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Special Communication

# Epilepsy treatment in adults and adolescents: Expert opinion, 2016

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ABSTRACT

Introduction: There are over twenty anti-seizure medications and anti-seizure devices available commercially in the United States. The multitude of treatment options for seizures can present a challenge to clinicians, especially those who are not subspecialists in the epilepsy field. Many clinical questions are not adequately answered in double-blind randomized controlled studies. In the presence of a knowledge gap, many clinicians consult a respected colleague with acknowledged expertise in the field. Our survey was designed to provide expert opinions on the treatment of epilepsy in adults and adolescents.

Method: We surveyed a group of 42 physicians across the United States who are considered experts based on publication record in the field of epilepsy, or a leadership role in a National Association of Epilepsy Centers comprehensive epilepsy program. The survey consisted of 43 multiple-part patient scenario questions and was administered online using Redcap software. The experts provided their opinion on 1126 treatment options based on a modified Rand 9-point scale. The patient scenarios focused on genetically-mediated generalized epilepsy and focal epilepsy. The scenarios first focused on overall treatment strategy and then on specific pharmacotherapies. Other questions focused on treatment of specific patient populations (pregnancy, the elderly, patients with brain tumors, and post organ transplant patients), epilepsy patients with comorbidities (renal and hepatic disease, depression), and how to combine medications after failure of monotherapy. Statistical analysis of data used the expert consensus method.

Results: Valproate was considered a drug of choice in all genetically-mediated generalized epilepsies, except in the population of women of child-bearing age. Ethosuximide was a drug of choice in patient with absence seizures, and levetiracetam was a drug of choice in patients with genetic generalized tonic-clonic seizures and myoclonic seizures. Lamotrigine, levetiracetam and oxcarbazepine were considered drugs of choice for initial treatment of focal seizures. Lamotrigine and levetiracetam were the drugs of choice for women of child-bearing age with either genetic generalized epilepsy or focal epilepsy. Lamotrigine and levetiracetam were the drugs of choice in the elderly population. Lamotrigine was preferred in patients with co-morbid depression. Levetiracetam was the drug of choice in treating patients with hepatic failure, or who have undergone organ transplantation. Compared to the 2005 and 2001 surveys, there was increased preference for the use of levetiracetam and lamotrigine, and decreased preference for the use of phenytoin, gabapentin, phenobarbital and carbamazepine.

Discussion: The study presented here provides a "snapshot" of the clinical practices of experts in the treatment of epilepsy. The experts were very often in agreement, and reached consensus in 81% of the possible responses. However, expert opinion does not replace the medical literature; instead, it acts to supplement existing information. Using the study results is similar to requesting an expert consultation. Our findings suggest options that the clinician should consider to achieve best practice.

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## 1. Introduction

There are now over twenty anti-seizure medications and two implantable anti-seizure devices available commercially in the United States [1–10]. The list is long and does not even include extended release formulations [11–14], advances in vagus nerve stimulation technology [15–17], or modifications in dietary therapies [18]. The growing number of possible treatments for epilepsy represents a boon for patients by providing more options to achieve a good outcome and better quality of life.

The multitude of treatment options for seizures can present a challenge to clinicians, especially those who are not subspecialists in the epilepsy field. A review of the literature for the busy clinician

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will often not clarify which treatments are the best for a certain patient. For example, there are over fifteen drugs approved to treat focal seizures [19–21]. Randomized controlled trials (RCTs) provide the highest level of evidence. These studies are commonly used by the U.S. Food and Drug Administration (FDA) to assess the efficacy and safety of anti-seizure drugs compared with placebo [22–26]. However, very few RCTs directly compare multiple active treatments in a single trial, and thus, cannot address the question of superiority. RCTs are usually performed in patients with treatment-resistant seizures without other significant medical conditions, thus limiting their usefulness when treating special populations such as pregnant women, the elderly, or patients with organ failure [27–39]. Other types of studies such as meta-analyses, uncontrolled clinical trials, retrospective case series, and single case reports are considered less rigorous. The methodologies are more susceptible to bias, and the results are considered less reliable. Thus, many clinical questions are not adequately answered in the literature.

In the presence of a knowledge gap, many clinicians consult a respected colleague with acknowledged expertise in the field. The expert consensus method used by Karceski et al. [40] mimics a simplified epilepsy consultation process by surveying epilepsy experts in the United States on their treatment preferences in certain clinical situations. This type of survey was repeated in 2005 [41] and also used to gather opinions on treatment of pediatric epilepsy [42], European expert opinion on the treatment of pediatric epilepsy [43], and Chinese expert opinion on the treatment of adult epilepsy [44]. Since the last similar US survey in 2005, the FDA has approved the use of seven new anti-seizure drugs [1,6,12–13,22, 24–25,45–53] and the responsive neurostimulation system [54–55]. The following study represents an update of epilepsy expert opinions.

