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EFFICACY AND SAFETY OF EPIDIOLEX (CANNABIDIOL) IN CHILDREN AND YOUNG ADULTS WITH TREATMENT-RESISTANT EPILEPSY: INITIAL DATA FROM AN EXPANDED ACCESS PROGRAM

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Content:

RATIONALE:
Cannabidiol (CBD) is the most abundant non-psychoactive cannabinoid in the cannabis plant. Animal studies demonstrate anticonvulsant efficacy in multiple species and models. Anecdotal reports suggest efficacy in children with treatment-resistant epilepsies (TRE), especially Dravet syndrome. Here we report preliminary results in children with TRE in an expanded access treatment program.

METHODS:
Children and young adults with severe, childhood onset TRE participating in an expanded access compassionate use program for CBD at 2 sites (NYU and UCSF) were enrolled in a prospective observational study after obtaining informed consent. All patients entered a baseline period of 4 weeks when parents/caregivers kept prospective seizure diaries, noting all countable motor seizure types. Patients then received a purified 98% oil-based CBD extract, of known and constant composition (Epidiolex: GW Pharmaceuticals), at a dose of 5 mg/kg/day in addition to their baseline AED regimen The daily dose was gradually increased by 2-5mg/kg increments at 1-2 intervals until intolerance occurred or a maximum dose of 25 mg/kg/day was acheived. Patients were seen per protocol at regular intervals of 2-4 weeks. Laboratory testing for hematologic, liver, kidney function, and concomitant AED levels was performed at baseline, and after 4, 8 and 12 weeks of CBD therapy.

RESULTS:
23 patients received at least 3 months of treatment (13 were female; 10.4 years, range 3-26). Diagnoses included Dravet Syndrome (9), Myoclonic-Absence Epilepsy (4), Lennox-Gastaut (3), Generalized Epilepsies (2), CDKL5 (2), Dup15q (1), SNAP25 - 1), and malformation of cortical development (1). The average number of concomitant antiepileptic drugs was 2.7. Efficacy results for the 23 patients are summarized in Table 1. After 3 months of therapy, 39% of patients had a >50% reduction in seizures; there was a 32% median reduction in seizures. Seizure-freedom at 3 months occurred in 3/9 Dravet patients and 1/14 other patients. One patient with Dravet had marked seizure worsening; the only serious adverse event. None of the 23 subjects withdrew during the 3-month treatment period. Clobazam dose was reduced in 5 subjects due to sedation after initiation of CBD; these patients were on high doses of multiple AEDs and clobazam was reduced due to its sedative effect and potential interaction. Side effects reported in >=9% of subjects are summarized in Table 2. Some side effects, such as diarrhea, weight loss, and decreased appetite, required reduction of the dose of Epidiolex from 25 to 20 mg/kg/day resulting in improvement of symptoms. The large majority of adverse events were mild or moderate and many were transient. No significant laboratory abnormalities were observed.

CONCLUSIONS:

These preliminary results from an uncontrolled study support the animal studies and anecdotal reports showing that CBD may be a promising treatment for TRE and it is generally well-tolerated in doses up to 25mg/kg/d. These initial results should be investigated in randomized controlled studies.

TABLES:

	Baseline (n = 23)	**Month 3 (n=23)**
All patients		
Median seizure frequency (range)	28 (4-1578)	11 (0-245)
Responder rate (>50% reduction) n [%]		9 [39%]
Median % reduction from baseline		-32%
Seizure free n [%]		4 [17%]
Dravet syndrome patients	**Baseline (n = 13)**	**Month 3 (n=9)**
Median seizure frequency (range)		5.2 [0-82]
Responder rate (>50% reduction) n [%]		4 [44%]
Median % reduction from baseline		-40%
Seizure free n [%]		3 [33%]

* Median is used since data are not normally distributed

All patients	23
Any adverse event	18 (78%)
Common AEs	
Somnolence	13 (57%)
Fatigue	13 (57%)
Concomitant AED level increased	5 (22%)
Decreased appetite	5 (22%)
Weight gain*	5 (22%)
Diarrhea	5 (22%)
Increased appetite	4 (17%)
Weight loss	2 (9%)

AED - antiepileptic drug; * Reported by parent as excessive at inter-visit interval

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