Drug-Resistant Epilepsy Gets New Definition

BY DIANA MAHONEY

BOSTON — A new consensus definition of drug-resistant epilepsy promises to improve patient care and facilitate clinical research, according to the chair of a task force appointed by the International League Against Epilepsy Commission on Therapeutic Strategies.

According to the definition, epilepsy patients who have failed adequate trials of two tolerated, appropriately chosen and used antiepileptic drug regimens, whether as single or combination therapies, should be considered drug-resistant and referred for specialty evaluation.

The identification of drug-resistant, or refractory, epilepsy substantially influences clinical decision making as well as treatment research and development. Appropriately labeling a patient as drug resistant, for example, might lead to more timely consideration of surgical or other nonpharmacologic treatment, such as vagal nerve stimulation, he said. In addition, recognizing drug resistance in patients may provide insight into the neurobiology of the disease, which in turn can inform the development of new treatment, Dr. Patrick Kwan said at the annual meeting of the American Epilepsy Society.

The lack of a precise definition for refractory epilepsy until this time has meant the reliance on diverse criteria by clinicians and researchers, "which makes it difficult to compare findings across studies and to develop evidence-based practice recommendations," said Dr. Kwan of the Chinese University of Hong Kong, Prince of Wales Hospital.

In an effort to level the playing field, the new definition is built on a framework that comprises a general scheme for categorizing patients' responses to each therapy and determining trial adequacy, he said.

For example, if a patient stops taking a given drug, it's important to know the circumstances of the withdrawal, according to Dr. Jacqueline French, professor of neurology at New York University and cochair of the therapeutic strategies commission.

"Was the drug ineffective after being titrated to its clinically effective dose range or was it withdrawn because of an adverse effect?" The former scenario will have some bearing on the presumed efficacy of other antiepileptic drugs, she stressed in a press briefing. The latter scenario, on the other hand, does not indicate a clinical failure of the drug with respect to its efficacy for seizure control, and as such should not be placed under the "drug-resistant" umbrella, she said.

The definition also requires that therapeutic interventions be appropriate for patients' epilepsy and seizure type and have been proven effective previously, preferably in randomized, controlled studies, Dr. French said.

With respect to trial adequacy, the task force deemed the following information necessary for assessing whether a drug intervention study is appropriate and informative for evaluating efficacy:

- The nature of the intervention, such as the type of drug.
- The mode of application, including the formulation, dose, dosing interval, and patient compliance.
- The duration of exposure.
- The occurrence of seizures and adverse effects during the trial period.
- The nature of the intervention, such as the type of drug.
- Whether there was an effort to optimize dose.
- The reasons for drug discontinuation, if applicable.

The outcomes of trials that do not fulfill these criteria should be considered "undetermined," and as such should not be included in the drug failure count, Dr. Kwan stressed. Practically, this means that some patients may "fail," in some manner, multiple antiepileptic drugs before they fail two appropriate, informative trials, he said.

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Recognizing drug resistance may provide insight into the neurobiology of epilepsy, Dr. Patrick Kwan said.

Following two adequate, therapeutic trials, patients who do not achieve seizure freedom, defined by the task force as being seizure free for at least 1 year or three times the longest interseizure interval, should be referred from primary care or general neurology care to specialist centers for further evaluation, Dr. Kwan said.

Although it is expected that the definition will be adopted by clinicians at all health care levels, primary care physicians in particular will have a major role in applying the definition, as they are the most likely to have long-term relationships with these patients, he said.

Importantly, "by applying the definition, practitioners [and patients] can be alerted to the type of information that should be collected during clinical consultation," Dr. Kwan and his task force colleagues wrote online in Epilepsia. "The proposed definition also has implications for the design of randomized drug trials and should prove useful in the selection of patients for such trials in which the criteria for considering a patient drug resistant are often poorly described," they wrote, noting that a "standard definition of drug resistance can help ensure comparable results across trials" (Epilepsia 2009 Nov. 3 [doi:10.1111/j1528-11672009.02397.x]).

The definition is intended to be applicable to all patients, regardless of age of onset, type of epilepsy, seizure frequency, or seizure etiology, according to task force member Dr. Alexis Arzimanoglou of University Hospitals of Lyon (France). "The early detection of [drug-resistant] epilepsy should lead to early referral to a specialty center for evaluation and treatment," he said. The definition "offers a new path for the early identification of those patients who may be cured from their epilepsy."

Dr. Kwan stressed that the proposed definition is not the last word on drug-resistant epilepsy, but rather it represents "a testable hypothesis and a common starting point. Revision may be needed as more high-quality data become available." ■

Disclosures: *Members of the task force, whose work was funded by the ILAE, disclosed no relevant financial conflicts.*

Anticonvulsant Drug Use Elevated in Sudden Death Cases

BY MITCHEL L. ZOLER

ORLANDO — Patients who experienced sudden cardiac death had a significantly higher rate of treatment with a sodium channel–blocking, anticonvulsant drug, compared with people who did not have sudden death, in a case-control study of more than 10,000 people.

"This finding may explain a proportion of the sudden deaths seen in epilepsy patients," Dr. Abdennasser Bardai said at the annual scientific sessions of the American Heart Association.

About 10% of epilepsy patients have an unexpected death unrelated to seizure, a phenomenon so common that it's been named "sudden unexplained death in epilepsy." Dr. Bardai and his associates hypothesized that many of these deaths might be triggered by anticonvulsant drugs, especially those that block sodium channels such as carbamazepine, lamotrigine, and phenytoin. Although the sodium-channel blockade these drugs cause is aimed at neurons, the same property can affect cardiac cells and may potentially cause arrhythmia.

To explore a possible link between anticonvulsant use and sudden death, the researchers used data collected in the Integrated Primary Care Information database, which has records for more than 1 million residents of the Netherlands. They focused on medical records for people aged 18 or older during 1995-2007 in cases for which at least 1 year's record existed.

Among the more than 478,000 people who met these criteria, 926 experienced sudden death, defined as a natural death heralded by a sudden loss of consciousness within 1 hour after the onset of acute symptoms, or an unwitnessed, unexpected death of someone seen in stable medical condition less than 24 hours before, with no evidence of a noncardiac cause. The researchers matched each case with about 20 other people from the database of the same gender and of similar age, reaching a total of 9,832 controls. The mean age of the cases and controls was 72 years; 26% were men.

In a multivariate analysis that controlled for age, gender, smoking, alcohol abuse, concomitant medications, cardiovascular disease, arrhythmia, hypertension, diabetes, heart failure, and hypercholesterolemia, people who died from sudden death were 2.5-fold more likely to be on treatment with an anticonvulsant drug than were controls, a statistically significant difference, reported Dr. Bardai, a cardiovascular diseases researcher at the Academic Medical Center in Amsterdam.

In a second adjusted analysis that divided anticonvulsant drug use into agents that block sodium channels and those that don't, the sudden death cases were 2.9-fold more likely to be on a sodium channel–blocking anticonvulsant, compared with controls, a statistically significant difference. In contrast, the fraction of sudden death cases on treatment with an anticonvulsant that does not block sodium channels was not significantly different from the rate at which these drugs were used by the controls.

In a final set of analyses, Dr. Bardai and his associates calculated the use of specific anticonvulsant drugs among the sudden death cases and controls. The only significant relationship they found was that the sudden death cases were 3.4-fold more likely to be on treatment with carbamazepine, a sodium channel–blocking anticonvulsant, compared with the controls. ■

Disclosures: *Dr. Bardai said that he and his associates had no financial disclosures.*