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Examining the Economic Impact and Implications of Epilepsy

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Epilepsy is a complex disease that comprises a spectrum of brain disorders that can cause seizures.¹ It is the fourth most common neurological disorder after Alzheimer disease, migraine, and stroke, affecting 3.4 million individuals in the United States, with approximately 150,000 new diagnoses made each year.²⁻⁴ Commonly diagnosed in children, epilepsy incidence increases with age, with approximately half of new seizures occurring in patients 65 years of age and older.^{3,5} Epilepsy is also associated with several comorbid conditions, such as stroke, neurodegenerative disease, genetic disorders, head trauma, congenital disorders, brain infections, and brain tumors.⁵⁻¹³

Given the lack of clear guidelines for therapeutic selection and the need for individualized care, achieving seizure control can be challenging. Despite the availability of more than 20 antiepileptic drugs (AEDs), roughly 36% of individuals with epilepsy live with uncontrolled seizures.¹⁴ A person is considered to have uncontrolled epilepsy if they are not seizure-free (seizures that continued to occur within the previous 12 months) despite antiepilepsy treatment.¹⁴ Uncontrolled epilepsy has been shown to negatively impact patients' quality of life (QOL) and ability to function independently.¹⁵ Uncontrolled epilepsy is also associated with increased healthcare resource utilization (HRU).¹⁶ According to 2014 data, epilepsy or convulsion diagnoses led to more than 1 million emergency department (ED) visits and 280,000 hospital admissions.¹⁷ With average hospital stays of 3.6 days for patients with epilepsy, the aggregate hospital costs for epilepsy totaled approximately \$2.5 billion.¹⁷

This article reviews the implications of uncontrolled epilepsy, including direct and indirect costs, as well as other factors that contribute to epilepsy-related HRU and the broader economic impact of the disease. In addition to examining the effects of the disease on QOL and challenges to disease management, this article explores potential areas of focus to reduce HRU related to epilepsy care, including access to newer AEDs, adherence to treatment regimens, and the impact of titration and maintenance regimens.

DIAGNOSIS AND SEIZURE TYPES

Before exploring the economic impact of epilepsy, it is important to review components of diagnosis and classification of seizures. According to the International League Against Epilepsy, epilepsy can be diagnosed upon any of the following events¹⁸:

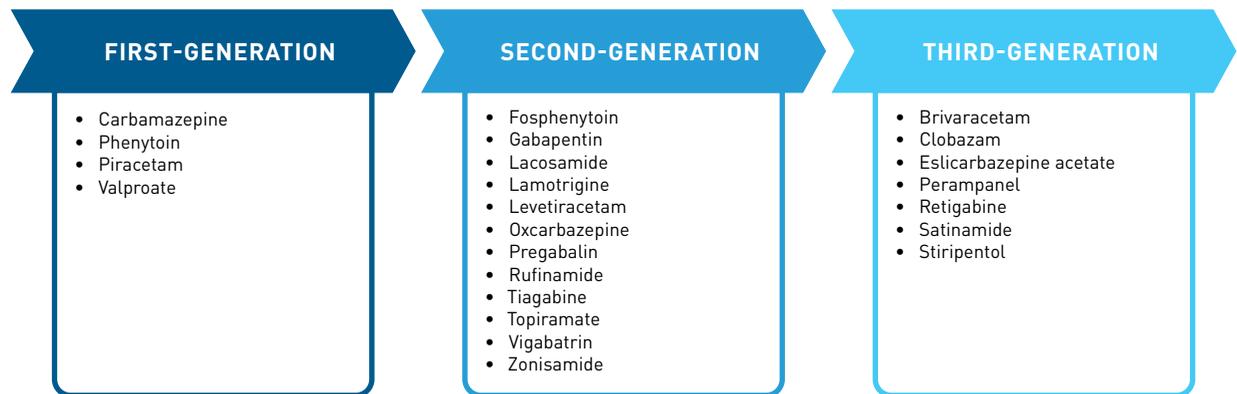
- At least 2 unprovoked seizures occurring more than 24 hours apart
- 1 unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring across the next 10 years
- Diagnosis of an epilepsy syndrome

