

## Demographics and Cost of Epilepsy

Based on a presentation by John F. Annegers, PhD

### *Presentation Summary*

Over the past decade, there has been considerable interest in cost-of-illness studies for many diseases, including epilepsy. However, the nature of epilepsy and the wide spectrum of its clinical course make it difficult to assess the overall costs of the disease.

Differences in incidence rates by age, gender, etiology, and other demographic variables further complicate the task of assessing costs. The incidence is highest in the first decade of life and in the elderly.

A cost-simulation study based on incidence and prognosis sheds light on how costs are estimated. This type of study also serves as a prelude to cost-of-disease studies, cost-

benefit studies, and cost-effectiveness studies.

Approximately 70% of patients with new-onset epilepsy will achieve remission relatively quickly and at relatively low cost. The picture is far less rosy for patients with intractable seizures; for them, the outcome is fair to poor, and the lifetime costs are high.

An empiric version of the cost-simulation study is now under way. Its objectives are to identify incidence cases of epilepsy in two cohorts, collect longitudinal data on each case, estimate the costs of care over time and across service, measure patterns of resource use over time, and use the resultant direct cost estimates as a national cost model.

**T**he nature of epilepsy and the wide spectrum of its course make it difficult to assess the overall costs of the disease, said John F. Annegers, PhD, an epidemiologist at the University of Texas School of Public Health in Houston.

The onset of epilepsy can occur at any age and has many causes and a highly variable course. Some patients respond completely to an initial course of therapy with an antiepileptic drug (AED); some continue to have seizures until the

“right” AED at the “right” dose is found; some achieve partial control; and some have intractable, lifelong seizures. Overall, approximately 70% of patients with new-onset epilepsy, which is defined as recurrent, unprovoked seizures, ultimately achieve remission.<sup>1</sup>

Differences in incidence rates by age, gender, etiology, ethnicity, and population (ie, patients enrolled in managed care plans, which overwhelmingly represent a worker population rather than the general population) further complicate

the task of assessing the costs of epilepsy, Dr. Annegers pointed out.

### **Incidence and Prevalence**

The prevalence of epilepsy in the United States is just under 1%; at this rate, it affects about 2.6 million people, roughly 17% of whom are children and adolescents under the age of 17.<sup>2</sup> The incidence is higher in the first decade of life and in the elderly.<sup>3</sup>

The cumulative incidence, or the risk of ever having epilepsy over the course of a lifetime, is 3.5%, or 10% if other seizures (such as febrile convulsions, single unprovoked seizures, and seizures associated with injury, stroke, and alcohol withdrawal) are included.<sup>4</sup> The prevalence is lower than the cumulative incidence, because epilepsy is not always a lifetime disease, as evidenced by the many patients who ultimately achieve remission.<sup>5</sup>

The peak incidence in the very young and the very old, the relatively low prevalence, and the cumulative incidence set epilepsy apart from other chronic diseases such as diabetes and hypertension, Dr. Annegers noted.

### **Etiology**

To address differences in incidence rates by etiology, age, gender, and other demographic factors, Dr. Annegers described an ongoing study in which he is participating. Funded by the Epilepsy Foundation of America, it compares the incidence and costs of seizure disorders and epilepsy in two patient populations: one group lives in Rochester, Minnesota, and patients in the other are enrolled in the Kelsey-Seybold Clinic, a health maintenance organization (HMO) in Houston, Texas.<sup>6</sup>

In the Kelsey-Seybold group, the etiology of epilepsy was idiopathic (ie, unknown) in 74% of the patients compared with 48% in the Rochester patients, which is a much older population. As such, the Rochester group had a higher incidence of epilepsy because of etiologies associated with the elderly, such as cerebrovascular disease, degenerative

nerve disease (particularly Alzheimer's disease), trauma or traumatic brain injury, and benign or malignant brain tumors.

"Part of the problem of assessing the costs of epilepsy is that many patients, especially older patients and those with severe epilepsy, have these and other comorbidities," Dr. Annegers said.

Other causes of epilepsy in the two cohorts include infection and developmental disorders, which also add to the problem of assessing costs, because it is difficult to determine how much of the cost is attributable to epilepsy per se and how much to the underlying disorders, which are often overwhelming medical problems in their own right. This is particularly true in the case of the child with mental retardation, cerebral palsy, and seizures or in the elderly poststroke patient, Dr. Annegers added.

