Efficacy of Medical Cannabis for Treating Refractory Epilepsy in Children and Adolescents, with Emphasis on the Israel Experience

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Approximately 25% of subjects with epilepsy are pharmacologically resistant, defined as the failure to arrest seizures after an adequate trial of at least two appropriate medications [1]. Second-line therapeutic options are then introduced, but in most cases these have only partial efficacy [2], hence the need for additional treatment options. There is now concrete evidence to suggest the efficacy of cannabis in the treatment of epilepsy, particularly in the refractory group.

CANNABINOIDS: DESCRIPTION AND MECHANISM

Marijuana (*Cannabis sativa* and *Cannabis indica*) is a naturally growing plant containing more than 130 phytocannabinoids and 300 non-cannabinoid constituents [3,4]. Two compounds – the psychoactive Δ9-tetrahydro-cannibinol (THC), and the non-psychoactive cannabidiol (CBD) first described by Mechoulam and Shvo [5] – have garnered the most attention based on their abundance in the plant. In Israel, medical cannabis is approved for use in epilepsy as well as other medical conditions. Available ratios of CBD/THC in high consistency CBD extract distributed in Israel for the treatment of epilepsy are 2:1, 5:1, and 20:1, the last being the most commonly used ratio for epilepsy [6].

PROPOSED MECHANISM OF CANNABINOIDS AS ANTICONVULSANTS

Both THC and CBD were found to have anticonvulsive properties in both in vitro and animal models [7-9], while most studies suggest that CBD is more effective in reducing epileptic activity compared to THC [10-12]. However, the anti-epileptic mechanism of CBD has not been fully elucidated and is considered to be mediated by G protein-coupled cannabinoid receptor type 1 (CB1R) and type 2 (CB2R), as well as by other non-cannabinoid receptors [8,13-15]. CB1R mediates neuronal inhibition by decreasing calcium influx and increasing potassium efflux in presynaptic terminals, thus modulating epileptiform activity by inhibiting excitatory glutamatergic neurotransmission [16,17]. Other proposed anti-epileptic mechanisms of CBD are the blocking of NMDA receptors and modulation of GABAergic and glutamatergic synapses, as well as cannabinoid receptor-independent mechanisms [8,11,12,18-20].

CURRENT EVIDENCE IN HUMANS

The effectiveness of marijuana in the treatment of epilepsy was originally reported as early as 1800 BC [21]. Initial clinical trials in humans using CBD were described during the 1970s [4,22], but it was in the 1990s, with the discovery of an endogenous cannabinoid-signalling system, that interest was rekindled in the potential therapeutic effect of cannabis for treating nervous system disorders, including epilepsy. Since 2013, clinical studies have been emerging more frequently [23-28], and at present, 25 clinical trials are underway to study the effect of CBD-enriched products on seizure frequency, as well as their safety and drug-drug interaction [ClinicalTrials.gov]. The largest two published cohorts thus far are the GW Pharmaceutical prospective open-label study [24], and the Israeli retrospective-prospective registry published by Tzadok et al. [25]. The results presented here are primarily those that were published by the two groups, as well as additional data collected by the same groups and presented at conferences and in press release announcements [28-31].

GW PHARMACEUTICAL STUDY

A prospective, open-label trial using a standardized, purified 99% oil-based CBD extract (Epidiolex, GW Pharmaceuticals, London, UK) was conducted in 16 sites in the United States [24,28]. A total of 313 patients were recruited and included in the safety and tolerability analysis, of whom 261 who had at least 12 weeks of follow-up were included in the efficacy analysis. Of these, 135 had also reached 36 weeks treatment at the time of data analysis. Initial doses were 2–5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25–50 mg/kg. Median reduction in monthly motor seizures was 45%, whereas 47% of all patients experienced a ≥ 50% reduction in seizures and 9% of all patients were seizure-free with maintenance of clinical effect at 36 weeks. Subgroup analysis evaluating improvement per

syndrome/etiology revealed maximal improvement in patients with Lennox Gastaut syndrome (71%), followed by tuberous sclerosis (66%) and Dravet syndrome (50%) [28].

