ARTICLE INFO

Article history:
Received 12 May 2011
Revised 13 July 2011
Accepted 17 July 2011
Available online 26 August 2011

Keywords:
Vagus nerve stimulation
Costs
Resource utilization
Drug-resistant epilepsy
Refractory epilepsy
Complex partial seizures
Cost savings

ABSTRACT

We evaluated long-term medical and economic benefits of vagus nerve stimulation (VNS) therapy in drug-resistant epilepsy. A pre–post analysis was conducted using multistate Medicaid data (January 1997–June 2009). One thousand six hundred fifty-five patients with one or more neurologist visits with epilepsy diagnoses (ICD-9 345.xx, 780.3, or 780.39), one or more procedures for vagus nerve stimulator implantation, one or more antiepileptic drugs (AEDs), and 6 or more months of continuous Medicaid enrollment pre- and post-VNS were selected. The pre-VNS period was 6 months. The post-VNS period extended from implantation to device removal, death, Medicaid disenrollment, or study end (up to 3 years). Incidence rate ratios (IRRs) and cost differences ($2009) were estimated. Mean age was 29.4 years. Hospitalizations decreased post-VNS compared with pre-VNS (adjusted IRR = 0.59, $P<0.001$). Grand mal status events decreased post-VNS compared with pre-VNS (adjusted IRR = 0.79, $P<0.001$). Average total health care costs were lower post-VNS than pre-VNS ($18,550 vs $19,945 quarterly, $P<0.001$). VNS is associated with decreased resource utilization and epilepsy-related clinical events and net cost savings after 1.5 years.

1. Introduction

Epilepsy is a common neurological disorder affecting approximately 0.5 to 2% of the population in the United States [1] and imposes a substantial economic burden on the health care system. Numerous cost-of-illness studies have quantified the direct and indirect costs associated with epilepsy in the United States [2–5] and other countries [6–11]. One study reported that annual direct medical costs of epilepsy per patient in the United States range from $1620 to $52,558, depending on disease severity [12]. The existing cost estimates probably underestimate the true costs as most data predate the year 2000.

Uncontrolled seizures are associated with many detrimental effects, including cognitive and memory impairment, high rates of depression, reduced lifetime income, increased health care resource utilization, higher risk of accidental injuries, and much higher mortality [13–18]. Antiepileptic drugs (AEDs) are the first step toward treating recurrent seizures. Despite treatment with AEDs, 20 to 30% of patients still suffer from uncontrolled seizures [19]. A subset of these drug-resistant patients can have good clinical outcomes from epilepsy surgery [20]. Unfortunately a substantial number of patients are not good surgical candidates or are found to be poor surgical candidates after presurgical evaluation [21]. Such patients may benefit from vagus nerve stimulation (VNS), a therapy approved by the US Food and Drug Administration (FDA) in 1997 as adjunctive treatment for patients 12 years or older with complex partial seizures resistant to AEDs. The efficacy of VNS (VNS Therapy, Cyberonics, Inc., Houston, TX, USA) in reducing seizure frequency has been demonstrated in clinical trials and observational studies [21–25].

Payers are increasingly demanding evidence that the costs of drugs and technologies are justified by outcomes. Very few studies have evaluated the effect of VNS on health care utilization and costs. A previous study reported an annual cost savings of $3000 when comparing 18 months before and after VNS implantation among 43 patients in Sweden [26]. Another study reported that the average annual direct medical costs decreased from $4826 to $2496 for 25 patients who underwent VNS in Belgium [27]. The cost estimates in both studies were reported in 1999 US dollars. In 2007, the average quarterly resource utilization for 12 months before implantation was compared with that 48 months after implantation in 138 patients treated in the United States, and the investigators found that use of

☆ Partial results from the study were presented as a poster at the 64th Annual Meeting of the American Epilepsy Society, San Antonio, TX, December 3–7, 2010, and as a platform presentation chosen among the top 5% showcased in Scientific Program Highlights Plenary Session at the 63rd Annual Meeting of the American Academy of Neurology, Honolulu, HA, April 9–16, 2011.

