Doctor, Why Can't You Pick the Right Medication for My Epilepsy?

A Pragmatic Algorithm to Select Appropriate Antiseizure Medications in Patients With Epilepsy.

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Objective: Antiseizure medications (ASMs) are the first-line treatment for epilepsy. Many ASMs are available; this offers the opportunity to improve therapy by tailoring it to individual characteristics but also increases the possibility of health care professionals making inappropriate treatment choices. To assist health care professionals, we developed a pragmatic algorithm aimed at facilitating medication selection for individuals whose epilepsy begins at age 10 years and older. Methods: Utilizing available evidence and a Delphi panel-based consensus process, a group of epilepsy experts developed an algorithm for selection of ASMs, depending on the seizure type(s) and the presence of relevant clinical variables (age, gender, comorbidities, and comedications). The algorithm was implemented into a web-based application that was tested and improved in an iterative process. Results: The algorithm categorizes ASMs deemed to be appropriate for each seizure type or combination of seizure types into 3 groups, with group 1 ASMs considered preferred, group 2 considered second line, and group 3 considered third line. Depending on the presence of relevant clinical variables, the ranking of individual ASMs is adjusted in the prioritization scheme to tailor recommendations to the characteristics of the individual. The algorithm is available on a web-based application at: https://epipick.org/#/. Significance: The proposed algorithm is user-friendly, requires less than 2 minutes to complete, and provides the user with a range of appropriate treatment options from which to choose. This should facilitate its broad utilization and contribute to improve epilepsy management for health care providers who desire advice, particularly those who lack special expertise in the field.

Commentary

When physicians make the diagnosis of epilepsy, we face the daunting task of selecting a medication. We have been taught that the most effective antiseizure medication (ASM) is "the first one prescribed." This is supported by the seminal 2000 study by Drs Kwan and Brodie, which demonstrated that 47% of patients responded to the first ASM prescribed, while only 13% responded to a second ASM, and 4% responded to subsequent medication trials.[1] Although this allows us to understand that those who continue to have seizures after 2 appropriate ASMs are unlikely to respond to medications, thus helping us understand at what point seizures are pharmacoresistant, it also points out that less than half of patients become seizure free with their first medication. Given the anxiety that surrounds risk of seizure recurrence, these are not response rates that allow our patients to have tremendous confidence in their epilepsy physicians.

Why is the response to the first medication so low? How much can choosing the "right medication" affect outcomes? In a study of adults with uncontrolled seizures, 29% were found to be taking the wrong ASM for their type of epilepsy and another 18% were taking suboptimal doses.[2] Similarly, in children 37% were taking the wrong ASM and 10% were taking suboptimal doses, making their seizures "pseudorefractory."[3] Learning they have been prescribed an inappropriate ASM or suboptimal dose further erodes patient confidence in their medical team. This patient–physician confidence is essential for our practices. We know some of our patients truly have intractable epilepsy and will require treatments beyond medications. How can we discuss surgery with our pharmacoresistant epilepsy patients when they believe we just haven't prescribed the correct medication?

Early in my career, I was meeting with a family for an epilepsy subspecialty consultation. The child's seizures had already failed to respond to 3 different ASMs. I explained that epilepsy refractory to this many medications suggested the child was unlikely to become seizure free with additional medication trials. In response, the parent asked: "What's wrong with you? Why can't you just pick the right medication?" At other times, we may have been asked, "You went to school for *how* many years, and you *still* can't make me seizure-free?"

What can we do to improve our prescribing practices? How do we pick the best medication first? Perhaps we should review the studies, comparing efficacies of all the different ASMs in adults and children, based on specific seizure type and epilepsy syndrome. That would be an ideal way to select an effective medication. Unfortunately, these studies do not exist, although attempts have been made. Furthermore, this would not take into account comorbidities, tolerability, and cost.

In 2006, the International League Against Epilepsy (ILAE) performed a comprehensive evidence-based analysis of ASM efficacy as initial therapy. Unfortunately, they found there was a lack of properly conducted randomized controlled trials (RCTs) or comprehensive adverse effects data.[4] The ILAE tried again in 2013. Although there were several medications identified that had level A evidence ($\geq$1 class 1 studies or meta-analysis meeting class 1 criteria sources OR $\geq$2 class II studies), establishing them as effective as initial monotherapy, the authors stressed a lack of RCTs. They concluded that it was up to the individual physician to choose the appropriate ASM.[5] The American Academy of Neurology updated their practice guideline for treatment of new-onset epilepsy in 2018. However, the level of evidence provided for this guideline was B (ASM probably effective), C (ASM possibly effective), or U (data lacking to support or refute using).[6] Finally, the Swedish Medical Products Agency recently performed a systematic literature search to create updated practice guidelines, using the same rating scale as the ILAE.[5,7] From this, recommendations were made for initial treatment of focal or generalized seizures in children, adults, and the elderly. However, multiple ASMs were recommended as first choice. Furthermore, these recommendations were made from studies with a range of quality, from A (established as effective) all the way to D (potentially effective).[5,7] Therefore, evidence that would allow providers to identify the one most effective medication for each individual patient is lacking.

When we don't have the evidence, what is the next best thing? We could turn to expert opinion. A large group of epilepsy specialists across the United States was given a survey of 43 multiple-part scenario questions, with respondents providing information on what they felt would be the preferred medication for each scenario. This survey was completed in 2001, 20015, and 2016.[8] The results of identified medications that the experts recommended as treatments of choice for focal and generalized epilepsies.[8] Although this provided excellent information for clinical practice, multiple treatments of choice were offered, not a single best medication. Once again, it is up to the provider to choose the best medication for his/her patient.

Epilepsy experts recently created an algorithm using the Delphi process that takes into account seizure types, history, and other relevant information to identify potential misdiagnosis of epilepsy/seizure types and then provide medication recommendations.[9] Possible medications are identified as best, second best options, and "least desirable options though still acceptable."[9] Given that the initial provider is often not an epilepsy subspecialist, this tool has the potential to be of great service for identifying initial treatment options. Unlike previous studies, it also helps avoid misdiagnosing seizures or epilepsy syndromes. However, like all other studies, unfortunately, this only narrows the list of potential options and does not give us the one best option.

Perhaps it is time for us to humbly recognize our limitations as epilepsy doctors. It is important to recognize that we just don't know enough yet to identify the most effective and best tolerated medication for each patient right from the beginning. Given the lack of evidence, how to we build patient trust? We must have good communication with our families. It is important that they understand the complexity of using ASMs, as well as treatment of chronic disease, so they know what to expect. We must have close follow-up, especially at the beginning of our patient's epilepsy treatment journey, to make medication adjustments and answer questions. A new diagnosis of epilepsy is frightening and fraught with uncertainty. Whether or not the studies ever exist that identify the one best medication for each patient, the goal for treatments remains: No seizures. No treatment side effects. For now, that is our one best option.

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