Editorial

Continuing Burden of Refractory Epilepsy

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Abstract

Epilepsy is one of the most common neurological diseases, and uncontrolled seizures remain a significant problem for one-third of patients with epilepsy on drug therapy. Ongoing seizures affect the morbidity and mortality of patients with epilepsy. Premature death is up to 3 times higher in those with epilepsy than in the general population. Quality of life is affected by refractory epilepsy with physical, social, and psychological consequences. Patients may be stigmatized by society, institutions, and their own shame surrounding seizures. Questions remain on how to treat refractory epilepsy, also called drug-resistant, pharmacoresistant, or intractable epilepsy. Cenobamate, a novel antiseizure medication, may provide additional benefit for refractory epilepsy treatment.

Keywords

seizures, anxiety, depression, epilepsy, quality of life

Introduction

In a marketplace where there is a huge arsenal of antiseizure medications (ASMs), it is important to distinguish which medication to use in a given patient. Of note, the abbreviation *ASM* is replacing previous terminology of *antiepileptic drugs* or *AEDs*. When selecting an ASM, health care practitioners need to consider the type of seizure(s) the patient has been diagnosed with in addition to other comorbid conditions and allergies they may have. In a patient with refractory epilepsy, often, several trials of ASMs will occur in the hopes of decreasing the number and severity of seizures. This editorial will highlight the risks and difficulties associated with managing refractory epilepsy and the need for additional ASMs to decrease the morbidity and mortality of patients with intractable seizures.

What Is Refractory Epilepsy?

Refractory epilepsy terminology differences (ie, intractable epilepsy, drug-resistant epilepsy, pharmacoresistant epilepsy) are mainly technical when referring to patients who are still having seizures dispite ASMs; the confusion is often how many medications must be failed, seizure count in a certain time frame, and so on. About half of patients with epilepsy fail their first ASM therapy, and one-third of patients with epilepsy continue to have seizures despite adequate ASM trials (Figure 1).[1,2] In 2010, to improve patient care and facilitate clinical research, the International League Against Epilepsy (ILAE) task force defined drug resistant epilepsy as "failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[3(p. 1069)] It is especially important to define pharmacoresistant or refractory epilepsy in clinic trials of new ASMs to avoid wide differences in stated outcomes between studies with the same design and medication arising from heterogeneity in baseline characteristics.[4] By stratifying a patient's resistance, one can allow for a prediction of the probability of response when a drug is added.[4] For this editorial we have chosen refractory epilepsy as the term to describe patients continuing to have seizures despite adequate ASM treatment. A failure of treatment occurs when a patient does not achieve seizure freedom. Seizure freedom is defined as "freedom from seizures for a minimum of three times the longest preintervention interseizure interval (based on seizures occurring within the past 12 months) or 12 months, whichever is longer."[3(p. 1072)] Seizure freedom was chosen as the treatment goal because studies suggest that absolute seizure freedom is consistently associated with quality of life.[5]

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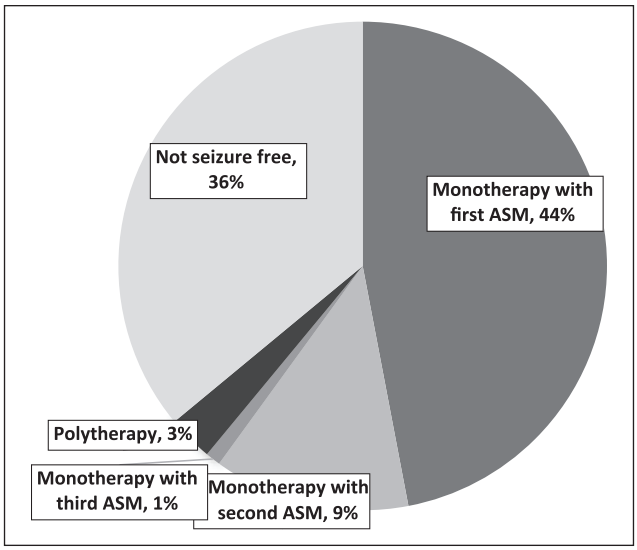

Figure 1. Percentage of seizure freedom with monotherapy and polytherapy.[2]
Abbreviation: ASM, antiseizure medication.

