



Intractable Epilepsy and Individuals with Intellectual Disabilities

by Sally James

Sometimes, in medicine, there is an element of serendipity. The right person happens to see data and connects the dots. Nicholas Poolos, MD, PhD, found himself at one great intersection of data and ideas and followed through to discover that one combination of drugs may reduce seizures for patients with especially difficult cases of epilepsy. Poolos is an associate professor of neurology and a research affiliate of the Center on Human Development and Disability.

Besides running a laboratory where he does basic science research, Poolos is a neurologist specializing in epilepsy. He and his colleagues at the UW Regional Epilepsy Center consult at several residential centers providing services for adults with intellectual disabilities. The centers keep detailed records and frequently physicians try different drugs in different combinations hoping to ease the seizures of patients with epilepsy. “I stumbled upon the realization that we could do something with this data. I was very excited but my expectations were quite low,” he explained in an interview.

Epilepsy is one of the most common causes contributing to neurological disability in children. The prevalence of epilepsy is estimated to be about 1 percent of the population. Current treatments do not reliably prevent seizures and associated brain damage in about one-third of patients who are called “refractory.” There are an estimated 3 million patients in the United States with epilepsy. Most of them can reduce their seizures with antiepileptic drugs, but for about one million – drugs do not produce seizure freedom. Those patients might have three seizures in a month. The serendipity for Poolos came “like a ton of bricks” one day when he saw the Excel spreadsheets kept by one center – and he realized the data could be a gold mine for analyzing which combinations of drugs yielded better results. He says there are about 20 different drugs available and most physicians must rely on trial and error to find which work best.

In a paper published last year in the journal *Neurology*, Poolos described how he and his colleagues, Lindsay Warner, a UW undergraduate, and Sophia Humphries and Steve Williams, pharmacists, analyzed eight of the most common medications for refractory epilepsy. They studied records for the various combinations of the eight drugs. The records they used reached back 30 years and came from two centers: Fircrest Residential Habilitation Center (85 patients) in Shoreline, Washington, and Rainier



Nicholas Poolos runs a science research laboratory as well as providing services for adults with intellectual disabilities who also experience severe epilepsy.

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Nicholas Poolos on “refractory” epilepsy patients who may benefit from the combination lamotrigine/valproate treatment.

Residential Habilitation Center in Buckley, Washington (63 patients). Out of 32 most frequently used combinations of medications, only the combination of valproate and lamotrigine had superior results. This one combination reduced seizures by 50 percent over other regimens. While this does not give most patients a seizure-free life it does provide hope. Further investigation of that combination may reveal some underlying mechanism of the biochemistry. With some further understanding of why this combination works better for some patients, Poolos hopes to reach a regimen that gives refractory patients their lives back – seizure-free lives. “I intend to continue working on this. There’s plenty we don’t understand,” he said.

While a single two-drug combination did appear significantly better, the study also showed that three-drug combinations produced no benefit over combinations of two drugs at a time, Poolos wrote. This was a somewhat surprising finding. More research with more patients could answer some additional questions.

In the laboratory, Poolos and his colleagues study links between epilepsy and neuronal ion channel dysfunction. Dysfunctional ion channels can cause hyper-excitability in neurons, which in turn produces seizures. The team hopes to discover new molecular targets for antiepileptic drugs by dissecting the signaling pathways underlying ion channel dysfunction in epilepsy. His work outside of the laboratory, seeing patients at Regional Epilepsy Center and at the residential centers, gives him what some call a bench-to-bedside appreciation for how discoveries may directly benefit patients; in his case, it includes individuals with significant intellectual disabilities. The expression bench-to-bedside refers to translational research, where basic science discoveries are translated into changes in treatment for patients.

There are mathematical challenges in trying to measure every possible combination of more than the eight top drugs that Poolos chose for his first study. There is very little literature on what medications work best in refractory epilepsy and Poolos hopes this study will counteract some of the lack of hope for these patients. “Just because no single drug will work, do we assume that nothing works?” he asks. He has applied for a two-year grant from the National Institutes of Health to try to explore more about the mechanisms that may be at work in this drug combination. In the meantime, as treating physicians read this journal article, they may choose to prescribe the lamotrigine/valproate combination and possibly improve the quality of life for many existing patients. Changing clinical practice is not easy, he said. It typically takes years for a discovery to work its way from medical journals into everyday practice.

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

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