### **Costs**

Over the past decade, there has been considerable interest in cost of illness studies for many diseases, including epilepsy, Dr. Annegers continued. Such studies have two major components: direct costs, which include physician and drug costs and hospitalization and emergency room care, and indirect costs, which include lost wages as a result of absenteeism, unemployment or underemployment, and economic losses associated with excess mortality.

Cost of illness studies attempt to determine the total cost of epilepsy by factoring in the type and cost, its direct and indirect costs, and the utilization costs for diagnostic work-ups and adverse drug effects, he explained.

Cost-benefit studies are the second step in an economic analysis. In these studies, which are only in their infancy in epilepsy, the focus is on determining which changes in care or the system of care would make treatment most cost-effective in the long run. Such a change in care could be the introduction of a new drug with fewer side effects and/or greater efficacy, Dr. Annegers explained.

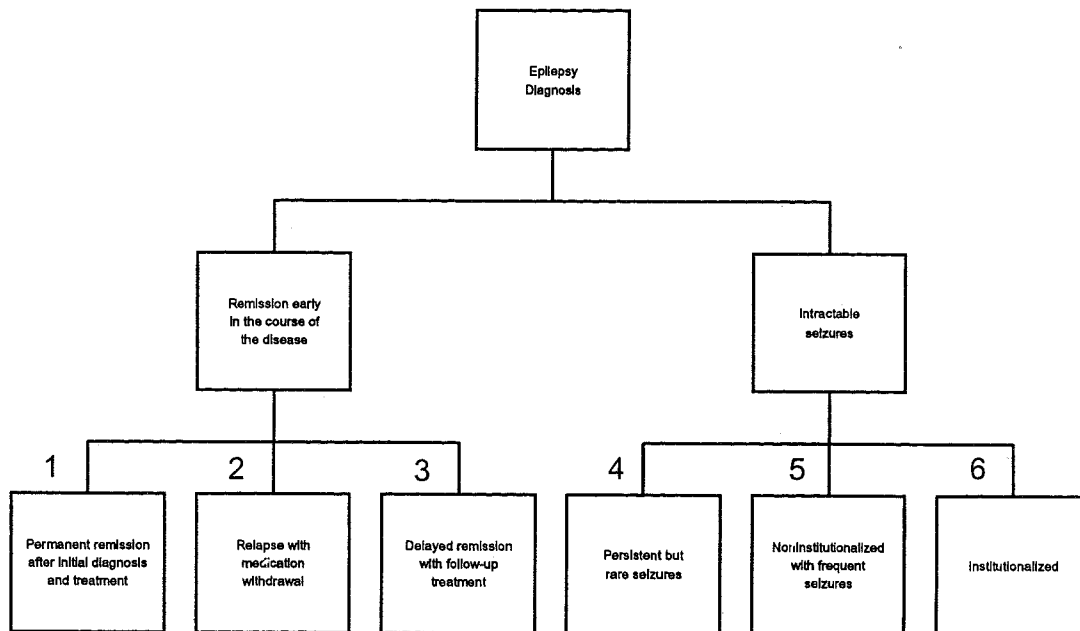
To put cost of illness studies into sharper focus, Dr. Annegers described a cost-simulation study based on the incidence and prognosis of epilepsy.<sup>2</sup> The simulation study, which was used as the model for the ongoing Epilepsy Foundation of America study, cited data in which the direct costs of epilepsy in the United States in 1991 dollars were estimated to be \$1.8 billion and the indirect costs to be \$8.5 billion. Residential care, vocational rehabilitation, special education, and research were included in the direct costs, as were the costs of medical treatment.

As a first step, Dr. Annegers, who is one of the authors of the study, and his co-investigators used the incidence of epilepsy in the United States—150,000 new cases each year—and divided the newly diagnosed cases into six prognostic groups (Figure 1). The first three groups, consisting of 75% of the patients

in the six groups, achieve remission early in the course of disease. Group 1 achieves permanent remission after initial diagnosis and treatment, group 2 relapses after withdrawal of medication, and group 3 achieves delayed remission after follow-up treatment. The remaining 25% have intractable seizures; those in group 4 have persistent but rare seizures, those in group 5 have frequent seizures but do have other major neurologic deficits (mental retardation or cerebral palsy), and those in group 6, who have other deficits, may be institutionalized or living in group homes because of epilepsy and other neurologic deficits and/or multiple handicaps.