### 1.1. The experts

We identified a group of physicians specializing in epilepsy who are considered experts based on publication record in the field of epilepsy, or a leadership role in a National Association of Epilepsy Centers comprehensive epilepsy program. A total of 42 epileptologists completed the survey, compared with 43 in 2005, and 45 in 2001. Of those who completed the current survey, 21% were female. The experts represented a geographic cross section of the United States, with 29% from the Northeast, 21% from the Southeast, 24% from the Midwest, and 26% from the West/Southwest. Fourteen (33%) also participated in the 2005 survey. As the survey addressed epilepsy in adolescents and adults, the group included both pediatric and adult epileptologists. The experts were provided with a $500.00 honorarium for their time as the survey took approximately 2.5–3 h to complete. The study was funded by the Department of Neurology at Mayo Clinic Florida, and approved by the Mayo Clinic IRB.

### 1.2. The survey

The aim of the survey was to address key decisions in the treatment of adults and adolescents with epilepsy. The majority of questions were the same as in the 2001 and 2005 surveys. Exact wording was used where possible to allow for comparison between the results of all three surveys. In some instances, new questions were added and previously asked questions were removed. The current survey also included the International League Against Epilepsy's (ILAE) 2010 revised terminology [56] in addition to traditional seizure classification terminology.

The survey consisted of 43 multiple-part patient scenario questions and was administered online using Redcap software. The experts provided their opinion on 1126 treatment options. The patient scenarios focused on genetically-mediated generalized (idiopathic generalized) epilepsy and focal (symptomatic localization related) epilepsy. The scenarios first focused on overall treatment strategy and then on specific pharmacotherapies. Other questions focused on treatment of specific patient populations (such as women who are pregnant or breast-feeding, medically stable versus medically ill elderly patients, patients with brain tumors, and post-organ transplant patients), epilepsy patients with comorbidities (renal and hepatic disease, depression), and how to combine medications after failure of monotherapy.

There were three types of questions. The first type identified an overall approach to the treatment of generalized or focal epilepsy. The experts identified the order in which they would recommend certain treatments by identifying the first best option and then selecting the next best option if the previous treatment choice failed. For example, if a certain monotherapy was designated as the first step and failed, the respondents selected the next best choice. Respondents selected the next best step until all potential options were used. Respondents were allowed to select more than one option, as more than one therapy could be deemed appropriate at any one step. An example of one of the overall strategy questions is depicted in Table 1.

The second question type asked the experts to rank their treatment recommendations in order of most appropriate to least appropriate using a modified 9-point scale developed by the Rand Corporation [57–59], where 1 = least appropriate and 9 = most appropriate. Experts were provided with the option to designate “Don't Know” if not experienced with or had limited knowledge regarding a treatment option. The rating scale was presented with each question as shown in Table 2.

The third question type addressed a series of scenarios involving driving questions. For each of the two seizure types, the experts were asked if patients with well-controlled seizures of greater than 2 years were advised to refrain from driving given two scenarios: the discontinuation of treatment and during treatment switch. If the experts answered affirmatively and advised cessation of driving, they were asked to provide the number of months they would ask patients to refrain from driving.

### 1.3. Data analysis for options scored on the step scale

Data by type of therapy were descriptively summarized using frequencies and means. The results from the 2005 and 2001 surveys were presented for comparative purposes.

### 1.4. Data analysis for options scored on the rating scale

For questions using the 1–9 scale, the data were descriptively summarized using mean, standard deviation, and 95% confidence intervals (calculated using the standard error of the mean). Consensus or non-consensus was determined as a distribution unlikely to occur by chance using a Pearson chi-square test. The responses grouped into three categories (1–3, 4–6, 7–9), and the responses were compared with a dataset with the equal representation in each three-level category.

### 1.5. Rating categories

Drugs were categorized as treatment of choice, first line, second line, or third line in the same manner as the 2005 survey. Drugs with an insignificant chi-square test were categorized as no-consensus. The drug was labeled as *Treatment of choice* if it was rated as extremely appropriate (“9”) by greater than 50% of the respondents. Otherwise, the lower limit of the CI was used to categorize the drug. If the lower limit was greater than or equal to 6.5, the drug was designated as first line. If the lower limit was between 3.5 and 6.5, the drug was categorized as second line, and if the lower limit was less than 3.5, the drug was categorized as third line. If the CI bordered on the next lower