

The Burden of Epilepsy to Patients and Payers

William J. Cardarelli, PharmD; and Brien J. Smith, MD, FAAN

Prevalence and Incidence of Epilepsy

Epilepsy is the most common neurologic condition worldwide, with an estimated global lifetime prevalence of 100 million people.¹ The prevalence of active epilepsy in the United States—defined as a history of epilepsy in addition to a seizure or use of an antiepileptic prescription in the last 5 years—is nearly 3 million people.² Approximately 200,000 new diagnoses of epilepsy occur each year, half of which manifest as generalized onset seizures, and nearly a quarter develop in children less than 15 years old.

Epilepsy is more likely to occur in certain patient populations—the very young (<2 years of age) and the elderly (>65 years of age).² Individuals with certain neurologic conditions, such as mental retardation, cerebral palsy, and Alzheimer's disease, are at increased risk of developing epileptic seizures; those with a parent who has epilepsy are also more likely to have it. Compared with other ethnicities, African Americans are generally more likely to develop epilepsy; however, the magnitude of the genotypic contribution to an increased rate of epilepsy is uncertain since lower socioeconomic status is also associated with greater risk of epilepsy.³ A study of epilepsy distribution in Brazil found a lifetime prevalence of 7.5/1000 people in lower economic groups compared with 1.6/1000 in less economically deprived populations.⁴ Interestingly, 38% of those with epilepsy in the Brazilian study had inadequate treatment, while 19% received no treatment.

With regard to ethnicity, a study of epilepsy and unprovoked seizure incidence in a multiethnic, urban health maintenance organization database reported an odds ratio of 1.04 for unprovoked seizures among African Americans (where non-Hispanic whites were the referent), 0.97 for Hispanics, and 0.25 for Asian Americans.³ A 2008 study from northern Manhattan in New York City found no significant differences between African Americans, Hispanics, and non-Hispanic whites for epilepsy risk, but observed very large differences when stratified by socioeconomic status.⁵ Individuals in households earning less than \$15,000 a year had an epilepsy incidence of 164.1 per 100,000 people, those in households earning between \$15,000 and \$49,999 had an incidence of 105.6 per 100,000, and those in households earning at least \$50,000 had an incidence of 61.7 per 100,000. The northern Manhattan study also found greater incidence among men compared with women (43.8 per 100,000 versus 33.9, respectively).⁵ Other epidemiological studies generally report a higher incidence in males than females, but seldom is this difference significant.^{6,7}

Quality of Life and Clinical Burden of Epilepsy

For patients with epilepsy, the burden of the disorder is substantial and complex, comprising obvious physiological dysfunction as well as psychological

Abstract

The extraordinary burden of epilepsy on quality of life (QOL) is well known, as is the very high economic burden associated with the disease. Epilepsy is associated not only with seizures, but also a variety of serious comorbidities, including respiratory, cardiovascular, and neurologic dysfunctions. Psychiatric conditions are very prevalent in the epilepsy population, and may have pathological mechanisms in common with epilepsy. Compared with healthy controls, patients with untreated epilepsy have scored significantly worse across a spectrum of neurocognitive tests. Patients with epilepsy and comorbidities—neurocognitive or otherwise—engage in higher rates of healthcare utilization than those without comorbidities. This, in part, explains why approximately 80% of overall medical costs for patients with epilepsy are for non-epilepsy-related care. The key driver of direct costs in epilepsy is medical service expenditures. For uncontrolled seizure disorders, this becomes even more problematic as medical service use increases. At the same time, the proportional cost of antiepileptic medications decreases as other costs escalate. Although the direct costs of epilepsy are substantial, the overwhelming majority of total costs, as much as 86%, are attributable to indirect costs such as job absenteeism. Ultimately, the burden of epilepsy for patients, in terms of severely reduced QOL, and for payers, in terms of both direct and indirect costs, would be best addressed and reduced by achieving optimal control of seizures.

