Children's Foundation Research Institute

Research Matters

SUMMER 2026

Jim Wheless, MD

Breakthrough for Dravet syndrome: Clinical trial dramatically reduces seizures, reverses cognitive decline

Le Bonheur Children's Hospital Chief of Pediatric Neurology James Wheless, MD, and his team are part of a groundbreaking clinical trial, published as the lead article in *The New England Journal of Medicine*, that targets the genetic root cause of Dravet syndrome, a rare and devastating form of epilepsy that begins in early childhood.

"It was the first time ever in the treatment of epilepsy that something like this had been done," Wheless said. "To look at not only efficacy — is it going to help their seizures — but are they better in other ways such as cognition and behavior. That's what made this study unique from a practical standpoint."

Across multiple centers including Le Bonheur, 81 patients were enrolled in phase 1 and 2a studies to test the safety and efficacy of the drug zorevunersen. Results showed that patients saw a dramatic 58.82% to 90.91% drop in seizures with only mild to moderate adverse events.

Understanding Dravet Syndrome

Dravet syndrome is a severe genetic epilepsy that typically appears in infancy. Children experience frequent, prolonged seizures — often resistant to standard medications — along with developmental delays, speech challenges, behavioral issues and problems with motor skills.

For years, treatment has focused on managing those symptoms, primarily the seizures. But researchers can now identify the specific gene mutations responsible, part of a rapidly growing list of hundreds of genetic causes of epilepsy.

"With the realization that we could test and say, 'This is what's causing your epilepsy,' that led to the next obvious thing that you could possibly ask me as a parent of that child: 'What can we do about it?'" said Wheless.

For Dravet syndrome, this is the SCN1A gene. While most people have two copies of the gene, children with Dravet syndrome have just one normal copy. This gene controls production of a protein needed to move sodium within brain cells that is critical for proper brain function.

A New Kind of Treatment

The new therapy tested by the Le Bonheur team, called zorevunersen, now offers a promising answer to that question.

The therapy tested in the recent trial uses an antisense oligonucleotides (ASOs), a class of treatments designed to target ribonucleic acid (RNA) and modify how disease-related genes are expressed, helping to correct the underlying biology of the disease.

For Dravet syndrome, zorevunersen works by increasing the production of the functioning SCN1A gene to produce as much as twice the amount of protein to restore protein levels to a more normal functional amount. The drug is delivered directly to the spinal fluid so that it can reach the brain.

continued on page 2

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCES

Le Bonheur Children's Hospital

continued from cover; "Breakthrough for Dravet syndrome"

The results of the trial not only showed a dramatic decline in seizures but also a reverse in the cognitive decline often seen with Dravet syndrome. Neurologists hope this means that treatments can now address the root of the disease instead of managing symptoms.

The trial marked a major milestone: a first-in-human study of this kind of gene-targeting therapy specifically for epilepsy — and one conducted in children, where the disease does its most significant damage.

The Results

The children enrolled in the study were already receiving the best available treatments. Even so, they continued to experience frequent seizures, often daily to weekly. Patients in the study had to have at least one per week to qualify to participate. In total, more than 80 children and adolescents with Dravet syndrome participated in the early phases of the trial, with most continuing into long-term follow-up.

Depending on the study phase, patients received one to three initial doses of the therapy, with many continuing on a maintenance schedule of repeat dosing every four months.

The initial phase of the trial focused on safety, gradually increasing doses while closely monitoring patients. It was safe — no serious side effects. The trial was cleared to continue.

By the second injection, families told Wheless they had never experienced that level of improvement before. Seizures were reduced or stopped on their own. This had never happened before, they told Wheless. They had always had to go to the emergency department for medicine to stop the seizures once they began.

"There were some kids early on that we could tell, wow, this is going to be a gamechanger," Wheless said.

The study results showed that seizures were reduced by anywhere from 58.82% to 90.91%, a dramatic improvement for patients already on optimized care. Decline in areas like communication, cognition and motor function not only stopped — it reversed.

"For some of these kids, they were literally saying the first couple of words to their parents they'd ever heard them say," Wheless said.

Looking Ahead

The success of the initial trial has already led to the next phase: a larger study aimed at securing broader approval from the U.S. Food and Drug Administration (FDA) and expanding access to more patients.

But the implications reach far beyond Dravet syndrome. Wheless believes this approach represents the beginning of a broader transformation in neurology — one driven by the ability to identify and target genetic causes of disease.

"The technology that's allowing us to diagnose genetically based epilepsies is really exploding," said Wheless. "That's really going to skyrocket in the next five years across all of neurology, not just epilepsy, but to other disorders in the past that we thought we couldn't treat."

Instead of managing symptoms, doctors may be able to change the trajectory of a disease — preserving development, improving quality of life and reducing the long-term burden on families.