“This approach allowed us to make decisions about what is attributable to epilepsy and what is not. That is why we included the last group in particular,” Dr. Annegers said. “Most of those in the group are children or adults with child-

**Figure 1.** Six Prognostic Groups



Source: Begley CE, Annegers JF, Lairson DR, Reynolds TF, Hauser WA. Cost of epilepsy in the United States: A model based on incidence and prognosis. *Epilepsia* 1994;35:1230-1243. Used with permission.

hood-onset epilepsy whose medical costs are only partially attributable to epilepsy.”

Emphasizing that this was strictly a simulation study which indicated a range of costs, Dr. Annegers noted that the total lifetime cost in 1990 dollars of all those with newly diagnosed epilepsy in 1990 was estimated at \$3 billion, with direct costs accounting for 38% of the total (a bit over \$1 billion) and indirect costs for 62% (a little less than \$2 billion). The cost per patient ranged from \$4272 for those with the most benign epilepsy, which is controlled immediately, to \$138,602 for those with persistent intractable epilepsy, which lasts a lifetime.<sup>2</sup>

In looking at the combined costs for all six groups, Dr. Annegers pointed out that the highest costs were incurred in the first year, largely because of the high costs related to the initial diagnosis, which included magnetic resonance imaging (MRI), computerized tomography (CT) scans, and hospitalization; thereafter, costs went down, with AEDs accounting for the largest portion.

#### **British Practitioners Study**

Because the British Practitioners Study is similar to the simulation study in several important ways, Dr. Annegers described it in some detail.

This major study on the costs of epilepsy was conducted in the United Kingdom, because the investigators had the advantage of a national sample of the population from the practitioners.<sup>7</sup> Like the simulation study, this investigation estimated direct costs of hospitalization and primary care and compared them with the direct costs of AEDs.

However, both the evaluation and treatment of epilepsy are different in the United Kingdom, because there are very few neurologists relative to primary care practitioners, and there is far less use of MRI and other expensive diagnostic procedures. In fact, most cases of epilepsy in Great Britain are managed by general practitioners and psychiatrists.

Another major difference is that practitioners (and the healthcare system) in Britain are less concerned about the cost of an AED than physicians and the healthcare system in the United States. British physicians tend to choose a drug on the basis of its efficacy and side effects rather than on the basis of efficacy, side effects, and cost. As a result, the costs of epilepsy in Britain are somewhat lower, but not dramatically so, because the lower costs associated with evaluation and diagnosis are partially offset by the increased use of more expensive AEDs, Dr. Annegers said.

#### **The Ongoing Study**

Returning his attention to the ongoing study funded by the Epilepsy Foundation of America, Dr. Annegers emphasized that he participated in an empiric version of the simulation study.

The current study measures the direct costs of epilepsy in two cohorts, the Rochester population, which Dr. Annegers has been studying for years, and the Kelsey-Seybold HMO population in Houston, which he has also been studying for some time.

The objectives of the study are to identify incidence cases in the two cohorts, collect longitudinal data on each case, estimate the costs of care over time and across service, measure patterns of resource use over time, and, based on the characteristics of the seizure disorder, use the resultant estimates as a national cost model.

Melissa Famulari, PhD, a labor economist who is collecting data to measure the indirect costs of epilepsy, is also participating in the current study.

Data collection to determine direct costs began not with the diagnosis of epilepsy but with the first unprovoked seizure for which a patient was taken to the emergency room or initially evaluated.

“If you start with the second seizure or once epilepsy has been diagnosed, these patients will already have incurred emergency room and work-up costs,” Dr. Annegers explained.

"We are enlarging on the definition of unprovoked seizure disorder to include single unprovoked seizures that never recur, on the premise that direct epilepsy-related costs were incurred in the evaluation," Dr. Annegers added.

Direct costs incurred by patients who were treated for febrile convulsions are not factored into the cost of epilepsy nor are the costs incurred by patients with acute symptomatic seizures secondary to encephalitis, stroke, or traumatic brain injury, unless these patients subsequently develop epilepsy.

The costs of symptomatic seizures are not part of the cost of epilepsy, Dr. Annegers explained, "they are really part of the costs of encephalitis, stroke, and traumatic brain injury."

### Conclusion

The nature of epilepsy and its highly variable course make it difficult to assess both the direct and indirect costs of the disease.

Differences in incidence rates by age, gender, etiology, and other demographic variables further complicate the task of assessing the costs. The incidence is highest in the first year of life and in the elderly.