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Reports

and social impairments. Patients with epilepsy have significantly poorer health-related quality of life (HRQOL) and higher rates of comorbidities than the general population.⁸ An analysis of data from the California Health Interview Survey found that compared with patients without epilepsy, those with epilepsy were 2 to 3 times more likely to have 14 or more physically unhealthy days in a year, at least 14 mentally unhealthy days, and at least 14 days in which normal activities were limited.⁸ Also, patients with epilepsy were more likely to suffer from respiratory issues such as chronic obstructive pulmonary disease and asthma, as well as hypercholesterolemia, heart disease, arthritis, and cancer.⁸

While seizures constitute the hallmark of epilepsy, in some patients, epilepsy is a disorder that can be associated with a cluster of impairments in areas such as cognition, social functioning, and psychiatric status.^{9,11} Of all psychiatric disorders comorbid with epilepsy, depression is the most common, affecting between 6% and 30% of patients.¹² A large-scale nationwide Canadian survey of people with epilepsy found that lifetime prevalence of major depressive disorder was 17.4% compared with 10.7% in those without epilepsy.¹⁰ The lifetime prevalence of suicidal ideation was 25% versus 13.3% for people with and without epilepsy, respectively. Suicide risk was estimated in some studies to be much higher—as much as 10 times higher in people with epilepsy.¹² Moreover, the relationship between depression and epilepsy has been hypothesized to be bidirectional; that is, the presence of one may increase the likelihood of developing the other. More precisely, it may be that depression and epilepsy share an etiological mechanism in common that may facilitate the emergence of one condition when the other is present.¹² It is also interesting to note that comorbid depression appears to have an exacerbating effect on seizure severity. In a 2003 survey from Yale, which employed the Seizure Severity Questionnaire, patients with both epilepsy and depressive symptoms had significantly more severe seizures. Compared with patients without depression ($n = 433$), those with severe depression ($n = 166$) had more severe tonic-clonic seizures ($P < .0001$) as well as partial seizures ($P < .01$).¹³ The same authors further established that people with epilepsy and comorbid depression used healthcare resources with greater frequency than those with epilepsy but no depression. Among patients with epilepsy, those with depressive symptoms receiving antidepressant medications had significantly more medical visits than those without depression ($P = .016$), while those with depressive symptoms who were not receiving treatment had even more medical visits ($P = .001$).¹⁴

Depression is not the only common psychiatric condition that occurs with greater frequency in people with epilepsy. Anxiety and mood disorders, panic disorder, and agoraphobia, among other conditions, are more likely to manifest in those

with epilepsy versus those without.¹⁰ Although there are few available studies on the impact of psychiatric comorbidities in healthcare utilization among patients with epilepsy, a 2008 study from the Department of Veterans Affairs found that patients with comorbid psychiatric conditions—which constituted 48% of the 23,752 patients included in the analysis—were more likely to use emergency care and to be heavy users of primary care resources.¹⁵ These results are supported by data from an Australian study which identified healthcare utilization among patients in the Tasmanian Epilepsy Register. Patients with epilepsy and very high levels of psychological distress were significantly more likely to use the services of general practitioners, specialists, and emergency departments.¹⁶

A clear comparison of the effect of treatment versus no treatment on symptoms, comorbidities, and healthcare utilization is difficult because the overwhelming majority of people with epilepsy in developed nations receive some sort of treatment. Data from poorer nations, where treatment is far less common, may allow for comparisons. However, underdeveloped nations are subject to additional factors, many of which are environmental in nature, that contribute to higher rates of epilepsy than those seen in the developed world. Indeed, the rate of epilepsy in underdeveloped countries is believed to be double that seen in the developed world, largely as the result of diseases and conditions that produce neurological damage, including malaria, meningitis, neurocysticercosis, malnutrition, and complications surrounding childbirth.¹ Thus, it is not appropriate to make comparisons of untreated populations in the underdeveloped world with those in the developed world.

Nevertheless, there are several studies, particularly in newly diagnosed patients, that provide insight into the impact of lack of treatment, and data from these studies point to a significant deficit in terms of cognition, quality of life (QOL), and mortality in patients with untreated epilepsy. A 2010 study from the United Kingdom compared healthy controls ($n = 87$) with newly diagnosed patients who had yet to receive treatment for epilepsy ($n = 155$) who otherwise had no neurologic deficits based on MRI studies.⁹ Neurocognitive testing included measurement of psychomotor speed, memory, processing of information, mental flexibility, and mood profiles. Of 16 different tests, patients with untreated epilepsy performed worse on 13 (10 of which were significantly different from controls) (Table 1). Compared with healthy controls, a higher proportion of patients with epilepsy had abnormal scores for most test variables, especially those related to memory and psychomotor speed. Multiple comparisons were made between those with epilepsy who performed poorly on the cognitive testing versus those with epilepsy who did not demonstrate cognitive impairment, including compari-