The majority of seizures (about 57%) originate in one particular side of the brain and are known as focal seizures.^{5,19} Simple focal seizures can cause the individual to twitch or experience a strange taste or odd smell. Complex focal seizures, which can cause confusion for several minutes, may become generalized seizures.²⁰ Generalized seizures, which affect approximately 39% of individuals with epilepsy, are the result of electrical activity in both hemispheres of the brain.^{5,19} Several types of generalized seizures exist, including absence seizures, which are characterized by rapid blinking or a few seconds of staring into space, and tonic-clonic seizures, which can cause a person to cry out,

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Figure 1. Select Antiepileptic Drugs Organized by Generation²⁸⁻³⁰

Adapted from Singh KP, Verma N. *Pharmacol Rep.* 2019;71(3):491-502. doi: 10.1016/j.pharep.2019.01.011.

have muscle spasms, and lose consciousness.²⁰ Seizures with an unknown origin affect 3% to 12% of individuals with epilepsy.^{5,19}

The Institute of Medicine has identified several key characteristics of epilepsy³:

- Epilepsy has a range of severities.
- There are different types and causes of seizures.
- Patients are likely to have 1 or more coexisting medical conditions.

These complexities can make it challenging to coordinate health-care and other services.

THE PATIENT BURDEN AND QUALITY OF LIFE IMPACT

The impact of epilepsy on QOL can be significant for patients and caregivers.²¹ According to a report created by the Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies, epilepsy has been shown to have an impact on patients' ability to function independently or participate in social life.³ Some individuals with epilepsy do not engage in physical activity for fear of seizures, which increases the likelihood of depressive disorder and neuropsychological dysfunction.²² Individuals with epilepsy have higher rates of psychiatric comorbidities, including depression, anxiety, and psychosis.⁷ Approximately 24% of people with epilepsy have been diagnosed with a mental health disorder compared with 11% of those without epilepsy.⁸

Epilepsy also has an impact on patients' ability to work.³ In a behavioral risk factor surveillance survey across 19 states, people with a history of epilepsy were shown to have a lower annual household income and were more likely to be unemployed.²³ Notably, burdens in QOL appear to increase with seizure frequency, as patients with high seizure frequency report worse health utility scores, greater presenteeism (attending work while not physically or mentally capable of working), overall work impairment, and activity impairment.¹⁵ In

addition to the impact of epilepsy on patients, caregivers of those with epilepsy may develop mild-to-moderate QOL burden regardless of the patient's frequency of seizures and duration of the syndrome.²⁴

Another area of impact on patients' ability to function independently is the potential for losing driving privileges, given the risk for crashes in the event that the driver experiences a seizure.²⁵ Although studies have shown varying ranges of increased risk of vehicular accidents among individuals with epilepsy, the severity in damage of accidents has been shown to be higher among those with epilepsy.²⁶ Loss of driving privileges among those with uncontrolled epilepsy can impact their life by further limiting education, employment, and social opportunities.²⁷ Although individuals with controlled epilepsy are permitted to drive, they are often subject to monitoring and restrictions. According to the Epilepsy Foundation, the most common requirement from individual states is that individuals with epilepsy be seizure-free for a certain period of time.²⁷ For example, in California, patients must be seizure-free for 3 to 6 months (with exceptions) before being able to drive, whereas in the state of New York patients must be seizure-free for at least 1 year. Medical reports may also need to be submitted regularly in order to maintain one's driver's license. Visit epilepsy.com/driving-laws for specific information on each individual state's laws regarding epilepsy and driving.