Why Seizure Freedom?

More recently, epilepsy experts and the Epilepsy Foundation have begun the movement "Aim for Zero." This movement is largely motivated by the fact that each year 1 in 150 people with uncontrolled seizures or 1 in 1000 people with epilepsy die from sudden unexpected death in epilepsy (SUDEP).[6,7] Additionally, those who experience 3 or more generalized tonic-clonic seizures per year are at a 15-fold increased risk of SUDEP.[8] In general, those living with epilepsy are 3 times more likely than the general population to die a premature death, many of which are a result of preventable causes.[9] Status epilepticus, unintentional injuries, and suicide are additional causes of mortality in epilepsy. Premature death is significantly more common in low-to-middle income families than in high-income families.[9]

The Burden of Refractory Epilepsy

Apart from mortality, refractory epilepsy affects quality of life. In 2016, epilepsy accounted for more than 13 million disability-adjusted life years.[9] In children and young adults, epilepsy causes the most burden compared with any other neurological disease, and 30% to 40% of children have a coexisting intellectual disability.[10,11] Additionally, lost wage-based productivity associated with epilepsy was almost equal to combined wage losses from anxiety, asthma, and depression combined when evaluating direct and indirect costs.[12]

Having epilepsy alone may result in psychosocial problems, such as depression and anxiety.[13] There is a correlation between seizure frequency and levels of anxiety and depression, perceived stigma, and marital and employment status.[14] Refractory epilepsy can cause increased levels of anxiety and depression, and presence of depression and anxiety can make seizures worse.[9] About 20% of people with epilepsy have depression; about 20% have anxiety; and psychiatric comorbidities are up to 10-fold higher in those with epilepsy than in the general population.[15-17]

The stigma associated with epilepsy can contribute to poor physical and social health. In all, 33% of respondents in a study said that they have experienced externalized stigma, and 90% of respondents experienced internalized stigma, or shame, in having the diagnosis or fear of being discriminated against.[18] Countries and states have a variety of laws regarding the driving ability of patients with ongoing seizures. This can include institutionalized stigma such as a lifetime ban on driving or internalized stigma arising from the shame of being unable to get to work or participate in social activities.

The Future of Refractory Epilepsy

Epilepsy is treatable; however, management of epilepsy, particularly refractory epilepsy, often requires multiple ASMs with different mechanisms of action.[19] In fact, adjunctive therapy may be more effective when initiated immediately after failure of the patient's first ASM.[20] The new medication cenobamate may provide a unique treatment strategy for refractory epilepsy. Cenobamate introduces a unique mechanism to control refractory seizures through its action on slow and fast sodium channels as well as γ-aminobutyric acid ($GABA_A$) receptors.[21] Studies show promising benefits of cenobamate for refractory epilepsy, with percentage change in seizure frequency ranging from 36% to 56% depending on the dose.[21]

In recent years, new ASMs have been developed. However, the prevalence of refractory epilepsy remains unchanged.[22] In fact, the probability of attaining seizure freedom decreases drastically with each unsuccessful ASM trial.[23] Clinicians have little guidance on how to approach polytherapy for epilepsy.[24] There is a need to systemically evaluate the almost endless possibilities for polytherapy in refractory epilepsy. Novel medications, such as cenobamate, and mechanisms to control seizures should be continually investigated.

Conclusion

Refractory epilepsy remains a significant problem in the world of neurology. Experts in the field agree that seizure freedom is the goal for all patients with epilepsy, when appropriate. To achieve seizure freedom, research must continue for rational polytherapy and new mechanisms of action for ASMs.

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