Table 1. Patients With Epilepsy Performed Significantly Worse Than Healthy Controls on Most Cognitive Measures^a

| Variable | P ^a |
|---|--------------------|
| Finger tapping | |
| Dominant | <.001 ^b |
| Nondominant | .003 ^b |
| Log visual reaction time, ms | |
| Dominant | .563 |
| Nondominant | .022 |
| Log computerized visual search task, s | .082 |
| Serial word recognition | .187 |
| Serial figure recognition | <.001 ^b |
| Story recall | |
| Immediate | <.001 ^b |
| Delayed | <.001 ^b |
| Rey Auditory Verbal Learning Test | |
| Immediate | <.001 ^b |
| Delayed | <.001 ^b |
| Verbal fluency | <.001 ^b |
| Adult Memory and Information Processing Battery | |
| Information processing | <.001 ^b |
| Psychomotor speed | <.001 ^b |
| Binary choice reaction time, ms | .986 |
| Simultaneous word recognition | .157 |

^aversus healthy controls.
^bSignificant at $P < .01$.
Adapted from Taylor J, et al. *Epilepsia*. 2010;51(1):48-56.

sons by sex, age, education, epilepsy type, number of seizures at baseline, and epilepsy-related variables. None of these, however, were shown to be significantly different between the 2 groups. The authors suggested that untreated epilepsy may have been a causative factor in the cognitive disability seen among many of the patients. Although antiepileptic drugs (AEDs) have been thought to contribute to a decline in cognitive variables, at least part of the cognitive decline may be from the disease itself.

There is also evidence that an elevated risk of mortality is an additional burden associated with untreated epilepsy. An Italian study in people with chronic epilepsy from a remote rural section of Bolivia (where treatment was extremely rare) revealed that there was a substantially higher death rate than expected (based on Bolivian mortality data).¹⁷ After a 10-year follow-up, the investigators found a 3-fold increased risk of death among patients with untreated epilepsy.

These data are consistent with results from a study of newly diagnosed patients with epilepsy from a county in northern Sweden. After a follow-up of approximately 10 years, mortality was approximately 2.5 times higher in those with symptomatic epilepsy compared with those from the general population.¹⁸ The potential for seizures to exert deleterious effects was underscored by a 2009 retrospective chart review of data in 109 pediatric patients from a Cincinnati, Ohio, children's hospital (53 of whom had experienced a single seizure and 56 of whom had newly diagnosed untreated epilepsy).¹⁹ HRQOL was evaluated using the Pediatric Quality of Life Inventory (PedsQL). Both patient groups had significantly lower PedsQL scores compared with normative data across domains, including emotional, social, school, and psychosocial domains. In addition, no significant differences were observed between those with newly diagnosed epilepsy and those who had experienced a single seizure.

Economic Burden of Epilepsy

Although the economic costs of epilepsy in the United States are highly variable, estimates are enormous. One study published in 2000 and cited by the Centers for Disease Control and Prevention estimated an annual cost of \$12.5 billion, 14% of which was attributed to direct costs and 86% to indirect costs.²⁰ A few recent analyses of direct and indirect epilepsy-associated costs in the United States suggest that total costs are even higher. Ivanova et al recently published 2 studies examining the economic burden of epilepsy among privately insured patients. The first study examined the overall epilepsy population and the second focused on those with partial onset seizures. These studies constitute the best and most up-to-date data available for both the direct and indirect costs of epilepsy.

Direct Costs of Care

Ivanova's study assessed the direct costs of epilepsy in privately insured patients from a third-party payer perspective.²¹ Data were derived from a claims database (Ingenix Employer Database) comprising 3 million beneficiaries associated with 17 large companies during the years 1999 to 2005. Within this group, the study examined costs for 4323 people (aged 16-64 years) who had documentation of at least 1 epileptic condition. The control group included demographically matched beneficiaries without an epilepsy diagnosis.

Patients with epilepsy had significantly more comorbidities than matched controls.²¹ Also, they were at increased risk of having any of the 22 different comorbidity categories assessed, and were at significantly higher risk for most, including migraine, demyelinating CNS diseases, congestive heart failure, dementia, rheumatologic disease, renal disease, cancers, and AIDS.

