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Delay of Treatment, After Diagnosis, as a Contributor to the "Treatment Gap" in Epilepsy

Assessment and Effect of a Gap Between New-Onset Epilepsy Diagnosis and Treatment in the US

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Objective: To estimate the treatment gap between a new epilepsy diagnosis and antiepileptic drug (AED) initiation in the United States. Methods: Retrospective claims-based cohort study using Truven Health MarketScan databases (commercial and supplemental Medicare, calendar years 2010-2015; Medicaid, 2010-2014) and a validation study using PharMetrics Plus Database linked to LRx claims database (2009-2014). Persons met epilepsy diagnostic criteria, had an index date (first epilepsy diagnosis) with a preceding 2-year baseline (1 year for persons aged 1 to <2 years; none for persons <1 year), and continuous medical and pharmacy enrollment without epilepsy/seizure diagnosis or AED prescription during baseline. Outcomes included percentage of untreated persons (no AED prescription) up to 3 years' follow-up and comparative outcomes (incidence rate ratio, untreated persons/treated persons), including medical events and health-care resource utilization. Results: In the primary study, 59 970 persons met selection (or inclusion) criteria; 36.7% of persons with newly diagnosed epilepsy remained untreated up to 3 years after diagnosis. In the validation study (N = 30 890), 31.8% of persons remained untreated up to 3 years after diagnosis. Lack of AED treatment was associated with an adjusted incidence rate ratio (95% confidence interval) of 1.2 (1.2-1.3) for medical events, 2.3 (2.2-2.3) for hospitalizations, and 2.8 (2.7-2.9) for emergency department visits. Conclusions: One-third of newly diagnosed persons remain untreated up to 3 years after epilepsy diagnosis. The increased risk of medical events and health-care utilization highlights the consequences of delayed treatment after epilepsy diagnosis, which might be preventable.

Commentary

The "treatment gap" (the difference between people with active epilepsy and people who receive appropriate treatment)[1] in epileptic seizures presents challenges on several levels. Past studies addressing the "treatment gap" have focused on the initial diagnosis of epilepsy.[2,3] Conceptually, focal seizures can originate from any region of the cortex, and the associated signs and symptoms of seizures are unique to each individual. Therefore, theoretically, the semiology of seizures spans the spectrum of any sensory or motor phenomenon an individual can experience, which is different for each patient. Unsurprisingly, given the complexity of signs and symptoms related to epileptic seizures, there is a lengthy differential diagnosis of patients presenting with the possible diagnosis of epilepsy. These broad categories of differential diagnoses are appropriately called "imitators" of epilepsy.[4] Fortunately, the stereotypical patterns of epileptic seizures within individuals help in establishing a diagnosis. While seizure semiology differs between individuals, within a single individual, seizures tend to be stereotypical, sharing a common, reproducible pattern of signs and symptoms. Diagnosis of epilepsy calls for a detailed history to look for patterns of seizures.[5]

While the presenting signs and symptoms of epileptic seizures are complex and make diagnosing epilepsy challenging, other factors contribute to barriers for epilepsy diagnosis. Past studies document that limited access to health care and lack of public education about epilepsy limits diagnosis and treatment of epilepsy, especially in less socioeconomically developed regions.[6,7] However, past studies also show that delay in epilepsy diagnosis is prominent in areas where there is adequate access to medical care. In a study from Melbourne, Australia, in 220 adults who presented with an epileptic index seizure (the seizure which led the patient to seek medical attention), 41% had prior events. The delay from first event to presentation was >4 weeks in 36% of patients, >6 months in 21%, and >2 years in 14%. Initial seizures associated with a delay in presentation were nondisruptive or nonconvulsive and therefore more subtle in presentation. Relative socioeconomic disadvantage was also associated with delay to presentation. There was a median diagnostic delay of 8.7 months among those with a history of

prior events. In a study by Gasparini et al from Italy,[2] there was a similar diagnostic delay of 15.6 months in a cohort of patients with newly diagnosed cryptogenic focal epilepsy. The proportion of patients with a diagnostic delay of 4 weeks or more was 81%.

