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Recently Published Literature

Safety and Effectiveness of Pure Cannabidiol in Patients With Refractory Epilepsy: Results From an Open-Label Study


Several anecdotal reports and significant media coverage have drawn immense attention and demand for access toward the use of cannabidiol as a treatment option for patients with highly refractory epilepsy. As a result, many states in the United States have approved the use of local cannabidiol oil or hemp oil products for children and adults with epilepsy.

In this report, Devinsky and colleagues presented results from the first large-scale, prospective, open-label multicenter study that examined the use of an FDA approved cannabidiol as an add-on treatment to conventional antiepileptic drugs in patients with treatment-resistant epilepsy. Patients aged 1-30 years with intractable childhood-onset epilepsy from 11 independent epilepsy centers in the United States were included in the trial. A 4-week pre-cannabidiol baseline period was required during which parents or caregivers maintained prospective seizure diaries in order to report motor seizures. The primary outcome was to evaluate the safety and tolerability of cannabidiol; the primary efficacy outcome was median percentage change in the mean monthly frequency of motor seizures at 12 weeks.

- Of the 214 patients, 162 (76%) patients were included in the safety analysis, including 11 (7%) patients who stopped cannabidiol before 12 weeks; 137 (64%) patients were included in the efficacy analysis, including 10 (7%) patients who discontinued treatment during the 12 week observation period and were included in the analysis with the last observation carried forward. Twenty-five (15%) patients included in the safety analysis were not included in the efficacy analysis

- The most common epilepsy types were Dravet syndrome (33 [20%] in the safety analysis and 32 [23%] in the efficacy analysis) and LGS (31 [19%] in the safety analysis 30 [22%] in the efficacy analysis groups)

- The mean cannabidiol dose at 12 weeks was 22.9 mg/kg (SD 9.1) in the safety analysis group and 22.7 mg/kg (SD 8.5) in the efficacy analysis group

- Most of the adverse events (AEs) were considered mild or moderate and transient. Forty-eight (30%) patients reported serious adverse events (SAEs), which included one sudden unexpected death in epilepsy considered not related to study drug. Status epilepticus, diarrhea, pneumonia, and weight loss were reported as SAEs in 20 patients and were considered possibly related to cannabidiol use

- One patient had a significant increase in transaminases (recorded as hepatotoxicity) leading to cannabidiol discontinuation; another patient taking valproate developed hyperammonemia, which also led to cannabidiol discontinuation

Continued on page 2
• Overall, no correlation was drawn with the number of reported AEs and cannabidiol dose at week 12 (Spearman’s rho -0.014, P=0.37). Diarrhea was reported as a cannabidiol-related side effect, which was more likely to occur in patients taking more than 15 mg/kg per day of cannabidiol compared with patients taking less than 15 mg/kg per day

• Somnolence or fatigue was reported in 43 (51%) of the 85 patients also taking clonazepam compared with somnolence in 16 (21%) of the 77 patients not taking clonazepam

• Over the 12-week treatment with cannabidiol, baseline median monthly frequency of motor seizures decreased from 30.0 (interquartile range [IQR] 11.0-96.0) to 15.8 (5.6-57.6). The median change in monthly motor seizures from baseline was -36.5% (IQR 64.70 to 0). During the 12-week treatment period, 5 (4%) patients were free of all motor seizures

• Fifty-four (39%) patients had a reduction of 50% or more in motor seizures, whereas 29 (21%) had a reduction of 70% or more and 12 (9%) had a reduction of 90% or more

• In patients with LGS (n=30), a median reduction of 36.8% (IQR -60.3 to -18.8) in motor seizures was reported and 11 (37%) patients reported a reduction in seizures of ≥50%; no seizure freedom was reported after 12 weeks of treatment with cannabidiol. The median change in total monthly seizures of all types was -35.5% (IQR -55.1 to -16.4)

• In patients with Dravet syndrome (n=32), the median reduction in monthly motor seizures was 49.8% (IQR -64.3 to -12.4). Sixteen (50%) patients had a reduction of ≥50% and one (3%) patient was free from motor seizures during the 3 months of treatment. A median reduction of 42.7% (IQR -64.6 to -20.6) in monthly total seizures for all seizure types was reported

• Patients taking concomitant clonazepam or valproate experienced ≥50% reduction in seizures compared with patients not taking clonazepam or valproate. However, only clonazepam use independently predicted a reduction of 50% or more in motor seizures (OR 2.7, 95% CI 1.2-5.8; P=0.01) (This may be partially explained by the drug-drug interaction between clonazepam and cannabidiol, which results in elevated clobazam levels)

This prospective open-label clinical study demonstrated clinically meaningful reduction in seizure frequency with cannabidiol treatment in patients with severe refractory epilepsy, such as LGS and Dravet syndrome. Acceptable safety and tolerability profiles were observed, with only 5 (3%) of 162 patients discontinuing treatment due to adverse events, such as somnolence, diarrhea, decreased appetite, and fatigue. Limitations to this study include the open-label and uncontrolled study design and the clonazepam-cannabidiol drug interactions, but other factors such as the need for evaluating the effect of cannabidiol on nocturnal seizures was also mentioned. Blinded and randomized controlled studies assessing the safety and efficacy of cannabidiol, and its drug interactions, are currently ongoing.