TREATMENT SPECTRUM AND CHALLENGES

Given the impact of epilepsy on patient QOL, reducing the risk of seizure activity and achieving seizure control is essential. AEDs are the mainstay of treatment for epilepsy.¹⁴ Mechanisms of action vary among AEDs, which are generally characterized as first-generation (agents available before 1993), second-generation (agents available between 1993-2011), or third-generation (agents available after 2011) (**Figure 1**).²⁸⁻³⁰

One of the most significant challenges of treatment is that there is no clinical evidence to support a clear first-choice drug or add-on drug

for any given patient.³¹ Moreover, predicting treatment response is not possible based on clinical features or laboratory results. Therefore, treatment selection should be individualized, and patients can be matched to a therapeutic regimen based on clinical profile, seizure type, and preference.³² Combination regimens may offer benefits toward the goal of timely intervention with reduced risk of adverse events (AEs) and recurrence, particularly when combining agents with different mechanisms.³³

Evidence from a 30-year longitudinal study suggests that epilepsy is uncontrolled in approximately 36% of cases, despite appropriate treatment.¹⁴ In addition to the difficulty of attaining seizure control, the longitudinal findings suggest that outcomes in newly diagnosed patients with epilepsy have not changed over a span of roughly 3 decades, despite the approval of many new agents.¹⁴ For patients who have tried multiple AEDs, the capacity for seizure control and the ultimate goal of seizure freedom, defined as no seizures over a 12-month period, has been shown to diminish with each subsequent treatment; although 45.7% of patients achieved seizure freedom with their first AED regimen, only 11.6% and 4.4% achieved seizure freedom with their second and third regimens, respectively.¹⁴

For patients who achieve seizure control, identifying optimal dosing that maintains control is a significant challenge. To reduce the potential for AEs, clinicians may employ drug titration to achieve an optimal maintenance dose.³⁴ Duration of titration varies based on the pharmacokinetic profile of the AED, patient response to treatment, and other factors.³⁴ However, for patients who achieve seizure control, a risk remains for a breakthrough seizure, defined as a seizure that follows at least 12 months of remission while on treatment.³⁵ Findings from 1 study showed that 34% of patients who achieved remission experienced a breakthrough seizure; of those patients, 63% went on to have seizure recurrence.³⁵ Suboptimal AED dosing as a result of drug titration has been associated with an increased risk of breakthrough seizures.³⁶ Changes to AED regimens have also been linked to increases in negative emotions such as fear, uncertainty, anxiety, and worry among patients.³⁷

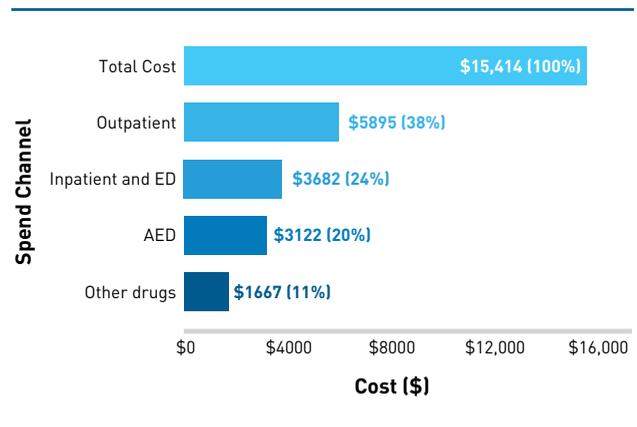
Given the challenges associated with achieving and maintaining seizure control, unmet needs remain for efficacious, well-tolerated treatments.

THE ECONOMIC BURDEN OF EPILEPSY

In addition to unmet treatment needs and the noted impact on patient QOL, epilepsy is associated with a substantial economic burden. Estimated direct costs of epilepsy are approximately \$28 billion per year, a significant portion of which can be attributed to increases in all-cause costs related to uncontrolled epilepsy.^{16,38} Outpatient and inpatient/ED comprise the majority of the total cost of epilepsy care.³⁹

Direct costs are influenced by treatment response, severity of disease, type of disease or seizures, therapeutic management, health-care infrastructure, and patient behavior. Access to care, treatment adherence, personal beliefs, and engagement affect these costs as well.^{40,41} Indirect costs primarily consist of the impact on work productivity, employment status,⁴⁰ and caregiver burden.⁴² Although indirect

Figure 2. Annual Cost per Person With Epilepsy by Spend Channel³⁹



AED indicates antiepileptic drug; ED, emergency department.

costs are difficult to quantify, the impact of epilepsy on patient QOL (noted above) infers significant indirect costs of disease.