A cost-simulation study based on incidence and prognosis sheds light on how costs are estimated. Approximately 70% of patients with new-onset epilepsy will achieve remission relatively quickly and at relatively low cost. For those with intractable seizures, the outcome is fair to poor, and the lifetime costs are high.

Similarly, for those who achieve remission, the diagnostic evaluation represents a significant portion of direct costs. For patients with intractable seizures, ongoing treatment and specialized care account for the bulk of direct costs.

An empiric version of the cost-simulation study is now under way. Its objectives are to identify incidence cases of epilepsy in two cohorts, collect longitudinal data on each case, estimate the cost of care over time and across serv-

ices, measure patterns of resource use over time, and use the resultant direct cost estimates as a national cost model.

*Approximately 70% of patients with new-onset epilepsy will achieve remission relatively quickly and at relatively low cost. For those with intractable seizures, the outcome is fair to poor, and the lifetime costs are high.*

### ... DISCUSSION HIGHLIGHTS ...

#### Incidence of Epilepsy

**Dr. Wheless:** The 74% incidence of epilepsy with an unknown etiology in the Kelsey-Seybold group seems much higher than the numbers we usually hear. Is it because we are not looking hard enough?

**Dr. Annegers:** No, I don't think so. These percentages do not show the differences in the age distribution. The managed care population we studied was almost exclusively younger than age 65. We also included all new-onset cases, which have a higher proportion of idiopathic than prevalent cases of epilepsy.

**Dr. Lesser:** I agree with that. Those of us who specialize in epilepsy see a skewed population. People come to us because there is a problem. We are much more likely to look for and find the cause in those with uncontrolled seizures. If you look at all comers, a cause is much less likely to be found.

*Dr. Annegers:* Often the prognosis is a little better in those with idiopathic rather than secondary epilepsy.

*Dr. Richards:* Is the increased incidence based on better measurement rather than on any change in the disease or the population per se?

*Dr. Annegers:* The secular trend seems to be fairly stable in epilepsy. There are some age-specific differences, but the numbers are a little bit better determined, and there is not a big change over time. There are some trends, but they are minor for the entire picture.

*Dr. Cloyd:* With a large number of middle-aged Americans moving into the over-65 group and with the prevalence and incidence of epilepsy increasing almost exponentially in that group, will these figures change substantially in the next several decades?

*Dr. Annegers:* Epilepsy in this country has been shifting from a disease of childhood to a disease of the elderly. In the Rochester population, which is actually quite elderly and has a fairly large proportion of the old-old (older than age 85), the incidence of seizures continues to increase with age. It is fairly stable from age 20 to about age 65, but then there is a sharp rise. In the Rochester population from 1985 to 1994, one-third of all the new cases of epilepsy were in those age 65 and older.

*Dr. Ney:* Does the institutionalized group in this simulation study include adults who live in group homes?

*Dr. Annegers:* Yes. It would include, for instance, the person with Down syndrome who developed epilepsy at age 4.

*Dr. Lesser:* Would it also include a multiply handicapped child living at home or an adult living at home?

*Dr. Annegers:* Yes, it would. "Institutionalized" was a poor term to use, be-

cause many patients who were institutionalized in the past are not in institutions today. We really intend to say "other major neurologic deficits" in addition to having seizures. Controlling the seizures in many of these children would not change the comorbidities.

*Dr. Lesser:* But wouldn't that also depend on what happens? What if this is somebody who has fallen and has multiple fractures? Controlling the seizures could make a major difference in terms of his or her overall care.

*Dr. Annegers:* In that sense, yes.

### Costs of Adverse Events

*Dr. Cloyd:* In the simulation study, did you account for adverse drug effects and interactions that might be attributable to another drug? Let's say it is an asthma drug or a drug for diabetes.

*Dr. Annegers:* No, we did not differentiate, but we did attempt to give an estimated frequency and the costs of adverse reactions.

*Dr. Cloyd:* So if someone had an asthma attack as a direct result of an interaction, where did you assign that?

*Dr. Annegers:* I can't recall specifically, but we had little difficulty assigning most of the adverse effects to epilepsy. In the data we are collecting now, we are looking at every medical encounter, for every drug level, for every adverse effect, and making a decision about whether it is reasonable to attribute them to epilepsy.