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doi:10.1016/j.yebeh.2011.07.020

health care resources, such as emergency room (ER) and outpatient visits, decreased after implantation [28].

The sample sizes in the aforementioned studies were small and cost estimates are outdated. Furthermore, these studies did not examine both clinical and economic components of epilepsy care together. In the present study, we used data from five state Medicaid programs to examine the long-term impact of VNS on resource utilization, epilepsy-related clinical events, and costs of patients with drug-resistant seizures treated in a real-world setting in the United States.

2. Methods

2.1. Data source

Medicaid is a US government health insurance program designed to serve low-income citizens, the blind, and those with chronic disabling conditions. Medicaid is a state-administered program and each state sets its own guidelines regarding eligibility and services. For the present study, we obtained Medicaid data from five states: Florida, Iowa, Kansas, Missouri, and New Jersey. The combined data set contained complete medical and pharmacy dispensing claims for enrollees during covered years, including Medicare/Medicaid crossovers. Data spanned from January 1997 through June 2009, including nearly 12 million patients. Data were compliant with the Health Insurance Portability and Accountability Act, and can be linked on an enrollee-specific basis over time. Eligibility information, including enrollment start and end dates, was available on a monthly basis. The database included demographic variables, claims by types of services (e.g., hospitalization, outpatient, ER), dates of services, units of services (e.g., length of hospital stay), diagnoses and procedures codes, and outpatient prescription drug dispensing claims. Diagnosis-specific claims were identified by International Classification of Diseases, 9th Revision (ICD-9) codes. The VNS implantation procedure was identified by Current Procedural Terminology Version 4 (CPT-4) codes or Healthcare Common Procedure Coding System (HCPCS). Prescription drug claims were identified by National Drug Codes (NDCs).

2.2. Study design and sample

A retrospective longitudinal open-cohort design was employed (Fig. 1). The study population was selected based on the following inclusion criteria: (1) one or more neurologist visits with epilepsy diagnoses (ICD-9: 345.xx) or nonfebrile convulsions (ICD-9: 780.3, 780.39); (2) one or more pharmacy dispensing for AED; (3) one or more procedure claims for stimulator implantation; and (4) ≥6 months of continuous enrollment before and after the implantation date. The date of first medical procedure claim for stimulator implantation was termed the "index date."

Each patient's observation period extended from the index date until removal of the device, death, Medicaid data end date (Kansas: June 30, 2009; New Jersey: December 31, 2008; Florida: June 30, 2008; Missouri: June 30, 2008; Iowa: June 30, 2006), or end of the study period (maximum 3 years of follow-up), whichever occurred first. This period was referred to as the "post-VNS period." The period extending up to 3 years before the index date was used to assess baseline covariates, including demographics, Charlson Comorbidity Index (CCI) [29], other comorbidities, and use of AEDs and non-AEDs. As patient characteristics may vary over time, each patient's observation period was divided into distinct and uninterrupted quarters (90-day episodes). Each patient had up to 12 quarters of observation in the post-VNS period.

2.3. Outcomes

All outcomes were compared between the pre-VNS period (6 months before index date) and post-VNS period (up to 12 quarters), normalized on a per-patient per-quarter basis.

2.3.1. Rates of resource utilization and epilepsy-related clinical events

The incidence rates of health care services and epilepsy-related events were calculated as the number of services/events (i.e., unique visit days) divided by patient-quarters of observation. The following resource utilization services were examined: overall hospitalizations, seizure-related hospitalizations, overall ER visits, overall outpatient visits, seizure-related and neurologist outpatient visits. Epilepsy-related clinical events measured included: fractures (ICD-9: V664, 767.2, 767.3, 767.4, 800.xx to 839.xx), head trauma (ICD-9: 800.xx to 854.xx, 873.xx, 959.01), and grand mal status events (ICD-9: 345.3).

