In the early 1990s, researchers began looking at potassium channel openers for seizure control. Over the past 10 years, in vitro research and animal studies demonstrated that potassium channel openers could control seizure activity in a dose-dependent way. Clinical trials are now confirming these findings.

Among the calcium channel openers that have been studied, the agent retigabine has come to the fore as the strongest candidate for inclusion in the therapeutic armamentarium for epilepsy. An update on clinical trials data was presented at a satellite symposium chaired by Eric Hargis, secretary general of the International Bureau for Epilepsy, and president and CEO of the Epilepsy Foundation, during the annual meeting of the International League Against Epilepsy in Singapore in early July.

In his overview, Hargis reminded the audience that 30% of persons in whom epilepsy is diagnosed do not respond to antiepileptic drugs (AEDs) and that uncontrolled seizures take an enormous toll on the physical health and emotional and social well-being of affected persons. "There is a tremendous need for new treatment options," he said.

"The fundamental causes of epilepsy are related to abnormal nerve cell hyperexcitability," explained one of the symposium's featured speakers and key researcher in the development of retigabine, Roger J. Porter, MD, adjunct professor of neurology at the University of Pennsylvania in Philadelphia. He reiterated that new AEDs are needed to address the 30% of patients whose epilepsy is treatment-refractory. "[Seizures in] only 60% to 70% of patients are really controlled, and many of these patients still experience either uncontrolled seizures or substantial adverse effects from the treatments they receive," he said.

Strategies for AED development focus on potentiating seizure inhibition by intercepting neuronal hyperexcitability. Drugs, such as vigabatrin (Sabril) and tiagabine (Gabitril), that act on γ-aminobutyric acidergic (GABAergic) processes inhibit neuronal hyperexcitability, explained Porter. Glutamate antagonists targeting the N-methyl d-aspartate receptor also have been studied in effort to reduce neuronal excitation, "but thus far, we have not successfully developed a drug in this direction," he said. "On the other hand, modifying ion channels has been a very successful process for finding new AEDs. Voltage-gated sodium channel blockers in particular, as well as calcium channel blockers, have proved useful in seizure control, Porter noted.

The potassium channel opener retigabine, currently in phase 3 clinical trials, "works through the KCNQ—now called Kv7—channels, which modulate the M current, affecting cell excitability," Porter explained.

"These voltage-dependent potassium channels turn on during the period of excessive hyperexcitability of the neuron. They act as a molecular brake to tone down or stop the hyperexcitability. This is how a drug such as retigabine can have antiepileptic activity," explained fellow speaker Michael Rogawski, MD, PhD, professor and chair of the Department of Neurology at the University of California at Davis. The mechanism of action was discovered by German pharmaceutical researcher Chris Rundfeldt, PhD.

"This was a very surprising finding because until this time, no drug used to treat epilepsy had been found to open potassium channels," commented Rogawski. Then, Tatulian and colleagues showed that retigabine specifically targeted the KCNQ2/3 potassium channels, which were recognized as playing a key role in familial neonatal convulsions. The researchers conjectured that opening these
channels, therefore, could staunch neuronal hyperexcitability and attendant seizure activity. According to data on file with the manufacturer, Valeant Pharmaceuticals, the agent does not interact with other commonly used AEDs. Thus, it was studied as adjunctive therapy in a recently published phase 2b, dose-ranging, placebo-controlled trial led by Porter and Rajesh Sachdeo, MD, clinical professor of neurology at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, and director of the New Jersey Comprehensive Epilepsy Center. Porter, Sachdeo, and colleagues\(^5\) found that the best results of adjunctive retigabine therapy, in comparison with placebo, were achieved at dosages of 900 and 1200 mg/d.

The responder rates were 23% for patients who received 600 mg/d of retigabine, 32% for those who received 900 mg/d, and 33% for those who received 1200 mg/d, compared with 16% for patients who received placebo. The dropout rate in the study (32%) was high, which the authors attributed to the study's use of a forced titration schedule and a maximum tolerated dosage (1200 mg/d).

"We got our best response from the highest dose, but we also got additional adverse effects. This is a pitfall of using a forced titration technique," explained Porter in an interview with Applied Neurology. "You might be a patient who would do extremely well on 900 mg of the drug while 1200 mg is too much. Because of this, you may or may not be able to stay in the study, and if you do stay in it and are in the high-treatment group, you may do well with seizure control but have more adverse effects." Porter added that the FDA prefers a forced titration study design. "The data from this kind of study design give the FDA a very firm feel for what the drug can do at specific doses," he said.

Porter went on to explain that although such studies do not examine how the drug should be used in the clinical setting, they are necessary to working toward FDA registration of a potential pharmaceutical agent. "Getting the drug registered and learning how to use it are 2 different processes," he said.

Retigabine has a lot of potential, according to Porter, who was the first person to conduct clinical research with the agent and has championed development of the drug to the present day. "The most notable thing about retigabine is that it is the first-ever AED that is a potassium channel opener. Finding a potassium channel opener has long been aspired to, but the problem was finding a drug that would be successful but not toxic. Retigabine is the first to make it thus far," he said. Porter foresees that the agent will play a distinctive role in the drug armamentarium for epileptic seizure control because of its unique mechanism of action. "It may be combined with drugs that have other mechanisms of action—sodium channel blockers or GABAergic agents—and in that way especially, be very effective in patients who have seizures that are difficult to control," commented Porter. He added that it was promising and unusual for the first dose-ranging study (phase 2b) to provide dose-response data. "This is relatively unusual for a first study. It tells us that we have a good drug, and we orchestrated the study effectively and picked the right doses to use," he said.

Phase 3 trials are currently looking at the efficacy and safety of high-dosage (1200 mg/d) retigabine versus placebo (Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy [RESTORE] 1) and retigabine 600 and 900 mg/d versus placebo (RESTORE 2). RESTORE 1 has finished recruiting and includes 280 patients. Recruitment for RESTORE 2, which plans to include 510 patients, is almost complete.

**References**: References


7. World Health Organization. Epilepsy Fact Sheet. Available at:

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