THE ISRAELI REGISTRY

Seventy-four patients with refractory epilepsy of various genetic or structural etiologies were followed for at least 3 months [25]. The cohort was subsequently extended to include 129 patients (age 1–25 years) treated for at least one month [30]. Patients were treated with sublingual cannabis oil extract of one of two strains: "Cheese pie" and "Avidekel," both containing a CBD/THC ratio of 20:1, given three times daily. Daily dose ranged from 2 to 27 mg/kg/day. The response to treatment was evaluated as a parental reported change in the mean monthly seizure frequency. Of the 74 patients, 66 (89%) reported reduction in seizure frequency: the reduction was 75–100% in 13 patients (18%), 50–75% in 25 (34%), 25–50% in 9 (12%), and < 25% in 19 (26%). Five (7%) patients reported aggravation of seizures which led to CBD withdrawal.

ADVERSE REACTIONS

Adverse reactions (ARs) were reported in approximately 46–79% [24,25]. Of the 313 patients included in the safety analysis in the GW Pharmaceutical study [24,28], the most commonly reported ARs were somnolence (23%), diarrhea (23%), fatigue (17%), decreased appetite (17%), convulsions (17%), and vomiting (10%). Serious adverse events that were considered related to treatment were reported in 16 patients (5%), including altered liver enzymes, status epilepticus/convulsion, diarrhea (4 patients each), decreased weight (3 patients) and thrombocytopenia (1 patient), all of which were reversible. Fourteen patients (4%) discontinued treatment due to an adverse reaction. ARs reported by Tzadok et al. [25] included somnolence (22%), seizure exacerbation (18%), and irritability and gastrointestinal problems (7%). The frequency of ARs was quite comparable in the two large cohorts described. Press and co-authors [27] reported a relatively comparable increase in seizure frequency (13%). Nonetheless, the lack of a control group in those studies as well as the fact that most subjects taking cannabis are also being treated with at least three anti-epileptic drugs impede the assessment of cannabidiol-related serious adverse effects. Since most patients in the Israeli registry were cognitively impaired, the cognitive effect of CBD could not be fully assessed and remains an enigma, yet to be solved.

CBD DOSE

The historic adult dose range of CBD is 200–300 mg/day [4,23]. According to our experience [29], patients' daily dose did not exceed 27 mg/kg/day, or a total daily dose of 580 mg. In fact, most patients received less than 10 mg/kg/day [25]. The effectiveness of CBD in relatively low doses in the Israeli registry could be attributed to the fact that most patients were able to keep the oil drops sublingually for several minutes, thus practicing mucosal absorption, which is considered to be higher than oral delivery.

WHOLE PLANT-ENRICHED EXTRACT VERSUS SINGLE MOLECULE

The patients described by Tzadok et al. [25] were given a whole plant mixture with a fixed ratio of CBD/THC. It should be emphasized that the role of the different constituents of marijuana such as terpenes and flavonoids as well as the synergism of several yet unknown derivatives is not yet clear. This topic is currently being examined as some laboratories around the world are assessing the correlation between the preferred mixtures of phytocannabinoids and efficacy in different diseases. Notably, one should bear in mind that THC has a higher potential for cognitive impairment and chronic psychiatric disturbances [32] and thus should be used with caution, particularly in the pediatric population.

To summarize, in view of the good outcome in a significant number of patients, which is not significantly worse than other accepted options for patients with refractory epilepsy, it seems that medical cannabis should be considered a viable treatment option. Randomized, blinded, placebo-controlled trials to assess preferred drug formulation, safety profile, drug-drug interactions and true efficacy are still warranted.

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"You cannot shake hands with a clenched fist"

Indira Gandhi (1917-1984), Indian politician and central figure of the Indian National Congress party. Indira Gandhi was the daughter of India's first Prime Minister, Jawaharlal Nehru. She was assassinated in 1984