2.3.2. Direct health care costs

The following per-patient per-quarter costs were calculated: total medical costs (inpatient, outpatient, and ER), drug costs (AEDs and non-AEDs), and total health care costs (total medical costs + drug costs). Costs for medical services associated with an ICD-9 code of 345.xx or 780.3 were considered epilepsy-related costs. Costs were estimated from a public payer perspective using amounts paid by Medicaid and were inflation-adjusted to 2009 dollars based on the medical care component of the Consumer Price Index.

2.4. Statistical analysis

Descriptive analysis was conducted to summarize patient characteristics. Means were used to describe continuous variables, whereas frequency and proportions were used to describe categorical variables.

The incidence rate ratio (IRR), the ratio of the post-VNS incidence rate to the pre-VNS rate, was used to compare health care services and epilepsy-related events. An IRR < 1 indicates a decrease relative to the pre-VNS period; an IRR > 1 corresponds to an increase in the post-VNS

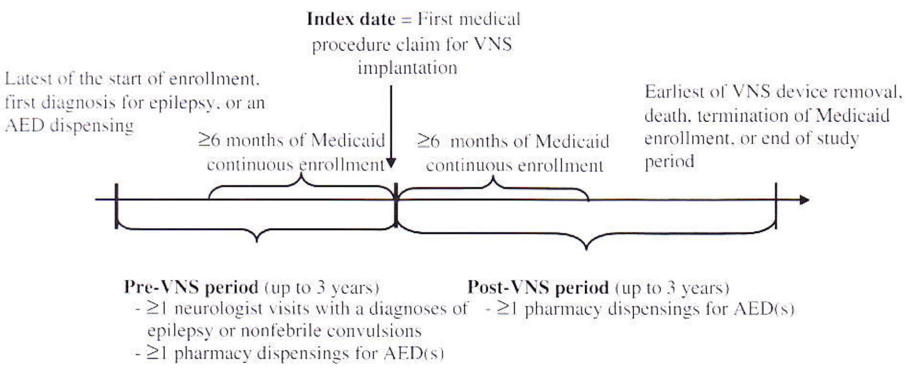

Fig. 1. Study Design.

period. The IRRs were modeled using univariate and multivariate random-effects Poisson regression models. To assess statistical significance relative to the null value of one, 95% confidence intervals (CIs) were calculated using robust standard errors that accounted for multiple quarterly observations per patient. Time trends of resource utilization and epilepsy-related events were estimated during the post-VNS period only using Poisson regression models that controlled for each quarter after VNS implantation. This model assumes that the trend is uniform over time and that the effect of VNS is to decrease the level of event rates. The regression coefficient can be interpreted as an estimate of the log of the relative incidence, adjusted for the other predictors in the model [30]. The estimated IRR was interpreted as the ratio of the incidence rate in post-VNS quarter X to that of incidence rate in post-VNS quarter $X-1$ (i.e., the quarter before X)'.

Comparisons between pre- and post-VNS periods for continuous variables (e.g., quarterly costs) were made using Wilcoxon signed-rank tests. Medical cost data are often not normally distributed as they are always positive values, have a large proportion of zero cost (i.e., no medical visits), and have some highly skewed large costs. As a result, we employed two-part models where the first part was a logistic model to estimate the probability of positive cost. The second part used generalized linear models (GLMs) with a log link function with a gamma distribution for positive costs. For cost components with <5% of zero values, adjusted cost differences were directly calculated using this model. Net total health care costs were calculated as the adjusted cost difference of the average quarterly cost in the post-VNS period cumulated quarterly over time minus the average quarterly cost in the pre-VNS period.

Multivariate regressions controlled for the following baseline covariates: age, gender, state, AED monotherapy versus polytherapy, number of AEDs used prior to VNS implantation, and the following time-varying covariates: depression, mental retardation, bipolar disorder, anxiety, use of antimicrobials, and use of analgesics and anesthetics.

