# The Patient Journey Prior to Neuromodulation in Drug-resistant Epilepsy: Patterns of Utilization and Cost of Healthcare Services and Pharmacotherapy Based on a Claims Database in the United States

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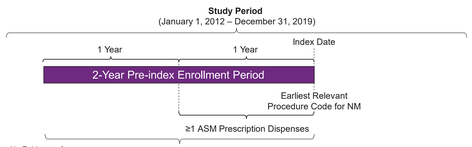
## Key Results

### Figure 1. Sample Selection Process




No Evidence of:
- Neurostimulation Removal, Replacement, Programming, or Complication; OR
- >1 Neurostimulation Devices Implanted on Index Date; OR
- Cranial Epilepsy Surgery; OR
- Parkinson's Disease

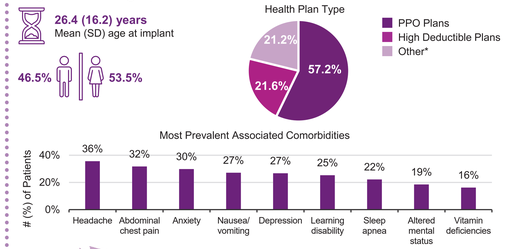
ASM = anti-seizure medication

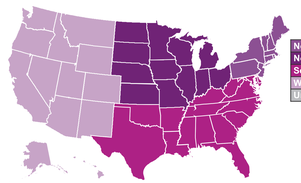
### Table 1. Sample Attrition

| Selection criterion | N | %* |
|---|---|---|
| ≥1 claims with procedure code for VNS, RNS, and/or DBS during study period* | 28,218 | — |
| Diagnosis of epilepsy on index date | 4,872 | 17.3 |
| ≥1 pharmacy claims for ASMs during 12-month period prior to index date | 3,824 | 78.5 |
| Continuous enrollment for 24-month period before and including index date | 1,600 | 41.8 |
| No evidence of craniotomy or cranial neurostimulator replacement, repair, or removal during pre-index** | 945 | 59.1 |
| No evidence of multiple neurostimulators implanted on index date | 929 | 98.3 |
| No evidence of prior neurostimulator implantation during pre-index | 876 | 94.3 |
| No evidence of cranial epilepsy surgery or Parkinson's disease during pre-index | 860 | 98.2 |

*January 1, 2012–December 31, 2019
**Including procedures for insertion or replacement of cranial neurostimulator pulse generator or receiver (RNS/DBS only), or of device removal/replacement (all 3 devices)
NOTE: Percentages calculated using population from prior category as the denominator.
ASM = anti-seizure medication; DBS = deep brain stimulation; RNS = responsive neurostimulation; VNS = vagus nerve stimulation

### Figure 2. Demographic and Clinical Information



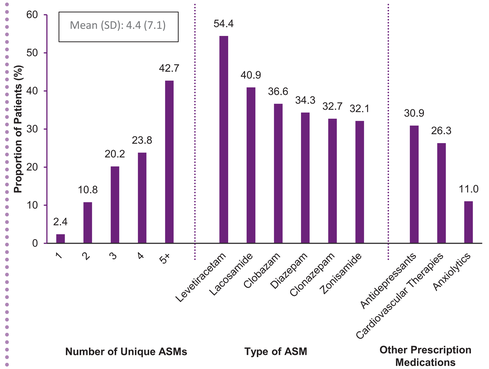



| | |
|---|---|
| North East | 131 (15.2%) |
| North Central | 196 (22.8%) |
| South | 357 (41.5%) |
| West | 171 (19.9%) |
| Unknown | 5 (0.6%) |

*Includes Comprehensive plans, HMO type of plans, POS type of plans, PPO type of plans, and Unknown

DBS = deep brain stimulation; HMO = health maintenance organization; POS = point-of-service; PPO = preferred provider organization; RNS = responsive neurostimulation; SD = standard deviation; VNS = vagus nerve stimulation

