Chapter 3
Cannabinoid Efficacy for Developmental Epileptic Encephalopathy (DEE) Intractable Seizure Control:
A Systematic Review of the Literature

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ABSTRACT

Seizures in 20-30% of epileptics are resistant to treatment with anti-epileptic drugs (AED). This chapter evaluates studies on the efficacy of cannabinoids as adjunctive therapy for control of intractable seizures, with a focus on developmental epileptic encephalopathies (DEE). A systematic review conducted by literature search through PubMed, EBSCO, and ProQuest electronic databases identified 16 studies in the last seven years. Moderate- to low-certainty of evidence supports the benefits of cannabinoids in reducing seizure frequency, intensity, duration, and epileptics' overall condition in many types of intractable seizures. Studies used either synthetic cannabidiol (CBD), highly purified plant-derived CBD (Epidiolex®), or less pure cannabis plant-based CBD oils, and extended over months to two years. Drug interactions of ingested CBD with concomitant valproate and clobazam could be avoided with sublingual CBD. Five percent of patients became seizure free. Future studies are warranted to optimize the anti-seizure effects of emerging cannabinoid treatment strategies.

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INTRODUCTION

Epilepsy affects 3 million adults and 470,000 children in the United States, and over 70 million people worldwide (Zack and Kobu, 2017). Sadly, 20-30% of epileptic patients suffer intractable seizures that cannot be controlled by treatment with any of the available antiepileptic drugs (AED) (Löscher et al., 2020). Unfortunately, patients with developmental epileptic encephalopathies (DEE) whose seizures begin in childhood and are associated with genetic syndromes affecting brain development often suffer from intractable seizures. Patients with intractable seizures do not attain the treatment goal of sustained freedom from seizure when they receive appropriately selected pharmacotherapies at tolerable levels (Kwan et al., 2010). Intractable seizures can be life-threatening, and patients are at increased risk of death from either status epilepticus, accidental injuries, or unexplained causes due to sudden unexpected death in epilepsy patients (SUDEP), (Téllez-Zenteno et al., 2005). For these reasons, the search continues for alternative treatments with renewed interest in examining the anti-epileptic effects of medical cannabis (Suraev et al., 2018). This chapter systematically reviews the certainty of the evidence, according to the Cochrane criteria, regarding the efficacy of pure cannabidiol (CBD, Epidiolex®) and other cannabis plant-derived medicinal products for control of treatment-resistant seizures in patients with Dravet syndrome, Lennox-Gastaut Syndrome (LGS), tuberous sclerosis complex (TSC), and other developmental epileptic encephalopathies (DEE) with known or unknown genetic mutations.

BACKGROUND

Treatment regimens recommended by the International League Against Epilepsy (ILAE) vary by the type of seizures which are operationally classified based on (a) onset – focal seizures (auras in which electrical impulses begin in just one area of the brain), generalized seizures (begin in both hemispheres and may lead to loss of consciousness), or seizures of unknown onset, (b) level of awareness – seizures while alert, or seizures with impaired awareness, and (c) by whether movements occur or not – motor seizures include automatisms, atonic (temporary loss of muscle tone that could cause abrupt falls), clonic (repeated jerking of arms and legs), epileptic spasms (clusters of brief sudden muscle stiffening), hyperkinetic, myoclonic (sudden muscle jerks), tonic (stiffening of the body), tonic-clonic (muscle stiffness and rhythmic convulsions), myoclonic-atonic, myoclonic-tonic-clonic, with drop seizures defined as either atonic, tonic, or tonic–clonic seizures involving the entire body, trunk, or head that could lead to a fall, injury, or slumping in a chair, while non-motor seizures include autonomic, behavior arrest (decrease or arrest of motor activity), cognitive (alteration in cognition), emotional (bursts of laughter, crying, panic, ecstasy, or anger), sensory (visual, auditory or tingling sensations), eyelid myoclonia, typical absence (sudden trance-like state lasting few seconds) and atypical absence (staring episodes lasting more than 10 seconds with eye blinking, chewing, lip smacking or finger rubbing movements) (Fisher et al. 2017a,b).

Developmental epileptic encephalopathy (DEE) of infancy and childhood comprises a heterogeneous group of severe epilepsies characterized by the onset of multiple seizure types in the first few years of life associated with a poor prognosis, genetic etiologies, frequent epileptiform activity on electroencephalogram (EEG), behavioral and intellectual impairment with either (i) minimal cognitive impairment ("developmental encephalopathy"), or (ii) progressive cognitive decline and developmental regression as a result of the detrimental effects of seizures and interictal epileptiform activity on the brain ("epileptic encephalopathy") (McTague et al. 2016, Raga et al. 2021). Etiologies of DEE include muta-