3. Results

3.1. Patient characteristics

Table 1 summarizes patient characteristics. A total of 1655 patients met the inclusion criteria; 1608 (year 1), 1352 (year 2), and 1108 (year 3) patients were followed-up over the study period. The average age was 29.4 ± 15.6 years, and the average post-VNS duration was 30.4 ± 8.9 months. During the 3 years immediately preceding VNS implantation, patients used an average of 3.2 ± 1.4 different AEDs. There was a high prevalence of neuropsychiatric comorbidities: mental retardation (47.4%) was the most common psychiatric comorbidity followed by disturbances of emotions specific to childhood and adolescence (31.8%) and depression (29.6%). A high proportion of patients (69.8%) used psychotropic medications before stimulator implantation.

Table 1
Patient characteristics ($N = 1655$).

Demographics	
Age[a]	29.4 ± 15.6
Gender	
Male	850 (51.4%)
Female	805 (48.6%)
State	
Florida	538 (32.5%)
Missouri	358 (21.6%)
New Jersey	411 (24.8%)
Iowa	155 (9.4%)
Kansas	193 (11.7%)
Observation period, post-VNS duration (months)	30.4 ± 8.9
AED therapy	
Pre-VNS[b]	560 (33.8%)
Monotherapy	
Polytherapy[c]	1095 (66.2%)
Number of AEDs used	3.2 ± 1.4
Post-VNS[d]	
Monotherapy	564 (34.1%)
Polytherapy	1091 (65.9%)
Number of AEDs used	2.9 ± 1.3
Deyo–Charlson Comorbidity Index (CCI)	0.9 ± 1.6
Comorbidities[e]	
Comorbidities associated with epilepsy	
Alzheimer's disease	11 (0.7%)
Brain tumor	46 (2.8%)
Meningitis	18 (1.1%)
Stroke	13 (0.8%)
Psychiatric comorbidities	1,418 (85.7%)
Adjustment reaction	160 (9.7%)
Anxiety disorders	253 (15.3%)
Bipolar disorder	143 (8.6%)
Childhood and adolescent disorder	527 (31.8%)
Depression	490 (29.6%)
Disturbance of conduct	203 (12.3%)
Mental retardation	784 (47.4%)
Mood disorders	353 (21.3%)
Personality disorders	95 (5.7%)
Schizophrenic disorders	141 (8.5%)
Specific nonpsychotic mental disorder due to brain damage	144 (8.7%)
Substance abuse-induced mental disorder	196 (11.8%)
Substance dependence/abuse	215 (13.0%)
Use of non-AEDs known to increase seizure risk[b]	
Anesthetics and analgesics	396 (23.9%)
Antimicrobials	1,466 (88.6%)
Immunomodulatory drugs	19 (1.1%)
Psychotropics	1,156 (69.8%)
Anesthetics and analgesics	396 (23.9%)
Antidepressants	673 (40.7%)
Antipsychotics	970 (58.6%)
Lithium	31 (1.9%)

***Note.* Values are means** ± SD or numbers (%).
[a] Age was calculated at the time of stimulator implantation.
[b] Calculated during the period up to 3 years before index date.
[c] Polytherapy refers to a ≥30-day overlap in therapy at any time.
[d] Calculated during the period up to 3 years after index date.
[e] Calculated during the combined pre- and post-index periods.

3.2. Rates of health care resource utilization and epilepsy-related clinical events

Table 2 summarizes the results of the pre–post comparison of resource utilization and epilepsy-related events. Compared with the pre-VNS period, resource utilization and epilepsy-related events were reduced during the post-VNS period. Specifically, seizure-related hospitalizations (adjusted IRR = 0.53, 95% CI = 0.49–0.58) and outpatient seizure-related visits (adjusted IRR = 0.83, 95% CI = 0.81–0.84]) decreased post-VNS implant relative to pre-VNS. This included a reduction in grand mal status events (adjusted IRR = 0.79, 95% CI = 0.70–0.90).

