Pioneering CBD for epilepsy treatment and prevention

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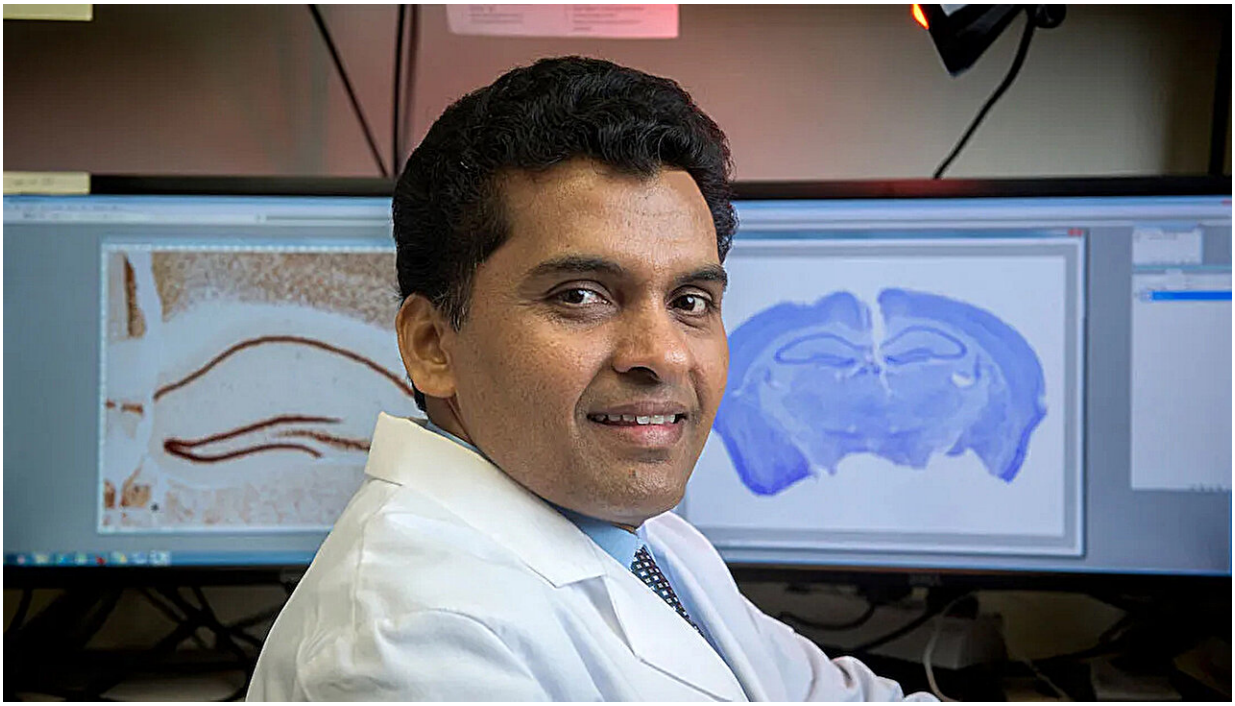

Regents Professor D. Samba Reddy leads a team of pharmacology researchers that has made breakthrough discoveries in using CBD to treat and prevent hard-to-treat forms of epilepsy. Credit: Texas A&M Health

The emerging field of medical cannabinoids has experienced a breakthrough in epilepsy and seizure disorders. A team led by D. Samba Reddy, Ph.D., RPh, a Regents Professor in the Department of Neuroscience and Experimental Therapeutics at the Texas A&M

University School of Medicine, has made progress in determining efficacy, safety and new applications of cannabinoid therapeutics. Reddy's work establishes a foundation for tailored and effective epilepsy treatments, offering hope to those facing its challenges.

The team's research on epilepsy has resulted in the publication of five key papers featured in the May 2023 issue of the journal *Experimental Neurology*.

"The medical cannabis research originated from the patient families and advocates in Colorado who have witnessed the positive effects of medical cannabis products," said Reddy, who is a founding director of the Texas A&M Health Institute of Pharmacology and Neurotherapeutics.

Comprehensive research endeavors led to the U.S. Food and Drug Administration (FDA) approving CBD for treating childhood epilepsy in 2018. However, Reddy says the exact functions of endocannabinoids, the spectrum effects and the mechanisms through which CBD counteracts seizures still require further investigation.