Genetic risk score to predict chronic kidney disease in sickle cell anemia

Rima Zahr, DO

Le Bonheur Pediatric Nephrologist Rima Zahr, DO, developed a genetic risk score that may help identify children with sickle cell anemia (SCA) who are at high risk for chronic kidney disease (CKD). Published in the *American Journal of Hematology* and supported by her K23 grant from the National Institutes of Health (NIH), the study focuses on using genetic variants to predict the development of persistent albuminuria, an early sign of kidney damage.

Zahr identified four key genetic modifiers associated with CKD risk in SCA — APOL1, HMOX1, BCL11A and alpha-thalassemia — and used them to create two polygenic risk scores (PRS-3 and PRS-4). These scores classify patients into risk categories ranging from low to very high risk.

The research evaluated 324 children and young adults enrolled in the Sickle Cell Clinical Research and Intervention Program (SCCRIP). Both risk scores were strongly associated with persistent albuminuria. Children in the highest-risk categories were 14 to 19 times more likely to develop persistent albuminuria than those in the low-risk groups. The findings were further validated in 253 adults with SCA, where high-risk individuals were 12 times more likely to have persistent albuminuria.

Because people with sickle cell anemia face an increased risk of progressive kidney disease and limited access to kidney transplantation, early identification is critical. Zahr hopes this genetic risk score will enable earlier monitoring, treatment and interventions, ultimately reducing the burden of CKD and improving long-term outcomes for patients with sickle cell anemia.

New Dosage for an Old Drug: Le Bonheur CVICU develops new guidance for clopidogrel in patients younger than 24 months

After seven years of research involving four institutions, Le Bonheur Children's Hospital recently published research in the *Journal of Pediatric Pharmacology and Therapeutics* with new dosing guidelines for the use of clopidogrel for children younger than two years. The drug, commonly known as Plavix, was studied in 0 to 24-month-old patients in Le Bonheur's Cardiovascular Intensive Care Unit (CVICU).

"Research on antiplatelet drugs like Plavix has become increasingly essential with new pediatric cardiology developments," said Pediatric Cardiac Critical Care Intensivist Mario Briceno-Medina, MD. "CVICU patients now have less invasive heart surgery alternatives, such as inserted devices like stents and shunts, however, the presence of devices leads to increased risk of blood clotting around them."

While past guidelines suggested a static dosage of Plavix for children younger than 24 months, this new research from Le Bonheur shows that patients may require a gradual, age-based escalation of clopidogrel dosing to be most effective.

In 2018, Le Bonheur's CVICU staff first observed an increase in the prescription of Plavix, an antiplatelet medication used to prevent serious blood clots, heart attacks and strokes. The rise in Plavix usage led staff to reconsider the guidelines provided by the 2008 Platelet Inhibition in Children on cLOpidogrel trials (PICOLO).

An increase in the use of devices for children with heart conditions means an increased risk of blood clotting. A team in Le Bonheur's Cardiovascular Intensive Care Unit developed new guidelines for using the antiplatelet drug Plavix (clopidogrel) for these patients younger than 24 months.

Rather than a gradual dosage, the PICOLO trials recommended a sudden fivefold increase from the dosage in 0 to 24-month-old patients to patients 24 months and older. Immediately after patients reached 24 months, dosage jumped from 0.2mg/kg/day to 1mg/kg/day.

"Questions about the PICOLO trial dosage have been going on for a while, and we worked off what they did," said Mark Rayburn, PharmD, a Le Bonheur pharmacist. "At Le Bonheur, we had enough patients to model out the dosage and follow them in-house for longer."

Between 2018 and 2021, the Le Bonheur team conducted an initial retrospective cohort study and proposed a linearly increasing dosage scheme. They evaluated platelet inhibition in blood samples from 44 patients younger than 24 months.

The team's research concluded that pediatric cardiac patients may require a gradual escalation of Plavix dosing, in contrast to the existing guidelines recommended by the PICOLO trial.

Le Bonheur physicians and pharmacists worked together to develop new guidelines for patients in the Cardiovascular Intensive Care Unit (CVICU) on clopidogrel, commonly known as Plavix. From left to right, Cardiac Critical Care Intensivist Mario Briceno-Medina, MD, Pharmacist Carli Coalter, PharmD, and Pharmacist Mark Rayburn, PharmD, were part of the team that worked to find the most effective dosing scheme for this patient population.

Le Bonheur's new guidelines stayed within the range of the PICOLO trials but increased dosing gradually throughout 24 months. Dosage began at 0.2 mg/kg/day and reached as much as 1mg/kg/day, typically averaging an increase every three months. The guidelines were so successful at preventing clotting in patients that Rayburn initiated a formal research project. This research project involved collaboration between Le Bonheur pharmacists and physicians. Beyond Le Bonheur, the team members included participants from the University of Memphis, Children's Hospital of Philadelphia and Children's Health in Dallas.

"The collaborative aspect of the research was very important to me," said Rayburn. "Pharmacists, by assessing the laboratories, help the physicians achieve their goal of helping the patients."