Table 3 summarizes the results of the time trend analysis. Over time, resource utilization and epilepsy-related events decreased over the post-VNS period. For example, the incidence rates per 100 patient-quarters of observation for overall hospitalizations post-VNS were 0.36 (year 1), 0.21 (year 2), and 0.18 (year 3). The aggregate adjusted quarterly trend for overall hospitalizations in the entire post-VNS period (IRR = 0.88, $P<0.0001$) corresponded to a quarterly decrease of about 12% in the incidence of hospitalizations following stimulator implantation, as compared with the pre-VNS period. Similarly, the incidence rates per 100 patient-quarters of observation for grand mal or status epilepticus events were 0.11 (year 1), 0.08 (year 2), and 0.04 (year 3) post-VNS (IRR = 0.89, $P<0.0001$), corresponding to a quarterly decrease of 11% in the incidence of grand mal status epilepticus events per quarter following stimulator implantation relative to the pre-VNS period.

Table 2
Rates of health care resource utilization and epilepsy-related clinical events in the pre-VNS period versus the post-VNS period.

Outcome measure	Pre-VNS		Post-VNS		Univariate IRR[a] (95% CI)	Adjusted IRR[a,b] (95% CI)
	Number of events	Incidence rate (per 100 patient-quarters)	Number of events	Incidence rate (per 100 patient-quarters)		
Hospitalizations	1,038	0.35	3,886	0.26	0.74 (0.69–0.79)	0.59 (0.55–0.63)
Seizure-related hospitalizations	649	0.22	2,132	0.14	0.65 (0.59–0.71)	0.53 (0.49–0.58)
Number of hospitalization days	6,386	2.14	23,823	1.57	0.73 (0.71–0.75)	0.57 (0.56–0.59)
Emergency room visits	4,619	1.55	17,095	1.13	0.73 (0.71–0.75)	0.61 (0.59–0.63)
Outpatient visits	58,154	19.52	288,679	19.07	0.98 (0.97–0.99)	0.81 (0.80–0.82)
Outpatient seizure-related visits	14,011	4.70	66,721	4.41	0.94 (0.92–0.95)	0.83 (0.81–0.84)
Outpatient neurologist visits	2,949	0.99	13,387	0.88	0.89 (0.86–0.93)	0.85 (0.82–0.89)
Epilepsy-related clinical events						
Fractures[c]	561	0.19	2,632	0.17	0.92 (0.84–1.01)	0.66 (0.60–0.73)
Head traumas[d]	1,222	0.41	5,355	0.35	0.86 (0.81–0.92)	0.73 (0.68–0.78)
Grand mal status epilepticus[e]	335	0.11	1,213	0.08	0.71 (0.63–0.80)	0.79 (0.70–0.90)

[a] IRRs were estimated using quarterly incidence rates. An IRR >1 indicates a higher incidence of the event during the post-VNS period compared with the pre-VNS period, whereas an IRR <1 indicates a lower incidence of the event during the post-VNS period.
[b] Adjusted for age, gender, state, AED monotherapy versus polytherapy, number of AEDs used prior to stimulator implantation, and the following time-varying covariates: depression, mental retardation, bipolar disorder, anxiety, use of antimicrobials, and use of anesthetics and analgesics.
[c] ICD-9 codes: V664, 767.2, 767.3, 767.4, 800.xx to 839.xx.
[d] ICD-9 codes: 800.xx to 854.xx, 873.xx, 959.01.
[e] ICD-9 code: 345.3.

3.3. Health care costs

Table 4 compares the quarterly costs between pre-VNS and post-VNS periods; costs of vagus nerve stimulator implantation were included in quarter 1 post-VNS. On average, the quarterly total health care costs during the pre-VNS period were $19,945, whereas overall, during the post-VNS period, the average quarterly total health care costs were $18,550 (adjusted cost difference: $3186 $P<0.0001$). Average annual total health care costs were $95,587, $62,417, and $58,719 for years 1, 2, and 3 post-VNS. In the post-VNS period, outpatient costs accounted for 51% ($9541) of the total health care costs. The subset of epilepsy-related costs was also lower during the post-VNS than pre-VNS period ($4718 vs $7321 per patient per quarter, $P<0.0001$).

