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Review

Cannabinoids in treatment-resistant epilepsy: A review

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ABSTRACT

Treatment-resistant epilepsy (TRE) affects 30% of epilepsy patients and is associated with severe morbidity and increased mortality. Cannabis-based therapies have been used to treat epilepsy for millennia, but only in the last few years have we begun to collect data from adequately powered placebo-controlled, randomized trials (RCTs) with cannabidiol (CBD), a cannabis derivative. Previously, information was limited to case reports, small series, and surveys reporting on the use of CBD and diverse medical marijuana (MMJ) preparations containing: tetrahydrocannabinol (THC), CBD, and many other cannabinoids in differing combinations. These RCTs have studied the safety and explored the potential efficacy of CBD use in children with Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS).

The role of the placebo response is of paramount importance in studying medical cannabis products given the intense social and traditional media attention, as well as the strong beliefs held by many parents and patients that a natural product is safer and more effective than FDA-approved pharmaceutical agents. We lack valid data on the safety, efficacy, and dosing of artisanal preparations available from dispensaries in the 25 states and District of Columbia with MMJ programs and online sources of CBD and other cannabinoids. On the other hand, open-label studies with 100 mg/ml CBD (Epidiolex®, GW Pharmaceuticals) have provided additional evidence of its efficacy along with an adequate safety profile (including certain drug interactions) in children and young adults with a spectrum of TREs. Further, Phase 3 RCTs with Epidiolex support efficacy and adequate safety profiles for children with DS and LGS at doses of 10- and 20-mg/kg/day.

This article is part of a Special Issue titled "Cannabinoids and Epilepsy".

1. Introduction

Epilepsy is one of the most common chronic neurological disorders. Treatment-resistant epilepsy (TRE) arises from a failure to achieve sustained seizure remission after trials of at least two, appropriately selected antiepileptic drug (AED) regimens that are tolerated at therapeutic dosages [1]. Despite the introduction of many therapies, including drugs, neuromodulation, and surgical and dietary interventions, the burden of TRE remains enormous, affecting approximately 30% of patients [2–4]. Patients struggling with TRE suffer from both severe morbidity and markedly increased mortality [5–8]. Notwithstanding the new therapeutic measures, it remains unclear if the frequency of TRE cases has been reduced during the past two decades [4]. Even patients with 'treatment-responsive' epilepsy suffer from disabling side effects and breakthrough seizures under multiple settings (e.g. missed doses [9], sleep deprivation [10], and excess alcohol consumption [11]). For almost all patients diagnosed with epilepsy, quality of life (QOL) is adversely affected by both the disease and therapies used to control seizures, with devastating personal and substantial economic consequences [12].

All epilepsies can be treatment resistant, although seizures associated with the epileptic encephalopathies (e.g. Dravet Syndrome (DS) [13] and Lennox-Gastaut Syndrome (LGS)) [14], Febrile Infection-Related Epilepsy Syndrome (FIRES) [15], and epilepsy associated with Tuberous Sclerosis Complex (TSC) [16] are among the most refractory to medical therapies. For some (e.g. DS [17] and FIRES [18]), there are currently no U.S. Food and Drug Administration (FDA)-approved therapies. Further, by definition, available AEDs provide only limited success in controlling seizures in TREs. Although certain AEDs reduce seizure frequency in disorders such as DS [19] and LGS [20], there are limits to their safety and efficacy. This is especially relevant when these AEDS are used in multidrug regimens and at high doses. The repercussions of TREs are significant, especially as TREs starting in the first few years of life are associated with high rates of cognitive, behavioral, and motor delays [21]. Further, many believe that the burden of seizures and interictal epileptiform activity directly contribute to these neurodevelopmental delays.

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Table 1
Table 1 summaries findings from several surveys, case studies, case series, and placebo controlled trials related to isolated cannabinoids, oral cannabis extracts, and smoked cannabis use in the context of epilepsy.

