Cannabidiol in Patients With Intractable Epilepsy Due to TSC: A Possible Medication But Not a Miracle

Cannabidiol as a New Treatment for Drug-Resistant Epilepsy in Tuberous Sclerosis Complex.

Hess EJ, Moody KA, Geffrey AL, Pollack SF, Skirvin LA, Bruno PL, Paolini JL, Thiele EA. *Epilepsia* 2016;57(10):1617–1624. doi: 10.1111/epi.13499.

OBJECTIVE: Tuberous sclerosis complex (TSC) is an autosomal-dominant genetic disorder with highly variable expression. The most common neurologic manifestation of TSC is epilepsy, which affects approximately 85% of patients, 63% of whom develop treatment-resistant epilepsy. Herein, we evaluate the efficacy, safety, and tolerability of cannabidiol (CBD), a nonpsychoactive compound derived from the marijuana plant, as an adjunct to current antiepileptic drugs in patients with refractory seizures in the setting of TSC. METHODS: Eighteen of the 56 patients who have enrolled in our current expanded-access study of cannabidiol for patients with treatment-resistant epilepsy carry a diagnosis of TSC. After an initial baseline period of 1 month, patients began treatment with CBD. The initial dose of 5 mg/kg/day was increased by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day, if tolerated. Weekly seizure frequencies, percent change in seizure frequencies, and responder rates were calculated during the 2nd, 3rd, 6th, 9th, and 12th month of treatment with CBD. RESULTS: The median weekly seizure frequency during the baseline period was 22.0 (interquartile range [IQR] 14.8–57.4), which decreased to 13.3 (IQR 5.1–22.1) after 3 months of treatment with cannabidiol. The median percent change in total weekly seizure frequency was −48.8% (IQR −69.1% to −11.1%) after 3 months of treatment. The 50% responder rates over the course of the study were 50%, 50%, 38.9%, 50%, and 50% after 2, 3, 6, 9, and 12 months of treatment with CBD, respectively. In patients taking clobazam concurrently with CBD (n = 12), the responder rate after 3 months of treatment was 58.3%, compared to 33.3% in patients not taking clobazam (n = 6). Twelve (66.7%) of 18 patients in this study experienced at least one adverse event thought possibly related to CBD; the most common adverse events were drowsiness (n = 8, 44.4%), ataxia (n = 5, 27.8%), and diarrhea (n = 4, 22.2%). SIGNIFICANCE: Although double-blind, placebo-controlled trials are still necessary, these findings suggest that cannabidiol may be an effective and well-tolerated treatment option for patients with refractory seizures in TSC.

Commentary

Cannabis has been used for more than 100 years as a potential treatment for epileptic seizures. Cannabidiol (CBD) is one of the nonpsychoactive components of the cannabis plant. In recent years, the use of CBD has gained popularity in social media as a treatment for multiple diseases and symptoms, including intractable epilepsy, especially the early onset epileptic encephalopathies. However, the pharmacologic mechanisms are not yet fully understood (1). This has led to multiple studies to determine the safety and efficacy of CBD in children and adults with intractable epilepsy. Thus far, the clinical data are somewhat limited. The reports demonstrating the greatest efficacy were surveys of parents with children treated with CBD and were wrought with bias. Prospective studies overall have demonstrated >50% reduction in seizures in 32 to 84 percent of participants (1). An open-label trial of CBD in patients with treatment-resistant epilepsy showed a median reduction in monthly motor seizures of 36.5% (2). Cannabidiol has yet to gain FDA approval.

In the open-label trial of CBD in children and adults with severe, intractable, childhood-onset epilepsy published earlier this year, 214 patients were enrolled: 162 continued in the study long enough to be included in the safety and tolerability analysis and 137 in the efficacy analysis. The most common epilepsy syndromes were Lennox-Gastaut syndrome and Dravet syndrome, although other epilepsies were also included. Overall, CBD was well-tolerated; although adverse events occurred in more than 79% of patients, only 3% discontinued treatment because of adverse events. The median reduction in motor seizures was 36.5%, and the median reduction in all seizures was 34.6%. For all seizure types, 37% of patients had a >50% reduction. In patients with Lennox-Gastaut syndrome, 37% had a >50% reduction in seizures, although there was no reduction in generalized tonic-clonic seizures. In patients with Dravet syndrome, 50% had a >50% reduction in seizures. Furthermore, efficacy was greater in patients taking concomitant clobazam or valpro-

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ate; 51% taking clobazam versus 27% not taking clobazam had a >50% reduction in motor seizures, and 54% taking valproate versus 33% not taking valproate had a >50% reduction in motor seizures (2).