**Persistent Impairment of Cognitive Networks in Patients With LGS**


In patients with LGS, the EEG pattern is characterized by slow (1.5-2.5 Hz) spike-and-wave (SSW) and 10-20 Hz generalized paroxysmal fast activity (GPFA). LGS is considered an epileptic encephalopathy marked by severe cognitive impairment and intellectual decline, which often continues if seizures are inadequately controlled. Disruption of normal interactions within and between cognitive networks is considered to be a potential mechanism for cognitive decline in patients with LGS.

In this study, Warren et al. evaluated the cognitive interactions in patients with LGS and in healthy control subjects using task-free functional magnetic resonance imaging (fMRI), extracted networks of interest using group-level independent components analysis (ICA), and calculated temporal correlations within and between networks for each subject. The network interactions in patients with LGS were compared with the network behavior of control subjects. In addition to these assessments, concurrent scalp EEG was obtained to evaluate whether the abnormal network interactions were persistent by assessing fMRI periods with and without the occurrence of interictal epileptiform discharges.

- Fifteen patients with LGS (mean age of 28.7 years) and 17 healthy controls (mean age of 27.6 years) were evaluated using task-free EEG-fMRI
- LGS patients displayed disrupted functional networks characterized by weak or reduced within-network connectivity and impaired between-network segregation, including stronger connectivity between the default-mode and dorsal attention networks, all key cognitive processes
- Abnormal network interactions identified during discharge-affected and discharge-unaffected fMRI periods suggest that cognitive network abnormalities may persist in the absence of scalp-detectable epileptic activity
- No significant relationship could be drawn between age of seizure onset or epilepsy duration and network interactions in LGS; however, several patients in this study were adults

Results from this study suggest that abnormal functional interactions, which remain persistent during periods with and without scalp-detectable activity, may be a potential cause of cognitive impairment in patients with LGS. Specificity of network abnormalities would be better understood in future studies evaluating and comparing network interactions across patients with varying types of epilepsies who possess a wide range of cognitive abilities.

**Link to Abstract**

Please note that the above study was funded by grants from GW Pharmaceuticals and the Epilepsy Therapy Project of the Epilepsy Foundation
FDA AND OTHER REGULATORY UPDATES

Positive Results Announced For Epidiolex® From Phase 3 Trial

March 14, 2016

Epidiolex® (cannabidiol), manufactured by GW Pharmaceuticals, recently announced positive Phase 3 results for the treatment of Dravet syndrome. Clinical trial results showed that treatment with cannabidiol led to a median 39% seizure reduction compared with 13% seizure reduction with placebo and an acceptable safety and tolerability profile.

Dr. Jacqueline French, Chief Scientific Officer for the Epilepsy Foundation, stated that “Although anecdotal evidence supported an effect of cannabidiol in serious childhood epilepsies, this is the first scientific evidence that confirms this effect.”

Link to News Release

EPILEPSY NEWS

LGS Foundation Announces National Walk for Epilepsy 2016

The LGS Foundation is accepting registrations for the upcoming 10th Annual National Walk for Epilepsy in Washington, DC, on April 16, 2016. The meeting location, contact information, and other relevant information can be found here.

The LGS Foundation Is Calling All Patients to Participate in the Rare Epilepsy Network (REN)

The REN, funded by the Patient-Centered Outcomes Research Institute, is now open for participation by families to help researchers understand LGS and search for better treatments and improve quality of life for patients and their families. The LGS Foundation is one of the partner organizations involved in REN. Per the group’s website, REN’s specific mission is to build a database to provide patients and their families an opportunity to participate in research that will improve quality of care. Please visit the LGS Foundation website for more information. To enroll, please go to: REN.

ACCESS TO MORE THAN 4,000 RESOURCES IS NOW AVAILABLE ON THE LGS RESOURCES REGISTRY ON LGSHOPE.COM

Parents and caregivers can access a wide range of solutions to everyday challenges they face when caring for a patient with LGS via the LGS Resources Registry on LGSHope.com. The LGS Resources Registry can also be accessed through the LGS Foundation website. Currently, the registry includes helpful addresses and other relevant contact information for a wide range of resources. These include epileptologists/neurologists, state and county funds/grants for special needs children, school/education information sources, individualized education programs, state and local support groups, home/vehicle modification support, and other offerings. All of these entries are searchable by location.

REGISTER FOR THE 2016 LGS FOUNDATION FAMILY AND PROFESSIONAL CONFERENCE

The 4th International Family and Professional Conference on Lennox-Gastaut Syndrome will be held in Denver, Colorado on April 29 to May 1, 2016. Please visit the LGS Foundation to learn more about the conference. Families and professionals from across the country will come together at the conference to discuss new developments in science and research as well as resources and services, and to share their personal experiences with LGS. For a copy of the preliminary agenda, please click here. To register, please click here for more information.
If you do not wish to receive this newsletter, please email us at LGSadmin@lgshope.com

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