EPILEPSY CURRENTS

Current Literature

In Clinical Science

Drug Resistant Epilepsy and New AEDs: Two Perspectives

Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study.

Chen Z, Brodie MJ, Liew D, Kwan P. *JAMA Neurol* 2018;75:279–286.

IMPORTANCE: A study published in 2000 showed that more than one-third of adults with epilepsy have inadequate control of seizures with antiepileptic drugs (AEDs). This study evaluates overall treatment outcomes in light of the introduction of more than 1 dozen new AEDs in the past 2 decades. OBJECTIVE: To assess long-term treatment outcome in patients with newly diagnosed and treated epilepsy. DESIGN, SETTING, AND PARTICIPANTS: This longitudinal observational cohort study was conducted at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland. A total of 1795 individuals who were newly treated for epilepsy with AEDs between July 1, 1982, and October 31, 2012, were included in this analysis. All patients were followed up for a minimum of 2 years (until October 31, 2014) or until death, whichever came sooner. Data analysis was completed between March 2015 and May 2016. EXPOSURES: Treatment with antiepileptic drugs for patients newly diagnosed with epilepsy. MAIN OUTCOMES AND MEASURES: Seizure control was assessed at the end of the study period. Probability of achieving 1-year seizure freedom was estimated for each AED regimen prescribed. Multivariable models assessed the associations between risk factors and AED treatment outcome after adjustments were made for demographic and clinical characteristics. RESULTS: Of the 1795 included patients, 964 (53.7%) were male; the median age was 33 years (range, 9–93 years). At the end of the study period, 1144 patients (63.7%) had been seizure free for the previous year or longer. Among those achieving 1-year seizure freedom, 993 (86.8%) were taking monotherapy and 1028 (89.9%) had achieved seizure control with the first or second AED regimens. Of the total patient pool, 906 (50.5%) remained seizure free for 1 year or longer with the initial AED. If this AED failed, the second and third regimens provided an additional 11.6% and 4.4% likelihoods of seizure freedom, respectively. Only 2.12% of patients attained optimal seizure control with subsequent AEDs. Epilepsy that was not successfully controlled with the first AED had 1.73 times greater odds of not responding to treatment for each subsequent medication regimen (odds ratio, 1.73; 95% CI, 1.56–1.91; $P < .001$). CONCLUSIONS AND RELEVANCE: Despite the availability of many new AEDs with differing mechanisms of action, overall outcomes in newly diagnosed epilepsy have not improved. Most patients who attain control do so with the first or second AED. The probability of achieving seizure freedom diminishes substantially with each subsequent AED regimen tried. More than one-third of patients experience epilepsy that remains uncontrolled. https://www.mdlinx.com/neurology/medical-news-article/2018/01/03/epilepsyantiepileptic-drugs-longitudinal-cohort-study/7498791/

Commentary

There is a long and interesting history of antiepileptic drug (AED) development. Bromides were introduced as a treatment for epilepsy in 1857 (1), and by the end of the 19th century were the standard therapy (2). Initially synthesized in 1904, phenobarbital was initially used as a sedative and hypnotic before eventually coming into more general use for epileptic seizures in 1920 (1). By the 1940s, phenobarbital was the international mainstay of therapy for epileptic seizures. Using standardized techniques to assess multiple compounds for treatment of epileptic seizures, Merrit and Putnam developed phenytoin and reported the first clinical trial for the use of phenytoin for epileptic seizures in 1938. With more modern techniques to systematically develop AEDs, there were 13 newly marketed AEDs in the United States from 1939 to 1958 (1). Over the years, development of AEDs continues. Recent AED practice guidelines include a review of eight newer AEDs (all referred to as second-generation AEDs) published in 2004. A follow-up guideline published this year includes six new drugs approved by the US Food and Drug Administration since 2004 (all referred to as third-generation AEDs; 3).

AED development continues in hopes of finding an AED with improved efficacy without side effects. Despite over 150 years of AED drug development in the modern era, with a

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more systematic, standardized approach since the 1930s, many patients continue to have drug-resistant epileptic seizures. Recent studies estimate drug-resistant epileptic seizures occur in approximately 30% of all epileptic patients, causing increased risks of injuries, premature death, psychosocial dysfunction, and a reduced quality of life (4). Additionally, treatment of patients with drug-resistant epilepsy results in a significant increased healthcare expense. Annual total costs of drug resistant epilepsy in the United States approach $4 billion, with average annual health-care costs of $33,613 per patient with drug-resistant seizures (5).