3.4. Total net cost savings

Fig. 2 illustrates the cumulative adjusted cost difference from baseline over time where negative costs indicate net cost savings. At the sixth quarter (i.e., 1.5 years), cost savings in the post-VNS period started to outweigh the mean total costs of the stimulator device and implantation procedure and other costs incurred during the pre-VNS period.

4. Discussion

Despite advances in medical and surgical therapies over the past two decades, the management of epilepsy still poses challenges. More than 12 new AEDs, a number with unique mechanisms of action, have been approved in that time and the burden of drug-resistant epilepsy remains substantial. Poorly controlled seizures continue to be a significant clinical problem, affecting approximately 150,000 to 300,000 people in the United States as of 1990 [1].

Clinical and economic benefits of VNS in patients with drug-resistant seizures have been reported [26–28]. However, this is the first real-world study, to our knowledge, to evaluate the long-term impact of VNS on resource utilization, epilepsy-related clinical events, and costs, simultaneously in a very large cohort of 1, 55 patients. We found that average quarterly health care resource utilization (overall and seizure-related) decreased in the post-VNS period versus the pre-

Table 3
Time trend of health care resource utilization and epilepsy-related clinical events during the post-VNS period.

Outcome Measures	Incidence rate per 100 patient-quarters			Overall trend	
	First year ($N=1608$)	Second year ($N=1352$)	Third year ($N=1108$)	Adjusted IRR[a,b]	P value
Hospitalizations	0.36	0.21	0.18	0.88	<0.0001
Seizure-related hospitalizations	0.20	0.11	0.11	0.89	<0.0001
Number of hospitalization days	2.23	1.26	1.09	0.87	<0.0001
Emergency room visits	1.36	1.11	0.87	0.93	<0.0001
Outpatient visits	20.32	18.87	18.35	0.98	<0.0001
Outpatient seizure-related visits	5.23	4.07	3.86	0.95	<0.0001
Outpatient neurologist visits	1.28	0.69	0.60	0.88	<0.0001
Epilepsy-related clinical events					
Fractures[c]	0.18	0.18	0.16	0.98	0.3386
Head traumas[d]	0.40	0.38	0.27	0.95	0.0071
Grand mal status epilepticus[5]	0.11	0.08	0.04	0.89	<0.0001

[a]IRRs were estimated using quarterly incidence rates. An IRR can be interpreted as follows: for each additional quarter following the VNS implantation, the IRR was calculated as the incidence rate of the post-VNS period divided by the incidence rate of the pre-VNS period. An IRR <1 indicates a decreasing trend of incidence rates in the post-VNS period relative to the pre-VNS period.
[b]Adjusted for age, gender, state, AED monotherapy versus polytherapy, number of AEDs used prior to VNS implantation, and the following time-varying covariates: depression, mental retardation, bipolar disorder, anxiety, use of antimicrobials, and use of anesthetics and analgesics.
[c]ICD-9 codes: V664, 767.2, 767.3, 767.4, 800.xx to 839.xx.
[d]ICD-9 codes: 800.xx to 854.xx, 873.xx, 959.01.
[e]ICD-9 code: 345.3.

Table 4
Average quarterly costs for the pre-VNS period versus the post-VNS period.