*Dr. Lesser:* Let's take a common one; let's say a patient is on carbamazepine and is given erythromycin for something or other. The carbamazepine level doubles, and the patient develops toxicity and goes to the emergency room. To what would you have attributed that?

**Dr. Annegers:** That would be attributed to the epilepsy.

**Dr. Wheless:** We need to look at the number of people who are given an AED and then have an adverse affect that requires a medication change. If you had a drug, even an expensive one, that had fewer side effects and was better tolerated, would that figure into your cost savings because it might translate into fewer physician visits in the long run?

**Dr. Annegers:** We hope to have this information and correctly attribute all the direct cost items. When we have finished our study and have our model, we hope to be able to say, "Okay, we have this drug. It has the same efficacy as another drug but fewer side effects. What is the cost benefit?" We could then run the model, make a number of assumptions, factor in the price of the drug, and come up with an answer that reflects a difference in adverse effects costs in terms of hospitalization, physician visits, blood levels, and so on.

**Dr. Wheless:** That is important, because many patients who are started on one drug are maintained on another.

### Monitoring AED Efficacy

**Dr. Graves:** What about the cost of monitoring AEDs?

**Dr. Annegers:** Tests to monitor blood levels are an important cost element in epilepsy. Of course, it depends on how frequently they are done. Although the cost of an individual test is not high, the cost can add up if the tests are done frequently.

**Dr. Lesser:** I often wonder about how much testing is appropriate. My sense is that patients are frequently overmonitored. I often see patients who have previously been monitored with blood levels every month or two. These are

patients for whom I might order a test once a year or not at all.

Getting blood levels every month or two is like ordering an MRI every 6 months. I certainly wouldn't quibble over getting an initial MRI, because it could detect a tumor as the cause of the patient's seizures, and there are situations where repeat studies every 6 months are appropriate, but I certainly would not get one every 6 months for every patient. The issue is not the tests per se but how often they should be done.

*"A major concern in comparing European drug prices with US drug prices revolves around the contractual issues pertaining to the drugs and their manufacturers. In most cases, the prices are set in advance by the government."*

— Brian Nightengale, PhD

### Drug Prices

**Dr. Nightengale:** A major concern in comparing European drug prices with US drug prices revolves around the contractual issues pertaining to the drugs and their manufacturers. In most cases, the prices are set in advance by the government.

**Dr. Annegers:** Right, so the difference may be the result of some pricing schemes.

**Dr. Lesser:** I calculated the cost of a variety of medications based on their discounted prices at a local chain and at a national pharmacy. There was a ten-fold difference between the older and the newer AEDs, ranging from \$350 to

\$400 per year for the older agents to about \$2500 to \$3500 per year for the newer ones, depending on which pharmacy the patient used. And those prices reflect the actual doses you would use in a patient with intractable epilepsy.

### Older Patients

*Dr. Lesser:* With HMOs enrolling more Medicaid and Medicare patients, I assume there will be less disparity between the HMO and the general population in terms of epilepsy incidence by age.

*Dr. Annegers:* I don't know. It depends on which patients they enroll.

*Dr. Cloyd:* Would you attribute this disparity to a difference in the way symptomology is described or evaluated in an elderly population?

*Dr. Annegers:* I don't think so, because the standard of care and access to care are so different. I think it is best attributed to small numbers. You definitely have a lower incidence in our HMO population than in the general population.

*Dr. Wheless:* This brings up an interesting point. There is a group of patients with epilepsy that won't show up in managed care groups, yet they're out there. They may be underrepresented in managed care and overrepresented in the indigent, Medicaid, and Medicare populations.

*Dr. Annegers:* If we were using only our HMO population, we would completely miss or almost completely miss the high proportion of epilepsy in the elderly.

*Dr. Brown:* You might point out that since 1994 many Medicare managed care plans also offer a drug benefit that is not available with traditional Medicare, so you may adversely include some

of the seizure patients who are on more expensive medications in the managed care population.

*Dr. Annegers:* Let me emphasize that the reason we are doing the incidence cases is to get a representative sample that we can follow longitudinally. Also, within the HMO population, you wouldn't want to study the prevalence of epilepsy because that would be skewed by who enters the plan. We thought it was far better to use the HMO population for studying the incidence of new cases, so we are getting only the new cases from the HMO. Therefore, anything related to getting into the HMO itself, unless it's indirectly related to seizures, shouldn't be a factor.