Reports

Direct per patient annual costs in this privately insured patient population were significantly higher for those with epilepsy compared with matched controls: \$10,258 versus \$3862, respectively; the annual per-patient difference was \$6396 ($P < .0001$).²¹ Of these costs, 34% were for designated outpatient services, 28% for inpatient services, and 27% for drug costs (regardless of treatment type). A total of 20% of costs (\$2057) were directly related to epilepsy; almost half of this total (44%) was for AEDs, which ultimately comprised 14% of total excess direct costs. When direct costs were adjusted for baseline differences in patient characteristics, the calculations remained similar: \$10,016 versus \$4733 for those with and without epilepsy, respectively ($P < .001$).

Ivanova et al's second study analyzed expenditures for patients with partial onset seizures compared with matched controls, and used the same employer database described above.²² A total of 1859 patients with partial onset seizures were identified, and the results for this patient population were similar to those of the overall epilepsy population. Similar to a previous study, significantly higher rates of comorbidities were seen across multiple categories including migraine, depression, and demyelinating CNS diseases. With regard to expenditures, direct annual costs were significantly higher for those with partial onset seizures compared with matched controls: \$11,276 versus \$4087, a difference of \$7190 ($P < .001$). Outpatient services constituted 34% of these expenditures, inpatient costs were 28%, and (overall) drug costs made up 29% of total direct costs. Epilepsy-specific costs were 29% of this total (\$3290); among this total, 41% were attributed to epilepsy drug costs (\$1350, or 12% of total direct costs).

Cost of Prescription AEDs²³

From a pharmacy-only perspective, the cost of AEDs is substantial (\$25.41 per member per year [PMPY] in 2009). As a therapeutic class, AEDs rank 12th in total traditional drug spending. Although considerable, these costs are a fraction of those for cholesterol medications (\$69.80 PMPY), the top spending class.

Although total spending for AEDs was down 29.8% in 2009, the use of newer agents is expected to produce an increase in spending, followed by stabilization in 2011 and 2012.

Evidence supports that the primary driver of direct costs in epilepsy is related to heavy use of medical services among patients. A review of claims data for 2446 patients with epilepsy from a managed care database determined that of a total expenditure of \$5,950,260, medical costs accounted for \$5,564,152 and pharmacy costs for the remaining \$386,108.²⁴ An earlier study found that normative costs for the treatment of patients with epilepsy were about \$5000 annually; \$3600 of this amount paid for hospitalizations, largely due to uncontrolled seizures and treatment-related side effects.²⁵

A 2009 analysis of data from the PharMetrics database, covering over 50 million patients nationwide, identified 1213 managed care patients who used the emergency department after a loss of control of their epilepsy.²⁶ To determine the impact of loss of control on costs, direct costs related to the initial emergency department visit and costs associated with follow-up were assessed. Costs 6 months prior to the index emergency department visit included \$2014 of epilepsy-related expenditures and \$12,746 of non-epilepsy expenditures. After the emergency department visit, these 6-month costs significantly increased to \$7808 for epilepsy-related expenditures and \$15,275 for non-epilepsy expenditures. These data point to the cost utility of avoiding loss of control of epilepsy-related symptoms.

This study also suggested an association between antiepileptic drug (AED) formulation substitution and the need for emergent intervention (and increased costs).²⁶ A more recent analysis by Helmers et al on formulation substitution indicated that overall costs increase due to increased medical utilization after substitution.²⁷ Other studies, however, have found no evidence to support that A-rated generic AED switching is associated with acute exacerbations of epilepsy.^{28,29} Further research is needed to determine if AED formulation substitution provides therapeutic equivalence and whether the need for emergent medical interventions increases total costs (despite the perceived cost savings with generic substitution). Although the Epilepsy Foundation acknowledges that changes in formulation can result in adverse events (including loss of seizure control), the risk of such events can be minimized by properly monitoring AED blood levels, seizures, and toxicity.^{30,31} This issue will be explored in greater detail in a future supplement in this series.

Ivanova et al noted that direct costs of epilepsy for third-party payers are typically underestimated because they do not take non-epilepsy costs into account.²¹ They also noted that epilepsy-related costs are often missed. For example, if a patient with epilepsy has a car accident as a result of seizure, or experiences treatment for a comorbidity, healthcare providers may not be aware of the link between the patient's epilepsy and the condition for which he or she is being treated. Therefore, coding for these treatments is not associated with epilepsy in healthcare databases.