Breakthroughs for refractory epilepsy and prevention

The first of Reddy's five articles highlights the effectiveness of CBD and explores its distinct mechanisms that generate therapeutic benefits. By shedding light on the intricate pathways involving endocannabinoids, the article provides key insights on our understanding of cannabinoids in neurological disorders.

His second report explores the use of CBD in cases of refractory epilepsy, instilling hope for people grappling with difficult-to-treat seizures. It critically evaluates the efficacy and potential harms surrounding CBD therapy, presenting compelling evidence that supports

its clinical utilization while outlining its limitations as a widespread treatment option.

The addition of CBD as a supplementary treatment can sustain seizure reduction for up to four years in children with specific genetic epilepsies. Although side effects are more prevalent when used in conjunction with clobazam, a standard antiseizure medication, CBD exhibits direct effects on seizure control, paving the way for advanced evaluation of cannabinoid-based therapies.

Global meta-analysis in genetic epilepsies

In the third article, a collaborative clinical assessment study published with University of Houston researcher Rajender Aparasu, Ph.D., Reddy and his team explored a comprehensive global meta-analysis of clinical trials, aiming to gauge the overall effectiveness and safety of CBD treatment in children with genetic epilepsies such as Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous sclerosis complex.

The analysis revealed that CBD was effective in managing these genetic conditions, albeit with an increase in adverse events such as diarrhea, somnolence, sedation and potential drug interactions. The dosage of CBD and its co-therapy with clobazam significantly affect both its effectiveness and safety.

This diligent analysis of the contrast between clinical advantages and adverse effects provides a compelling case for including CBD in the arsenal of therapeutic options available to pediatric patients grappling with refractory epilepsy, Reddy says.

CBD's potential in epilepsy prevention

While CBD demonstrates robust antiseizure effects, its role in preventing epilepsy remains uncertain. Reddy, along with his trainees Robert Mbilinyi and Sreevidhya Ramakrishnan, conducted experiments to assess the preventive potential of CBD against epilepsy in adult kindling epileptogenic models.

Their findings, reported in the fourth *Experimental Neurology* article, unveiled CBD's capability as a preventive medicine against the development and persistence of chronic epilepsy. These landmark findings open new horizons for the proactive utilization of CBD in individuals at risk of developing epilepsy, potentially revolutionizing approaches to epilepsy prevention.

Optimizing seizure control with combination therapies

Reddy and his postdoctoral trainees Victoria Golub and Sreevidhya Ramakrishnan developed a new strategy to further optimize the use of CBD for better seizure control. Using the isobolographic technique, they scrutinized the effects of CBD when combined with other FDA-approved antiseizure medications.

In the fifth study, Reddy and his team revealed a remarkable synergistic protection against refractory focal seizures when CBD was combined with the neurosteroid ganaxolone and the benzodiazepine midazolam. The outcomes emphasizes the creative use of CBD in combination therapies, creating the path for expanded treatment possibilities and optimal approaches for managing refractory epilepsy in adults.

Unmet need for seizure control and curing epilepsy

People with known risk factors for epilepsy face a big problem: There

aren't enough medications available to help control their seizures and prevent epilepsy. This means there is a great need for better medications to address this issue.

As the impact of Reddy's research continues to resonate within the CBD community and the epilepsy field as a whole, his recent papers mark a significant milestone in the ongoing quest to leverage CBD's potential for the betterment of patients' lives, emphasizing the crucial importance of continued research endeavors in this promising area of medicine.

"These publications are timely as they not only provide a concise summary of the current evidence for practicing neurologists, but also emphasize the need for future basic and translational research to improve outcomes in one-third of epilepsy patients who do not respond to medications," said Sandipan Pati, M.D., a neurologist and epileptologist at the Texas Comprehensive Epilepsy Program at UT McGovern Medical School in Houston, Texas.

Rama Maganti, M.D., a senior neurologist and professor of neurology, said, "Reddy brings the current evidence of CBD's antiseizure effects to the forefront through multiple articles. He and his group researched a large amount of data on efficacy of CBD as an antiseizure medication extracted from human trials and animal studies. The articles were exhaustive and represent almost all the data currently available.

Maganti, who is the director of clinical neurophysiology and fellowship director of Comprehensive Epilepsy Program and the EEG Lab at University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin, continued, "While CBD is approved for seizures associated with developmental epileptic encephalopathies, in the real world, it is being increasingly used in patients with focal epilepsies, which are much more common and is often being used as an adjunctive medication. A few case series and small studies have shown its efficacy

in patients with refractory epilepsy as well.