Study	Compound	Study Type	N	Efficacy	Toxicity
Isolated cannabinoids					
Davis & Ramsey [26]	THC isomers	Case series of institutionalized children with intellectual disability and epilepsy treated for 3–7 weeks	5	1 seizure-free, 1 almost seizure-free	None reported
Mechoulam & Carlini [27]	CBD 200 mg/day	Prospective, placebo controlled trial in adults with treatment resistant epilepsy over 3 months	4 Rx 5 PB	2 subjects in CBD arm seizure-free, 1 with partial improvement No report of baseline seizure measurement	None reported
Cunha et al. [28]	CBD 200-300 mg/day	Prospective, placebo controlled trial in teenagers/adults with treatment resistant convulsive seizures (at least 1 per week) with 8–18 weeks of exposure	8 Rx 7 PB	4 subjects in CBD arm seizure-free, 1 in placebo arm No blinded assessments, one unexplained cross-over	Somnolence, Gastric discomfort
Ames & Cridland [29]	CBD 200-300 mg/day	Prospective placebo controlled trial in institutionalized adults with intellectual disability and epilepsy over 3 weeks	6 Rx 6 PB	No difference between groups	None reported
Trembly & Sherman [30]	CBD 300 mg/day	Prospective randomized, double-blind placebo controlled crossover study in adults with treatment resistant epilepsy; 6 months treatment and placebo	12	No difference between CBD and placebo	None reported
Devinsky et al. [31]	Purified oral 100 mg/ml CBD extract	Prospective open label trial in children and young adults with severe childhood onset epilepsy for 12 weeks	214	137 (64%) in efficacy (12 weeks): 36.5% median reduction in weekly convulsive seizure rate	Somnolence, diarrhea, decreased appetite, fatigue, convulsion, status epilepticus
Oral cannabis extracts					
Gowers [25]	*Cannabis indica* extract, 32 mg/day	Case report of a 40-year-old man with focal epilepsy resistant to bromides	1	Seizure-free for 6 months followed by recurrence with cannabis extract discontinuation. Resumed seizure control with resumption of cannabis use several months later.	None reported
Porter & Jacobson [32]	CBD/THC extracts of varying composition/dose CBD up to 28 mg/kg/day and THC up to 0.8 mg/kg/day	Survey among participants in a Facebook group for parents of children with TRE	19	16 (84%) reported improvement with CBD/THC, 2 (11%) became seizure-free	Drowsiness, fatigue, decreased appetite
Maa & Figi [33]	Oral cannabis extract, high ratio of CBD:THC	Case report of a 5-year-old girl with DS	1	>90% reduction in generalized tonic-clonic seizure frequency and ability to reduce background drugs	Somnolence, fatigue
Gedde & Maa [34]	Oral cannabis extract, high ratio of CBD: THC	Survey of parents whose children with TRE used the extract	11	100% had reduction in motor seizure frequency; 8/11 with complete or near complete seizure control	Somnolence, unsteadiness
Press et al. [35]	Oral cannabis extracts	Retrospective case series of children with refractory epilepsy at one center in Colorado	75	25 (33%) reported a >50% reduction in seizure frequency	Somnolence, fatigue, increased seizures. Rare: developmental regression, status epilepticus
Tzadok et al. [36]	CBD enriched cannabis extracts	Retrospective case study of children and adolescents with intractable epilepsy at five Israeli pediatric epilepsy centers	74	66 (89%) reported a reduction in seizure frequency: 13 (18%) 75–100% reduction, 25 (34%) 50–75% reduction, 9 (12%) 25–50% reduction, and 19 (26%) <25% reduction	Somnolence, fatigue, gastrointestinal disturbances, irritability. 5 patients discontinued use.
Smoked cannabis					
Keeler & Reifler [37]	Cannabis	Case report of 20-year-old man with refractory tonic-clonic seizures who was seizure-free	1	Cluster of seizures following a period of marijuana use	Increased seizures
Consroe et al. [38]	Cannabis	Case report of 24-year-old man with refractory generalized epilepsy	1	Patient became nearly seizure-free when he started daily cannabis use	None reported
Ellison et al. [39]	Cannabis	Case report of a 29-year-old man with refractory focal epilepsy	1	Suppression of complex partial seizures and exacerbation of seizures with withdrawal	None reported
Mortati et al. [40]	Cannabis	Case report of a 45-year-old man with cerebral palsy and refractory focal epilepsy	1	>90% reduction in nocturnal seizures and tonic-clonic seizures	None reported
Gross et al. [41]	Cannabis	Survey of active users seen at a single tertiary epilepsy center	28	19 (68%) reported improvement in seizure severity, 15 (54%) reported improvement in frequency	None reported
Hamerle et al. [42]	Cannabis	Survey of cannabis users seen at one tertiary epilepsy center	310 (13 active users; 297 ex-users)	2 active users reported improvement in seizures; 7 ex-users reported worsening of seizure frequency/severity	Increased seizures

TRE – treatment–resistant epilepsy; DS – Dravet Syndromes; Rx – active cannabis-based therapy; PB – placebo; CBD – Cannabidiol; THC – Tetrahydrocannabidiol.
(Modified with permission from Friedman & Devinsky, NEJM 2016 – reference [35])*.
Note that content of cited compounds has not been verified.