It is also worth noting a different type of error that can arise with coding and data collection. A seizure disorder, for example, does not always turn out to be epilepsy, but may be coded as such. The classic example of this is a patient with psychogenic nonepileptic seizures (PNES) who is coded as having epilepsy. This can result in significant costs due to the refractory course of the condition over several years, especially when diagnostic testing has not been completed. A study by Martin et al found that when people with PNES received a definitive diagnosis, the cost of their

diagnostic testing declined by 76%, medication costs reduced by 69%, outpatient visits decreased by 80%, and emergency department visits declined by 97%.³²

Indirect Costs of Care

The larger Ivanova study of the overall epilepsy population included an analysis of a subset of employed patients (n = 1886) to determine the indirect costs of epilepsy from an employer perspective, specifically with regard to disability- and medical-related absenteeism. Absenteeism-related costs were, not surprisingly, higher in patients with epilepsy compared with employed controls (\$3192 vs \$1242, respectively), with a difference of \$1950 ($P < .0001$). The majority of these costs were disability-related.²¹ When taken together, total direct costs and total indirect costs for employees with epilepsy were \$13,595 compared with \$5338 for employees without epilepsy, a difference of \$8257 ($P < .0001$). Similarly, employees with partial onset seizures had substantial and significantly higher indirect costs related to absenteeism compared with controls (\$3431 vs \$1511, $P < .001$).²²

Data from the Ivanova studies are consistent with a study, published in 2007, which included patients from European Union member countries (Table 2).³³ This study was essentially a literature review, compiling results from several studies with similar designs and comparable patient populations. Specific costs per patient are difficult to compare directly to patient costs in the United States because the payment system and healthcare infrastructure work in such different ways in the United States and Europe (and, to some extent, within Europe). In 2004, total costs of epilepsy were 15.5 billion Euros; annual direct costs accounted for 18% of total costs and medication costs constituted 400 million Euros.

The Economic Rationale for Effective Treatment of Epilepsy

For patients with epilepsy, incident cases have been more than twice as expensive as prevalent cases, reflecting the need to get patients stabilized to improve clinical outcomes and also manage costs.³⁴ A pharmacoeconomic analysis of Spanish childhood epilepsy costs found that the mean annual cost per child with epilepsy in 1998 was \$1853 for controlled epilepsy and \$4950 for uncontrolled epilepsy.³⁵ An Italian study conducted around the same time had similar results, with patients with uncontrolled epilepsy incurring much higher costs than those with controlled epilepsy.³⁶ Taken together, these studies indicate that more severe manifestations of epilepsy and greater seizure frequency are associated with higher rates of medical service use and, consequently, greater costs.^{35,36} Furthermore, the proportion of total costs represented by medication costs was higher in those

Table 2. Total Cost Distribution for Patients With Epilepsy in Europe³³

| Cost | Percentage of Total Costs |
|--|---------------------------|
| Sick leave | 51 |
| Adaptations (eg, wheelchair, stair lift) | 14 |
| Social services | 13 |
| Outpatient care | 8 |
| Hospitalization | 6 |
| Premature mortality | 4 |
| Drugs | 3 |
| Medical devices and procedures | 0.3 |

Adapted from Pugliatti M, et al. Epilepsia. 2007;48(12):2224-2233.

whose condition was well controlled, and became proportionally less significant in those whose epilepsy was poorly controlled. Overall, costs associated with epilepsy were generally lower for those patients receiving treatment in primary care and outpatient settings compared with hospitals.

Conclusions

Epilepsy is a disorder associated with an enormous burden in terms of reduced QOL and direct and indirect costs, with the majority of the economic burden resulting from non-epilepsy expenditures. The main variations in costs are related to medical and non-medical expenditures as opposed to pharmacologic costs, an observation which is generally consistent across epilepsy patient populations. Furthermore, patients with poorly controlled epilepsy experience far more personal suffering while incurring significantly higher overall costs. Reducing the QOL burden, as well as the cost burden of epilepsy, is best achieved by the most effective means of epilepsy control, including early diagnosis, efficacious therapies, and limited formulation changes.

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Author Affiliations: From Atrius Health, Harvard Vanguard Medical Associates, Watertown, MA (WJC); Comprehensive Epilepsy Program, Henry Ford Hospital, Detroit, MI (BJS).

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Address correspondence to: Brien J. Smith, MD, FAAN, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202. E-mail: smith@neuro.hfh.edu.

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