### Figure 3. Use of ASMs and Other Selected Prescription Pharmacotherapies

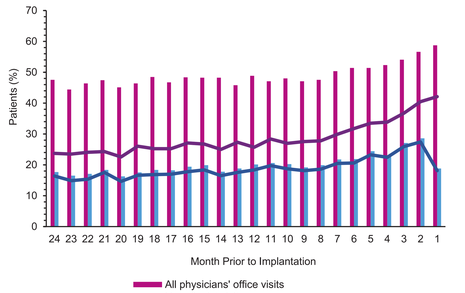



ASM = anti-seizure medication; SD = standard deviation

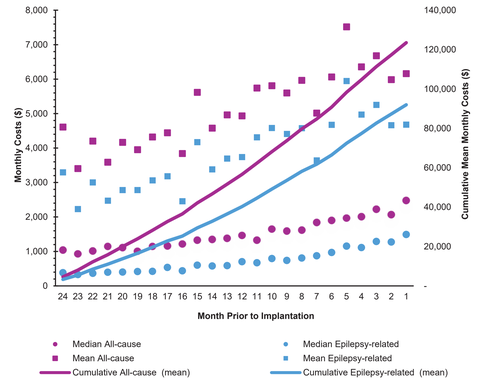
### Figure 4. Proportions of Patients with ≥ 1 Physician or Neurologist Visit, by Month prior to Implantation

**Mean # of Visits (SD)**

| | All-cause | Epilepsy-related |
|---|---|---|
| All Physicians' Office Visits | 20.2 (18.5) | 8.6 (8.0) |
| Neurologist Visits | 5.7 (7.7) | 5.1 (4.6) |




### Figure 5. All-cause and Epilepsy-related Healthcare Costs in Two-year Period Prior to Implantation




## Background

- Between 30% and 40% of adults with epilepsy are unable to attain adequate seizure control through anti-seizure medications (ASM):[1-3]
  - Individuals who fail to achieve sustained seizure freedom following treatment with at least two ASMs are considered to have drug-resistant epilepsy (DRE).[4]
  - The likelihood of adequate seizure control with pharmacotherapy decreases with each successive ASM regimen—those refractory to the initial ASM tried are almost twice as likely to not respond to each subsequent regimen.[5]
- Relative to those in whom ASMs are effective, patients with DRE have poorer quality of life, higher levels of use of healthcare services, and almost two-fold higher mean annual healthcare costs:[6,7]
  - Patients with DRE also experience greater levels of fear, fatigue, and feeling of "loss of control."
- Alternatives to ASMs include resective surgeries (e.g., temporal lobectomy, hemispherectomy) and non-resective surgeries such as neuromodulation:
  - Three neuromodulation devices (i.e., vagus nerve stimulation [VNS], responsive neurostimulation [RNS], deep brain stimulation [DBS]) have been approved by the United States (US) Food and Drug Administration (FDA) for patients with epileptic seizures refractory to ASMs.[8-10]
  - All three devices have demonstrated ≥50% reductions in seizure frequency; data suggest that, for many who undergo implantation, long-term efficacy is sustained.[11]
- Despite their demonstrated efficacy, <1% of surgical candidates ultimately complete a presurgical evaluation, and only between 4% and 8% of surgical candidates eventually undergo implantation:[7,12]
  - It may take as long as 20 years from DRE diagnosis to adequate seizure control.[2,13-15]

## Study Objective

- **To examine patterns of utilization and cost of healthcare services and pharmacotherapies among patients with DRE before neuromodulation.**

## Methods

- Merative® Commercial and Medicare Supplemental Database was used:
  - It is an administrative healthcare claims database with information on >215 million persons from large employer-sponsored and private (i.e., commercial) insurance plans (including Medicare supplemental plans) across the US.
  - Includes claims for medical (i.e., inpatient, outpatient) care and prescription pharmacotherapy, and enrollment data:
    - Available information for medical claims includes date(s) of service, diagnosis codes, procedure codes, and setting of care; for pharmacy claims, it includes date and quantity dispensed, and therapy-days provided:
      - Medical and pharmacy claims also include amounts reimbursed by insurers and patients (e.g., co-pays).
    - Enrollment data can be used to establish periods of eligibility for medical and pharmacy benefits.
  - Data are de-identified and fully compliant with the Health Insurance Portability and Accountability Act of 1996.
  - Database spanned January 1, 2012, to December 31, 2019.
- All patients who underwent implantation between January 1, 2012, and December 31, 2019, and had a diagnosis code for epilepsy on the date of implantation were selected:
  - Earliest date of implantation during this period was designated the "index date," and attention was focused on patients with evidence of implantation for DRE (vs. other indications) and a minimum of 24 months enrollment prior to index date (**Figure 1**).
- Demographic and clinical characteristics were assessed over the 48-month pre-index period, as were patterns of utilization and cost of healthcare services and pharmacotherapy:
  - Care was alternatively assessed as all-cause and epilepsy-related, with the latter defined as all medical care resulting in diagnoses of epilepsy and all ASM dispenses.