According to a 2014 retrospective analysis of US claims data, the annual cost of epilepsy per person was \$15,414; this included outpatient, inpatient, ED, and treatment costs (Figure 2).³⁹ Moreover, all-cause costs for individuals with uncontrolled epilepsy was an average of \$9399 greater than those with stable epilepsy (Figure 3).³⁹ These results echo findings from another study in which patients with high seizure frequency were shown to have higher rates of HRU, as well as both direct and indirect costs.¹⁵ Collectively, these data highlight the importance of finding the right treatment for patients in a timely fashion, to reduce the risk of uncontrolled epilepsy.³⁹

In addition to HRU by patients, cost sharing measures implemented in certain health plans may also potentially drive up overall spending. In a retrospective claims analysis of the Truven MarketScan Commercial Claims database, cost sharing—and subsequently higher out-of-pocket (OOP) spending—led to increased overall spending, a decrease in the proportion of days covered (PDC) (a measure of AED adherence), decreased inpatient hospitalizations, and an increase in epilepsy-related outpatient visits.⁴³ Specifically, a \$10 increase in OOP spending was associated with a 16% decrease in PDC. The investigators noted that policies that impose higher OOP costs on patients who fail to respond to a particular treatment financially disincentivize patients from taking a treatment that may yield better response. Another effect of this is that physicians may not prescribe agents that would be in the best interest of their patients.⁴³

REDUCING THE COST OF EPILEPSY CARE

Because the significant unmet need to address both the clinical and economic burden of epilepsy remains, it is important to identify areas of emphasis to improve the care of patients and reduce overall costs. Access to AEDs represents one potential avenue in which improvements may lead to lower costs. Some data suggest that restrictions

regarding access to AEDs could lead to increased numbers of ED visits, without reducing all-cause or epilepsy-specific healthcare costs.⁴⁴ Additionally, for newly diagnosed patients requiring AED polytherapy, patients with low Medicaid formulary restrictions may be associated with lower overall HRU and total costs compared with patients who have high restrictions.⁴⁵ In a study, patients with high formulary restrictions incurred mean costs of \$23,052 compared with \$20,650 for those with low restrictions. The findings also revealed that patients in the high-restricted group had more all-cause outpatient visits and fewer inpatient admissions compared with the low-restricted group.^{45,46}

Newer generation AEDs have also potentially been shown to reduce epilepsy-related hospitalizations.²⁸ Results from a retrospective analysis showed that the average number of days before epilepsy-related hospitalizations in patients taking at least 1 first-generation AED was 684 days, compared with an average 1001 days for those taking at least 1 second-generation AED (relative risk reduction, 31%). Lower

rates of epilepsy-related hospital encounters were also associated with deliberate treatment choices and treatment by a neurologist. Investigators also noted that hospitalization rates were increased among patients not receiving an AED and those with greater comorbidities.²⁸ These results suggest that treatment with AEDs may reduce long-term costs of care.

AED titration, noted previously as a contributor to breakthrough seizures, could also affect the cost of care among patients with epilepsy.³⁴ In a retrospective medical chart review, patients with epilepsy had a more than 4-fold higher risk of any seizure during the AED titration period compared with the maintenance period.³⁴ For the first 6 months of post-index follow-up, HRU, including hospitalizations, ED visits, outpatient visits, and laboratory tests, was 50% to 90% higher during the titration period. Additionally, total costs were nearly 2 times higher during the titration period and increased by 5% for each additional month of titration (Figure 4).³⁴ Thus, reaching a therapeutic dose early and with less titration may lead to reduced HRU and lower associated costs.³⁴

In addition to reducing titration and improving access to AEDs, adherence to AED regimens can have a significant impact on HRU.⁴⁷ Among a Medicaid population, nonadherence with AEDs has been associated with a 39% increase in hospitalization, a 76% increase in inpatient days, and a 19% increase in ED visits compared with those who were adherent to their regimens. Nonadherence with AED treatment was also associated with increased inpatient and ED costs.⁴⁷