The study by Chen et al. therefore addresses an important question about patients with newly diagnosed epileptic seizures and responses to AEDs. In an initial trial, published in 2000, the authors studied a cohort of 470 newly diagnosed epilepsy subjects from 1982 to 1998 (6). The current article reports an extension of the study to 1795 newly treated epilepsy subjects from 1982–2012, therefore allowing a comparison of AED treatment regimens over time. As previously mentioned in this discussion, many new AEDs came into clinical use during this time, allowing for comparison of multiple agents over time. Interestingly, in this cohort carbamazepine was the first agent of choice 100% of the time in 1982 but was unused in any patient, either as the first choice agent or as any part of the AED regimen, by 2012. To explore potential changes in choice of AEDs, patient characteristics, and treatment outcomes over the 30-year study period, the study cohort was divided into 3 subgroups based on the initial year they started AED treatment (each subgroup spanning 10 years).

Results showed that 63.7% of patients were seizure free for the previous year or longer at the end of the study period; 86.8% of patients who achieved 1-year seizure freedom were taking monotherapy, and 89.9% of patients achieved seizure control on the first or second agents. Approximately half (50.5%) of all subjects were seizure free for 1 year or longer with their initial AED. If the initial AED was ineffective, the second and third regimens resulted respectively in 11.6% and 4.4% chances of seizure freedom. After the second and third regimens, only 2.12% of subjects achieved optimal seizure control on subsequent AEDs. Comparison of the three time period subgroups showed that the proportion of patients seizure free at last follow-up were similar (61–64%), as was the cumulative probability of 1-year seizure freedom.

This study, which included a continual increase in the use of newer AEDs over time in both initial and subsequent treatment periods, showed a relatively unchanged rate of seizure-freedom over time. The result of seizure-free rate in the current trial was 63.7%, while the previous result from their report in 2000 (6) was 64.0%. This longitudinal, observational cohort study has many strengths, including a large sample size, prospective observations, and a long duration. The introduction of numerous second- and third-generation AEDs over the course of this trial failed to improve rates of seizure freedom. The findings confirm previous reports that many patients continue to have drug-resistant epileptic seizures, and the need for continued development of new agents to treat drug resistant seizures (4).

The stated results are robust. However, the study does not directly address the overall current role of established AEDs as compared to newer second and third generation AEDs in the current treatment of epileptic patients, which warrants further discussion. Overall, successful outcome for any treatment depends on both tolerability and efficacy of the treatment. A good example of this concept is the SANAD study comparing effectiveness of standard and newer agents for treatment of focal epilepsy.[7] Focusing on the results of lamotrigine and carbamazepine, this trial showed that when assessing time to treatment failure, lamotrigine was significantly better than carbamazepine. The advantage for treatment with lamotrigine was due to its tolerability advantage over carbamazepine. For the time taken to 12-month seizure remission, carbamazepine showed a nonsignificant trend for advantage over lamotrigine. Therefore, factors of increased tolerability and relatively equal efficacy played importantly in the final assessment in the SANAD trial and the conclusion that lamotrigine is clinically better than carbamazepine. Because the analysis by Chen et al. excluded patients who had persistently poor drug adherence, it is vulnerable to errors in assessing the tolerability of medications in relationship to final clinical efficacy. Because of the study design by Chen et al, the take-home message is not that second- and third-generation AEDs offer no advantage for epilepsy patients. Each patient should undergo individual assessment for tolerability and efficacy of AED treatment, and undergo treatment accordingly. In some instances, the best AED will be a second- or third-generation AED. Recent practice guidelines emphasize the need for more head-to-head trials for newer AEDs (3), which will help address the appropriate role of traditional vis-a-vis newer AEDs.