"Based on personal experience, in the real world, patients with focal epilepsy not only report improvements in seizures but also improvements in anxiety related to seizures. Reddy's work in experimental models strongly supports this notion as well."

The impact of research on CBD extends beyond epilepsy, holding implications for advancing the potential of cannabinoids in various neurological conditions, including chronic pain, traumatic brain injury, and post-traumatic disorders. CBD has multifaceted actions within the endocannabinoid system.

Current studies into the anti-inflammatory effects of CBD could have a significant impact, as chronic inflammation plays a pivotal role in seizure disorders and neurodegenerative conditions, including chronic behavior comorbidities. This research not only broadens understanding of CBD, but also offers promising avenues for the development of radical strategies targeting inflammation-associated neurological disorders.

"A familiar and FDA-approved product such as CBD has a lower regulatory threshold for approval of newer indications, as opposed to entirely new drugs with complex hurdles for approvals. This strategy cuts down the regulatory burden and time, and industry sponsors usually prefer this approach," said Mansoor Khan, Ph.D., RPh, Regents Professor and acting dean of the Texas A&M Irma Lerma Rangel School of Pharmacy.

"Reddy's expertise in epilepsy models can greatly aid in accelerating development, both in terms of safety and efficacy evaluations, and firmly establish 'proof-of-effectiveness' of CBD in clinically relevant experimental models. Reddy's recent papers on adult epileptogenic

models are splendid examples of such studies," Khan continued.

The mechanisms through which CBD elicits its therapeutic effects still puzzles scientists. Unlocking this mystery is crucial for identifying biomarkers that can aid in patient selection and predict treatment response.

In addition, larger-scale clinical trials encompassing diverse patient populations would be helpful for widespread use of CBD, including its impact on disease progression and overall quality of life. These endeavors would open a new chapter for cannabinoids in neurology.

Addressing the need for public education

As CBD garners recognition as a major therapy, Reddy says it is crucial to provide accurate and evidence-based information to patients, policymakers and the health care community. Such communications can ensure that individuals who stand to benefit from these treatments can do so with confidence and well-founded knowledge.

"Collaborative efforts between researchers, clinicians and industry stakeholders are crucial to accelerate cannabinoid therapeutics. The establishment of research consortia and networks can foster greater collaboration, data sharing, and the exchange of expertise and resources. Such forums can accelerate the translation of ongoing research, ensuring that the benefits reach patients in a timely and efficient manner," Reddy said.

Patients can have a wide range of responsiveness to cannabis products, influenced by various factors. Pharmaceutical-grade CBD offers distinct advantages in terms of purity, consistency and accurate dosing. It has received federal approval for specific purposes, particularly in seizure control.

Medical cannabis, on the other hand, refers to cannabis extracts that contain a combination of cannabinoids. Hemp, as defined by the 2018 Farm Bill, refers to products containing less than 0.3 percent THC and is not approved for treating or preventing any specific diseases.

"As academic researchers, our team's goal is to provide patients and their families with scientific information that forms the foundation for the right use of medical CBD products," Reddy said.

More information: Doodipala Samba Reddy, Building evidence on therapeutic efficacy and innovative mechanisms of cannabinoids in neurological disorders, *Experimental Neurology* (2023). DOI: 10.1016/j.expneurol.2023.114390

Doodipala Samba Reddy, Therapeutic and clinical foundations of cannabidiol therapy for difficult-to-treat seizures in children and adults with refractory epilepsies, *Experimental Neurology* (2022). DOI: 10.1016/j.expneurol.2022.114237

Ashna Talwar et al, Clinical efficacy and safety of cannabidiol for pediatric refractory epilepsy indications: A systematic review and meta-analysis, *Experimental Neurology* (2022). DOI: 10.1016/j.expneurol.2022.114238

Doodipala Samba Reddy et al, Efficacy of the FDA-approved cannabidiol on the development and persistence of temporal lobe epilepsy and complex focal onset seizures, *Experimental Neurology* (2022). DOI: 10.1016/j.expneurol.2022.114240

Victoria Golub et al, Isobolographic analysis of adjunct antiseizure activity of the FDA-approved cannabidiol with neurosteroids and benzodiazepines in adult refractory focal onset epilepsy, *Experimental Neurology* (2022). DOI: 10.1016/j.expneurol.2022.114294