Although these studies present compelling findings regarding the economic impact of epilepsy, material limitations associated with common retrospective health economics research and real-world experience in epilepsy are worth noting. In claims-based studies, for example, general codes for epilepsy in practice are often used rather than specific codes for partial-onset seizures. Additionally, selection bias may be induced by use of an outcome measure to determine

Figure 3. Mean Annual Overall Healthcare Cost in Adult Patients With Stable Versus Uncontrolled Epilepsy³⁹

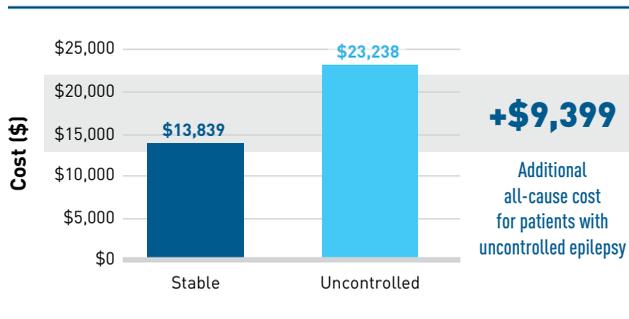
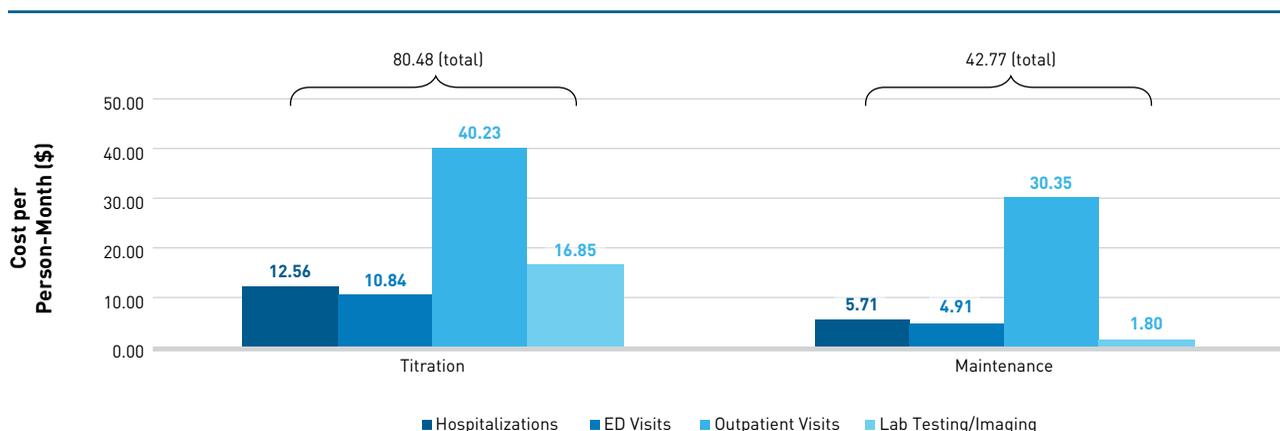


Figure 4. Epilepsy-Specific Healthcare Resource Utilization Cost per Person-Month During Titration and Maintenance³⁴



ED indicates emergency department.

Figure reprinted with permission from the *Journal of Managed Care & Specialty Pharmacy*. Fishman J, Kalilani L, Song Y, Swallow E, Wild I. Antiepileptic drug titration and related health care resource use and costs. 2018;24(9):929-938.

group eligibility, while the focus on hospital and ED encounters may be biased toward patients with more severe seizures and may not be representative of the epilepsy population as a whole. For medical record studies, care received outside of participating systems is not captured. Also, primary clinical outcomes are not typically found in electronic medical records structured data, while unstructured data are typically inconsistent across platforms. Finally, cost estimates are often based on charges rather than paid claims.

CONCLUSIONS

Significant unmet needs remain for patients with epilepsy, particularly those with uncontrolled epilepsy. Uncontrolled epilepsy is associated with a substantially greater burden in patient QOL as well as healthcare costs. Achieving seizure control requires an individualized approach to care that encompasses the substantial burden of disease for patients. Ensuring timely interventions through improved access to appropriate AED regimens may not only reduce HRU, but also improve the lives of individuals with epilepsy. ●

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