As in the past, there remains a great need for improved AEDs. Development of AEDs with improved efficacy remains a paramount issue in treating patients with drug-resistant epilepsy. The study by Chen et al. helps further define this important issue, highlighting the need for new, innovative treatments for patients with drug-resistant epilepsy.

by R. Edward Hogan, MD, FAES

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Commentary

It is rare to have three decades of longitudinal data. Although there are limitations to observational data collected during standard clinical care, they can contain a wealth of information. If we think about the history of the availability of antiepileptic drugs (AEDs) over the years, we are struck by the number of drugs currently available to patients compared to the early 1990s. It was an exciting time with the release of felbamate, the first new epilepsy medication available after approximately a 15-year hiatus. Since that time, approximately 15 drugs that are classified as AEDs have become available. Clinicians now have a diverse toolbox containing compounds with various pharmacokinetic properties and new mechanisms of action. With all of these new avenues of pharmacotherapy available, one would think we would begin to see a decrease in the number of refractory epilepsy patients. This is the main question addressed by this study: Do we see substantial improvement in the overall prognosis of epilepsy after the availability of many AEDs over the past 20 years? The answer is "No."

This is the fourth in a series of analyses from the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland, that has prospectively followed patients since 1982 (1, 3–5). Three decades of data from patients prescribed their first AEDs were included with information available in 1795 patients. Before patients were prescribed an AED attention was given to seizure type, adverse drug effects, and interaction profiles. The study endpoint was *seizure freedom*, defined as the absence of seizures for the previous 12 months or longer. For this analysis, the study group was divided into three subgroups based on time of initiation of their first AED and according to three time periods: 1982–1991, 1992–2001, and 2002–2012 for additional exploration of changes in patient characteristics, AED choice, and treatment outcomes. Terminal seizure control was defined to be a minimum of 2 years after the end of the cohort time period: 1993, 2003, and 2014.

If patients are not responding to therapy, there is a point where they may be classified as having drug-resistant epilepsy. Prior to 2010, there were multiple definitions for drug-resistant epilepsy. Definitions included the number of failed medications along with the seizure frequency used to determine failure. In 2010, the ILAE Commission on Therapeutic Strategies provided a standardized definition, a means for more uniformity across studies (5). It is important to determine which definitions prior studies used when assessing the prevalence of drug-resistant epilepsy patient across studies. Also of concern is the appropriateness of the failed treatments; therefore, the standard ILAE definition has made this distinction by defining *appropriate intervention* as one that has been shown to be effective. For this study, patients with previous drug use or family history of epilepsy in first-degree relatives were more likely to develop refractory seizures.

The study found more improvement in seizure freedom with the addition of a second medication—but only to a small degree. Thus, adding a second AED to the regimen can result in seizure freedom in a few patients, but addition of a third drug has an even smaller impact. No additional improvement is apparent with four or more AEDs. Interestingly, while the percentage of patients attaining seizure freedom remains similar, the number of patients on polytherapy attaining seizure freedom steadily increased from 3% during the first 15 years (1982–1997) to 9% in this report (4). Does this mean that the number on monotherapy decreased by 6%? It is worth noting that subsequent analyses included all previous patients. It would be interesting to see if these results are reflected in another external data set.

So why continue to develop new medications? Although this paper used seizure freedom as the outcome measure, patients may have benefited from other aspect of newer medications, such as fewer side effects and less complicated pharmacokinetics. If medications are easier to manage, drug adherence may be improved. Indeed, there was a shift by the Glasgow center in the medications prescribed, with older AEDs making up most of the drug regimens before 2002. This may be why carbamazepine was the most frequent drug used early on, with newer AEDs being predominantly prescribed beyond 2002. In contrast, valproate seems to be prescribed at a similar rate throughout the study, even though it is an older AED with a more undesirable side effect and pharmacokinetic profile when compared to newer medications. This may be explained by the observation that patients with generalized epilepsy had a better response to valproate than did patients with focal epilepsy to carbamazepine (6, 7).

Although this study did not see a notable improvement in the number of patients attaining seizure freedom after two or three treatment trials, could it be that order makes a difference? Could it be that the drug that worked in a patient and ended up being the fifth drug was more of a reflection of when it became commercially available? The data available in this study could be used to help answer these questions, although sample size will begin to suffer from smaller number of some of the medications. The final conclusion is that we need to identify treatments that can modify development of epilepsy. The ability to provide preventative treatments is limited, and this approach will not be possible until we address certain knowledge gaps and identify biomarkers. Everyone would like to find a magic bullet; however, it is most likely not possible with a disorder that is so heterogenous. This is consistent with the conclusion of the paper in that we should

not stop looking for better drugs but that we might need to do it in a different fashion.

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