While addressing the "treatment gap," the study by Kalilani et al differs from previous studies by evaluating patient cohorts with treatment delays *after* diagnosis of epilepsy. Therefore, the study provides important data about implementation of treatment after diagnosis. Kalilani et al analyzed 3 administrative databases, which contained millions of individuals, to identify patients with newly diagnosed epilepsy. They included patients who had an index date (the date of their first epilepsy diagnosis) with a preceding 2 years baseline within the database (1 year for ages 1 to <2 years; none for ages <1 year). To identify newly diagnosed patients, the investigators established a baseline definition of epilepsy diagnosis as any of the following criteria: (1) two *ICD-9-CM* (*International Classification of Diseases, Ninth Revision, Clinical Modification*) 345.xx (epilepsy and recurrent seizures) codes at separate encounters; (2) 1 *ICD-9-CM* 345.xx code and 1 *ICD-9-CM* 780.39 (other convulsions) code at separate encounters; (3) the *ICD-9-CM* code 345.3 (grand mal status), occurring twice and separated by at least 30 days, occurring with *ICD-9-CM* 780.39 and separated by at least 30 days or occurring with *ICD-9-CM* 345.xx on separate days. They assessed the sensitivity of their findings by analyzing the data after increasing the rigor of the epilepsy diagnostic criteria using 12 case definitions, with the most stringent definition of epilepsy requiring 4 or more separate *ICD-9-CM* codes of 345.xx as the primary code during encounters at least 30 days apart. Patients receiving a prescription for at least a 30-day supply of an AED during the follow-up period were classified as receiving treatment. The authors performed a primary study, which included 59 970 patients who met the inclusion criteria, 36.7% of whom remained untreated up to 3 years after diagnosis, as well as a validation study including 30 890 patients, 31.8% of whom remained untreated up to 3 years after diagnosis. Using the most stringent definition of epilepsy, which included 9004 patients, 4% remained untreated up to 3 years after diagnosis.

In addition to assessing treatment with AEDs after diagnosis, the authors also assessed outcomes in patients who did not receive an AED prescription. Epilepsy-related ED visits were considerably less common in the untreated than treated group (Relative Risk [RR] = 0.4), while non-epilepsy-related ED visits were more than 3 times as common, possibly indicating that the untreated group presented with epilepsy-related problems which were not recognized on subsequent visits. Additionally, there was a modest increased risk of burns, falls, fractures, motor vehicle accidents, and suicidality in patients who did not receive an AED prescription.

The authors show convincing findings with a rigorous study design. One challenging variable in any study is assigning appropriate diagnostic criteria within the involved cohort. To identify patients with newly diagnosed epilepsy, Kalilani et al used criteria validated in a Canadian-based study by Reid et al.[8] Reid et al evaluated several large insurance and claims databases, validating results with chart reviews from patients from 13 neurologists' practices. Given the much higher prevalence of epilepsy in the neurologists' practice as compared to the general population, there is a risk that the coding algorithms showed an inflated positive predictive value in the neurologists' practice group. A larger concern is how the results from Kalilani et al, which included patients with Medicaid and Medicare, apply to other populations with different demographics. The authors discuss this important issue in the article.

Using the primary case definition of new-onset epilepsy, 36.7% of patients were untreated within 3 years, while using the most stringent definition of new-onset epilepsy showed 4% untreated within 3 years. The patients in the most stringent definition group had more visits, and therefore better follow-up, focusing on their epilepsy diagnosis. For caregivers, this finding reinforces the importance of prioritizing the epilepsy diagnosis, communicating with patients about the diagnosis and its implications, and addressing barriers to treatment. Given the many effective treatments for epileptic seizures, Kalilani et al's documentation of a "treatment gap" after diagnosis highlights the need for better follow-up and earlier treatment implementation after diagnosis.

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