Outcome measure	Pre-VNS [*A*]	Post-VNS [*B*]	Unadjusted cost difference [*A* − *B*]	*P* value[a]	Adjusted cost difference[b]	*P* value[b]
Total medical costs	16,470 ± 44,349	15,721 ± 41,034	749	<0.0001	2491	0.0072
Inpatient	6,874 ± 38,592	5,740 ± 35,031	1134	<0.0001	1742	0.0303
Outpatient	9,020 ± 17,739	9,541 ± 16,512	−521	0.3184	802	0.3854
Emergency room	577 ± 2,041	441 ± 1,786	136	<0.0001	185	0.0020
Drug costs	3,475 ± 21,131	2,829 ± 8,560	646	<0.0001	708	<0.0001
AED	1,565 ± 1,335	1,476 ± 1,853	89	<0.0001	85	−0.0010
Non-AED	1,910 ± 21,065	1,353 ± 7,839	557	<0.0001	529	<0.0001
Total health care costs	19,945 ± 49,414	18,550 ± 42,313	1394	<0.0001	3186	<0.0001
Epilepsy-related costs	7,321 ± 31,495	4,718 ± 24,335	2602	<0.0001	3229	<0.0001

[a] *P* value was estimated using Wilcoxon signed-rank test.
[b] Adjusted for age, gender, state, AED monotherapy versus polytherapy, number of AEDs used prior to VNS implantation, and the following time-varying covariates: depression, mental retardation, anxiety, use of antimicrobials, and use of anesthetics and analgesics.

VNS period, even after adjusting for potential confounding factors. These results are similar to the findings from a previous study that reported the mean number of events in each quarter for overall visits, regardless of whether the visit was epilepsy related [28]. We also showed that vagus nerve stimulator implantation is associated with decreased epilepsy-related clinical events. This reduction included serious events: grand mal status, fractures, and traumatic head injuries. This is also the first study to present adjusted total health care net cost savings associated with VNS longitudinally and to show the time trend of resource use as well as epilepsy-related events. We show that resource use and epilepsy-related events gradually decreased each quarter after stimulator implantation.

The pre–post study design allowed us to eliminate intersubject variability, using patients as their own controls. We found that the addition of VNS to treatment was associated with statistically significantly lower use of health care resources and statistically significantly lower occurrence of epilepsy-related events compared with the period before stimulator implantation. The average cost in the first quarter after implantation, including the cost of the device and implantation, was high at $42,540 per patient per quarter, but this cost was outweighed at about 1.5 years postimplantation, producing net health care cost savings for Medicaid payers.

A number of notable characteristics of this large cohort deserve mentioning. The prevalence of psychiatric comorbidities (e.g., depression, mood disorders) in our cohort was high. This finding is expected as patients with drug-resistant epilepsy often have psychiatric and medical co-morbidities [31]. Of note, VNS was approved by the FDA in 2005 for treatment-resistant depression in patients 18 years or older [32]. Our study population also consisted of patients enrolled in Medicaid, which is the highest payer of mental health services in the United States [33].

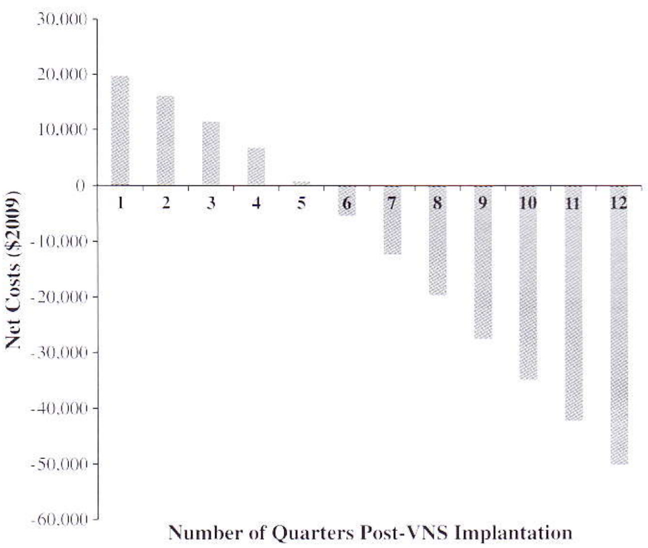

Fig. 2. Cumulative Adjusted Net Healthcare Costs From Baseline.