Hess et al. (3) recently studied the efficacy, safety, and tolerability of CBD in patients with treatment-resistant epilepsy due to tuberous sclerosis complex (TSC), an autosomal dominant genetic neurocutaneous disorder in which up to 90% of patients experience epilepsy, which is often pharmacoresistant (4). A retrospective analysis of 71 children with TSC and epilepsy demonstrated that 38% of patients had seizure remission at 24 months from all therapies combined, although 43% had subsequent relapse. In those patients who did not achieve seizure freedom following two different antiepileptic drugs [AEDs] (i.e., pharmacoresistant), up to half still experienced >50% seizure reduction with trials of a third or fourth medication (4).

Given the high likelihood of intractability of epilepsy due to TSC, multiple treatments for treatment-resistant epilepsy in patients with TSC have been studied, including vigabatrin, everolimus, clobazam, and a ketogenic diet. Vigabatrin has demonstrated efficacy in infantile spasms and as adjuvant therapy for intractable focal epilepsy due to TSC. When vigabatrin was used in 49 patients with focal epilepsy receiving two or more AEDs, >50% seizure reduction was seen in 30%; and 24.5% were seizure free or had >90% reduction in seizures (5). Similarly, 60% (12/20) of patients treated with everolimus showed >50% reduction in their refractory seizures (overall seizure reduction 69%) at 12 weeks, and efficacy was maintained in 83% (15/18) who continued the 4-year extension phase (6). In a retrospective study of clobazam in patients with TSC and treatment-resistant epilepsy, 69% had >50% reduction in seizures, although this was maintained in only six (19%) at 12 months (7). When 12 children with TSC and treatment-resistant epilepsy were treated with a ketogenic diet, 92% had >50% reduction of seizures at 6 months (8). Therefore, multiple potentially effective treatments exist for patients with intractable epilepsy due to TSC, although some patients continue to have poorly controlled seizures.

In the study of CBD in patients with intractable epilepsy and TSC by Hess et al., the median reduction in seizure frequency was 48.8%, and approximately 50% of patients demonstrated a >50% reduction in seizures. This response was maintained during the 12-month follow-up. Those also taking clobazam had a responder rate of 58.3% versus 33.3% for those not taking clobazam (3). These findings suggest that CBD is a potential antiseizure medication for intractable epilepsy due to TSC. However, we must be cautious when comparing these results to the expectations of patients and their families. While patients may view CBD as a promising therapy that helps when other AEDs fail, the efficacy of CBD for intractable epilepsy is comparable to the efficacy of vigabatrin, everolimus, and a ketogenic diet (50% of patients with >50% seizure reduction vs 30%, 60%, and 92%, respectively) (3, 5, 6, 8). Clobazam (7) also led to improvement in seizures, although this response was only present in a minority of patients (19% with >50% reduction) at 12 months.

Those taking clobazam and CBD had a higher responder rate (3). Perhaps this is due to the previously documented interaction between CBD and clobazam that leads to significantly elevated clobazam and norclobazam levels (9). Furthermore, CBD is not without side effects. Side effects commonly seen with other AEDS, including drowsiness, ataxia, diarrhea, and agitation, were reported in 66.7% of patients, although none were considered to be serious CBD-related adverse events (3).

Overall, the prospect of another potentially effective and well-tolerated AED for intractable epilepsy should always be viewed positively. However, we must have reasonable expectations for CBD. Through multiple studies it is demonstrating itself to be a potentially effective, well-tolerated AED, but it is far from a miracle cure.

by Katherine Nickels, MD

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