### Evaluation Protocols

*Dr. Wheless:* The initial evaluation is a big part of the cost of epilepsy management. It includes expensive items, such as MRI and CT scans. One of the things we frequently see is a patient who has a first seizure, goes to the emergency room, gets a CT scan, and then comes to see us as an outpatient. We usually have to do the evaluation all over again, because someone in the emergency room felt that something had to be done, even though the testing was probably inappropriate. Overuse and inappropriate use of expensive testing is a key part of the high initial cost of evaluation.

There should be a protocol, that is, some documentation of testing so efforts and expensive procedures aren't duplicated. Patients should be initially evaluated. If they aren't controlled, they can have an MRI done at their local hospital. When they come to an epilepsy center, we want to do a very specific MRI protocol, because it has a higher yield and is more sensitive than the so-called "routine MRI."

*Dr. Lesser:* There is a recent article on just that subject. Something like two-thirds to three-fourths of nonprotocol



MRIs were inadequate in correctly diagnosing the patient and missed the diagnosis in 70% or 80% of the patients.<sup>8</sup> We have sometimes found that HMO contract radiologists ask for our special protocol and then say they can't do it. If these radiologists use another protocol, the final result might be two expensive MRIs when what was really needed was one correctly interpreted MRI.

**Dr. Annegers:** That is a major issue. In our simulation, we are looking at what we thought was optimal and are finding higher utilizations, especially for CT and MRI.

**Dr. Ney:** There is a broader issue here: Many primary care physicians think of epilepsy centers as tertiary care referral centers for intractable cases only. I think some of the data presented here today suggests that it might be cost-effective to have these patients seen in special referral centers even sooner. There would be much less redundancy in tests and much less resource use.

**Dr. Richards:** I'm not disagreeing, but if you look at it from the emergency room's standpoint, I'm not sure of the purpose of all these CTs and MRIs. Were they done to evaluate epilepsy? If so, do they follow proper protocol, and was the emergency room staff able to do the correct CT or MRI? If the scans are being done to rule out anything from bleeding to trauma, then maybe they are not applicable to epilepsy.

**Dr. Wheless:** We looked at that in our emergency room, because the only indication for CT in epilepsy is trauma; that is the only one on which everyone agrees. The overwhelming majority of patients who come to the emergency room with seizures do not have trauma as the reason for coming in; they come in because of the seizure. This is also a medicolegal issue for the emergency room doctors. It is a perfect example of a situation where a protocol should be put in place. It could be something sim-

ple, like first consulting neurology if you want to order a CT scan for a seizure patient. Your costs would drop exponentially.

### Loss of Productivity

**Dr. Lesser:** What is known about productivity loss? What do those costs look like?

**Dr. Annegers:** We know there is increased unemployment, and there are two different scenarios. One is childhood-onset epilepsy. How does that affect one's life, education, and subsequent productivity? The second is the adult with adult-onset epilepsy. If a patient is an airline pilot or truck driver, that immediately changes his or her life in terms of occupation. Data from various studies suggest that unemployment is about twice the norm. There is also some excess mortality attributed to epilepsy, which is a component of productivity loss.

### ... REFERENCES ...

1. Annegers JF, Houser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729-739.
2. Begley CE, Annegers JF, Lairson DR, Reynolds TF, Hauser WA. Cost of epilepsy in the United States: A model based on incidence and prognosis. *Epilepsia* 1994;35:1230-1243.
3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993;34:453-468.
4. Hauser WA, Hesdorffer DC, eds. *Epilepsy: Frequency, Causes and Consequences*. New York: Epilepsy Foundation of America/Demos Publications;1990.
5. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota, 1935-1984. *Epilepsia* 1991;32:429-445.
6. Dubinsky S, Annegers JF, Newmark M. The incidence of epilepsy and unprovoked seizures in patients enrolled in multiethnic, urban, health maintenance organizations.

Abstracts from the annual meeting of the American Epilepsy Society, San Francisco, Calif. *Epilepsia* 1996;37(suppl 5):14.

7. Cockerell OC, Hart YM, Sander JW, Shorvon SD. The cost of epilepsy in the United Kingdom: An estimation based on the results of two population-based studies. *Epilepsy Res* 1994;18:249-260.

8. McBride MC, Bronstein KS, Bennett B, Erba G, Pilcher W, Berg MJ. Failure of standard magnetic resonance imaging in patients with refractory temporal lobe epilepsy. *Arch Neurol* 1998;55:346-348.