Attitudes and experience of cannabinoid-based therapies for epilepsy in the Australian community

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Purpose: Epilepsy Action Australia (EAA) sought to understand the attitudes toward and lived experiences of adults and parents of children living with epilepsy of cannabinoid-based therapies in an ever-changing climate of public opinion, government legislation and clinical trials in Australia. Method: Two studies were undertaken with the first informing the second study. A nationwide online survey was conducted assessing demographics, clinical factors, including diagnosis and seizure types and experiences with and opinions towards cannabis use in epilepsy. The second study (PELICAN) focused on experiences of 61 families of children with epilepsy under the age of 16 years who desired, were currently or had previously administered cannabinoid-based therapies to their children to manage seizures. Semi-structured interviews were conducted; samples collected with subsequent laboratory analysis.

Any compound capable of activating the cannabinoid receptor CB1 and/or CB2. Cannabinoids include Phyto cannabinoids, endocannabinoids and (semi-)synthetic cannabinoids. They exert a wide variety of biological activities including anti-inflammatory, anti-emetic, anticonvulsant, antiglaucoma, analgesic and neuroprotective effects; while some exert psychoactive effects, including euphoria

A disorder characterized by recurrent episodes of paroxysmal brain dysfunction due to a sudden, disorderly, and excessive neuronal discharge. Epilepsy classification systems are generally based upon: (1) clinical features of the seizure episodes (e.g., motor seizure), (2) etiology (e.g., post-traumatic), (3) anatomic site of seizure origin (e.g., frontal lobe seizure), (4) tendency to spread to other structures in the brain, and (5) temporal patterns (e.g., nocturnal epilepsy).

Identification of CBD, Δ9-THC, and the endocannabinoid system in the mid-20th century has led to advancement of cannabis-based therapies for epilepsy. Based on clinical trial data, Epidiolex is the first CBD medication approved by a national regulatory agency (US Food and Drug Administration for Dravet and Lennox Gastaut syndrome; European Medicines Agency for Lennox Gastaut syndrome). Approval of CBD as a treatment for these rare and severe pediatric-onset epilepsy syndromes is an important milestone, but the complete spectrum of use of cannabis-derived products, and the use of CBD for other epilepsy syndromes remains to be determined.

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. 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 100mg/ml CBD 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.

While the anticonvulsant mechanism of action of CBD has not been entirely elucidated, we discuss the most recent data available including its low affinity for the endocannabinoid receptors and possible indirect modulation of these receptors via blocking the breakdown of anandamide. Additional targets include activation of the transient receptor potential of vanilloid type-1 (TRPV1), antagonist action at GPR55, targeting of abnormal sodium channels, blocking of T-type calcium channels, modulation of adenosine receptors, modulation of voltage-dependent anion selective channel protein (VDAC1), and modulation of tumor necrosis factor alpha release. We also discuss the most recent studies on various artisanal CBD products conducted in patients with epilepsy in the USA and internationally. In the EAPs, there was a significant improvement in seizure frequency seen in a large number of

patients with various types of treatment-refractory epilepsy. The RCTs have shown significant seizure reduction compared to placebo in patients with Dravet syndrome and Lennox-Gastaut syndrome. Finally, we describe the available data on adverse effects and drug-drug interactions with highly purified CBD. While this product is overall well tolerated, the most common side effects are diarrhea and sedation, with sedation being much more common in patients taking concomitant clobazam. There was also an increased incidence of aspartate aminotransferase and alanine aminotransferase elevations while taking CBD, with many of the patients with these abnormalities also taking concomitant valproate. CBD has a clear interaction with clobazam, significantly increasing the levels of its active metabolite N-desmethylclobazam in several studies; this is felt to be due to CBD's inhibition of CYP2C19. EAP data demonstrate other possible interactions with rufinamide, zonisamide, topiramate, and eslicarbazepine.

Results: 976 responses met the inclusion criteria of the initial survey. 15% of adults with epilepsy and 13% of parents/guardians of children with epilepsy were currently using, or had previously used, cannabinoid-based products to treat epilepsy. Of those with a history of cannabis product use, 90% of adults and 71% of parents reported success in reducing seizure frequency. 41 of the 65 families participating in the second study (PELICAN) were currently or had previously administered cannabinoid-based therapies to their children. Analysis of the products highlighted a wide variability of cannabinoid content and low concentration of Cannabidiol (CBD) while ??9-tetrahydrocannabinol (THC??9) was present in nearly every sample.

Conclusion: The survey provides insight into the use of cannabis products for epilepsy some of the likely factors influencing use, as well as novel insights into the experiences of and attitudes towards medicinal cannabis in people with epilepsy in the Australian community while the PELICAN study highlighted the profound variation in the illicit cannabis extracts being utilized as therapies in epilepsy in Australia warranting further investigation.

Note: This work is partially presented at World Congress on Neuroscience and Epilepsy which is held during November 16-17, 2018 at Tokyo, Japan