## Results

- A total of 860 patients were identified who underwent neuromodulator implantation between January 1, 2012 and December 2019 and who met all other selection criteria (**Table 1**):
  - Represented 3.0% of all patients with evidence of neuromodulation and 17.7% of those with a diagnosis code of epilepsy index date.
- Mean (standard deviation [SD]) age of study subjects at index date was 26.4 (16.2) years; 46.5% were male (**Figure 2**).
- While 54.2% had no comorbidities recorded, 19.7%, 11.6%, and 14.5% had one, two, and ≥3 comorbidities, respectively:
- Thirty percent had anxiety, 26.7% had depression, and 16.2% had vitamin deficiencies consistent with long-term ASM use.
- Two-thirds (66.5%) of patients received ≥4 unique ASMs during pre-index:
  - Most commonly used ASMs included levetiracetam (dispensed to 54.4% of patients), lacosamide (40.9%), clobazam (36.6%), diazepam (34.3%), clonazepam (32.7%) and zonisamide (32.1%) (**Figure 3**).
  - Nearly one-third of patients (30.9%) received antidepressants, 11.0% received anxiolytics, and 26.3% received cardiovascular-related therapies.
- During the 24-month pre-index period, patients averaged (SD) 20.2 (18.5) all-cause physicians' office visit, or almost one per month:
  - Of those visits, 8.6 (8.0), or 42.6%, were designated as epilepsy-related.
  - Patients averaged 5.7 (7.7) neurologist visits during pre-index, of which most (5.1 [4.6], or 89.5%) were designated epilepsy-related.
- For most of pre-index, between 44.1% and 48.8% of patients experienced at least one physicians' office visit monthly (**Figure 4**):
  - In the last seven months before implantation, this increased from 50.3% of patients during the seventh month before implantation to 58.7% the month before implantation.
  - During 24 to eight months prior to implantation, between 14.7% and 19.8% of patients saw a neurologist monthly; this also increased from 20.5% in the last seven months before implantation to 27.4% in the month before implantation (it was 40.5% in the second month before implantation).
- Sixty-nine percent of patients had ≥1 all-cause emergency department (ED) visits; 55.8% had ≥1 epilepsy-related ED visits:
  - Mean (SD) number of epilepsy-related ED visits was 1.7 (2.6).
- Fifty-nine percent of patients had ≥1 all-cause hospitalizations; 56.7% had ≥1 epilepsy-related admissions.
  - Mean (SD) number of epilepsy-related hospitalizations was 1.1 (1.5), mean length of stay was 5.7 (12.1) days.
- Mean (SD) pre-index all-cause and epilepsy-related healthcare costs were $123,500 ($163,935) and $91,995 ($140,921), respectively (**Figure 5**).
  - Corresponding median (interquartile range) values were $74,567 ($3,800–$1,590,233) and $53,029 ($19–$1,516,001).
  - For comparison, mean annual expenditures for Americans with commercial insurance in 2019 (the last year of our study period) was $5,770.[16]
- Median monthly all-cause healthcare costs increased by 138.1% (from $1,042 [month 24] to $2,481 in the month prior to implantation)
  - Median epilepsy-related costs, by 289.9% (from $383–$1,492).

## Study Limitations

- The database lacked detailed clinical data; accordingly, seizure frequency and severity were unavailable.
- Claims data do not allow for definitive attribution of specific treatment(s) (medications or procedures) to specific disease(s). Our use of relevant diagnoses and medications to define epilepsy-related care was likely of high sensitivity but unknown specificity.
- While large, cohort is a convenience sample limited to commercially insured US patients with DRE who underwent implantation; the generalizability of our findings to all patients with DRE who underwent neuromodulation is unknown.

## Conclusions:

- **The two-year period before neuromodulation is characterized by relatively high levels of utilization and cost of medical care and prescription pharmacotherapy, most of which is epilepsy-related.**
  - **Relative to average annual healthcare costs among those with commercial insurance, patients in our cohort experienced approximately 10-fold and 12-fold greater healthcare costs in the second-to-last and last year prior to implantation, respectively.[16]**
  - **Our findings are likely conservative, as indirect costs and impacts to quality of life were unable to be considered.**
- **Patients with DRE who ultimately undergo neuromodulation often have comorbid mental health disorders such as depression and anxiety.**
- **Given that other research has found that healthcare costs are expected to decline following implantation, further research is needed to understand the clinical, economic, and psychological benefits associated with reducing time between DRE onset and implantation among qualifying patients.**

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**Conflicts of Interest Statements**

VD, FB, JM, RL, and EH are employees of LivaNova PLC or a subsidiary, and may hold stock or stock options. All authors report no conflict of interest related to this work. SL contributed to this work on behalf of her institution, independent of LivaNova support.

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