Despite the expense of VNS (device cost, implantation procedure, and potentially more frequent clinic visits to adjust), we found that all of these costs are outweighed by six quarters after implantation. This is due to decreased resource utilization and reduced occurrence of epilepsy-related events. Average costs in quarter 1 post-VNS were high as the costs of the device and the implantation procedure were included. However, costs in subsequent quarters gradually decreased. To illustrate, costs decreased from $42,539 (quarter 1) to $18,187 (quarter 2), to $17,052 (quarter 4), to $15,474 (quarter 8). Consistent with our findings, a study had reported that the purchase price of a vagus nerve stimulator can be absorbed in 2 to 3 years [26]. Outpatient visits accounted for more than 50% of the total health care costs incurred over the entire study period. This finding is not unexpected as patients visit neurologists regularly after implantation to adjust the device parameters. The average quarterly epilepsy-related costs decreased from $7321 in the pre-VNS period to $4718 in the post-VNS period. Though we did not directly assess the efficacy of VNS, the reduction in costs is likely attributable to the decrease in seizure frequency and/or severity.

Prior estimates of annual cost savings associated with VNS among patients with drug-resistant seizures were $2000 and $3000 per patient [26,27]. The cost findings from our study, in which we report quarterly costs, are not directly comparable to published estimates. One study [26] reported average costs for the 18 months pre-VNS versus 18 months post-VNS, whereas another study [27] reported average annual costs for the 24 months pre-VNS and the 24 months post-VNS. We estimated univariate and multivariate cost differences. Previous studies have reported only univariate costs. We also divided costs for total health care services, for epilepsy-related services. Previous studies have reported only hospital costs, including costs for intensive care unit, ward services, and ER visits or reported total costs consisting of costs for AEDs, clinic visits (epilepsy clinic and neurologist visit), hospital admissions, and laboratory tests [26,27].

There are some limitations to our study. Conclusions based on claims databases assume accurate assignment of billing diagnoses, rather than confirmed diagnoses from direct examination of patient records. Codes for epilepsy and for seizures are confusing, and sometimes are omitted entirely from claims if an underlying cause is considered to be the billing diagnosis. Data were available from only five states and, furthermore, were limited to patients enrolled in Medicaid. These patients are mostly of low socioeconomic status. Thus, it may not be possible to generalize our conclusions to broader populations. Though patients were continuously enrolled in Medicaid for an average of 29 months before implantation, the pre-VNS period of 6 months was not long enough to observe the entire course of each patient's epilepsy leading up to the implantation. Because of the unstable natural course of epilepsy, only the immediate 6 months before implantation were deemed relevant for comparison of outcomes going forward. It is possible that those 6 months were worse than the average for many patients, thus informing the decision for VNS. This could make our pre-VNS costs higher than would be representative for the entire course of the disorder. Furthermore, because data from earlier in the patients' histories were not considered, we may have left out important factors in our multivariate analyses (introducing an omitted-variable bias). Finally, we did not stratify our sample by any measure of epilepsy severity. It is possible that subgroups derive differential clinical and economic benefits from VNS.

5. Conclusions

Vagus nerve stimulation is a cost-effective therapy for drug-resistant epilepsy. The pre-VNS versus post-VNS analysis demonstrates a positive impact of VNS on both clinical and economic outcomes, based on a large cohort of more than 1600 drug-resistant patients in a real-world setting. VNS is associated with decreased resource utilization and epilepsy-related adverse events, resulting in net cost savings for public payers after about 1.5 years from implantation. Further research on privately insured patients to replicate potential cost savings for managed care organizations is warranted.

Conflict of interest statement

This study was funded by Cyberonics, Inc. ("Cyberonics"), Houston, TX, USA. The funding from Cyberonics was not contingent on the study results. Cyberonics participated in the study design, results interpretation, and article review as reflected in the authorship by Cyberonics employees M.T.B., B.D.O., and S.D.J. S.L.H. and E.F. are faculty members of Emory University, which has received research funds from Analysis Group, Inc. M.S.D., A.G., S.P.S., and T.M.S. are employees of Analysis Group, Inc., which has received research grants from Cyberonics.

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