In addition to Rayburn, collaboration at Le Bonheur involved two pharmacy residents, Katie DeAvilla and Carli Coalter, and Pediatric Cardiac Critical Care Intensivist Mario Briceno-Medina, MD.

"Although Plavix is an old medication, it will continue to be used quite a lot with all the changes happening in interventional cardiology," said Briceno-Medina. "Having an algorithm where we are more comfortable achieving the goal while using a minimal amount of drug makes a huge difference in clinical practice."

Briceno-Medica and Rayburn hope to see their publication become a dosing guideline in the Lexicomp, a medical drug database, to reach doctors around the world and support more CVICU patients vulnerable to clotting.

"These ideas are born as we try to figure out problems we may encounter every day. It takes someone to pay a little more attention, identify the issue and raise the question, 'what can we do about this,'" said Briceno-Medina.

Early vocal development in tuberous sclerosis complex predicts language but not autism outcomes

Tanjala Gipson, MD

Tuberous sclerosis complex (TSC) is a genetic condition often associated with epilepsy and language delays, yet language impairments are frequently not identified until children are around 7 years old. Le Bonheur Neurodevelopmental Specialist Tanjala Gipson, MD, is first author of "Early Vocal Development in Tuberous Sclerosis Complex Predicts Language but Not Autism Outcomes" published in *Pediatric Neurology*, which examined early vocal development in infants with TSC as a predictor of later speech and language outcomes.

The study built on previous research and data shared by the Tuberous Sclerosis Complex Autism Center (TACERN) and is part of Gipson's K23 grant from the National Institutes of Health. Using recordings from 108 12-month-old infants with TSC, Gipson measured vocalizations and canonical babbling — the speech sounds that form the foundation of language.

Infants with TSC showed lower canonical babbling ratios (CBR) and reduced vocalizations compared to typically developing infants. While reduced vocalizations did not predict later outcomes, lower CBR significantly predicted receptive and expressive language delays at 24 months. CBR was not associated with autism spectrum disorder.

"For families and clinicians, this research is a helpful and low-tech tool and holds promise as an inexpensive, noninvasive way to identify children with TSC who may benefit from earlier speech and language support," said Gipson. The research concluded that delayed canonical babbling may serve as an early marker of future language impairment, enabling earlier intervention and support for children with TSC.

Management of blunt thoracic aortic injury: Clinical practice guideline update

Erica Mitchell, MD

Blunt thoracic aortic injury (BTAI) is a life-threatening injury caused by severe trauma. Because BTAI often occurs alongside other serious injuries, evidence-based treatment is critical.

Le Bonheur Vascular Surgeon Erica Mitchell, MD, co-authored an update on the clinical practice guidelines for the management of BTAI in the *Journal of Vascular Surgery*. The expert panel addressed when to use nonoperative management (NOM) versus thoracic endovascular aortic repair (TEVAR), timing of intervention, adjunctive therapies and care for patients with associated injuries.

- Grade 1 and 2: NOM with minimal or no routine follow-up imaging for grade 1 and a single follow-up CTA for grade 2
- Grade 3: TEVAR after 24 hours for stabilized grade 3 to allow treatment of associated injuries
- Grade 4: Urgent or emergent repair is recommended for unstable patients
- Decisions about left subclavian artery revascularization, anticoagulation, anti-impulse therapy and TEVAR timing should be individualized based on anatomy, bleeding risk and multidisciplinary input
- In patients with traumatic brain injury and BTAI, the brain injury should be prioritized for grades 1-2, while in grade 3, the decision requires multidisciplinary collaboration

"These guidelines represent a meaningful step forward in standardizing care for a devastating injury while preserving the individualized judgment complex trauma patients require," said Mitchell.

Bedside ultrasound assessment to detect muscle loss in critically-ill children

Muscle loss is a key predictor of intensive care unit (ICU) acquired weakness, which can lead to longer hospital stays, increased mechanical ventilation and greater morbidity. To evaluate bedside ultrasonography as a tool for detecting muscle loss, Le Bonheur Critical Care Intensivist Nicolas Chiriboga, MD, and Registered Dietitian Alyssa Clark, MS, RD, LD, were part of a group that conducted a study published in the *Journal of Ultrasound in Medicine*.

The study followed 35 critically ill children ages 2–18. Using ultrasound measurements of muscle thickness and cross-sectional area in the quadriceps femoris, researchers found that within three to 10 days, 40% of patients lost muscle thickness and 57% lost muscle cross-sectional area. Children who received less protein relative to their goal were more likely to experience muscle loss.

"Our findings point to nutrition and inflammation as key modifiable targets for early intervention," said Chiriboga.

Researchers concluded that bedside muscle ultrasonography is a feasible, noninvasive and cost-effective way to detect muscle loss early in critically ill children, supporting timely nutritional and rehabilitation interventions. Further multicenter studies are needed to confirm these findings.

CONTACT US

If you have any research news or announcements you would like to include in an upcoming issue of *Research Matters*, please email **research@lebonheur.org**.