

MEDICAL CANNABIS IN PEDIATRICS (MYTH OR REAL POSSIBILITY)

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ABSTRACT

The public interest in cannabis for medical use is acknowledged, and anecdotal reports of effectiveness in individual patients are compelling. Our objective is to make an overview of the current scientific papers for medicinal cannabis use in paediatric population. Literature review was conducted utilizing, PubMed, Medline, and Google Scholar. Cannabis based products have promising potential for add-on treatment of certain conditions in paediatrics. Well-designed Randomized Clinical Trials (RCTs) with sufficient number of patients are imperative to demonstrate benefit of therapeutic use. In paediatrics, the greatest evidence for medicinal cannabis use is for seizure disorders. RCTs have demonstrated the safety and efficacy of oral Cannabidiol (CBD) for treatment of seizures associated with Lennox-Gastaut or Dravet syndrome.

Keywords: cannabinoids, medical marijuana, pediatrics.

INTRODUCTION

Use of medical marijuana has become a controversial topic within the medical community and among national legislative levels, but many countries and states have allowed its use. In pediatrics, many of the misconceptions regarding the use of medical marijuana arise from the association of the marijuana with its psychoactive effects.

Currently, many terms associated with marijuana are being used. Cannabis, also known as hemp, is a general term that refers to the three species of plants *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. Cannabis has long been used for hemp fibre, hemp seed and their hemp oils, hemp leaves for use as vegetables and as juices, medical purposes and as recreational drug.

Cannabis contains more than 460 compounds of which at least 80 of these are cannabinoids: tetrahydrocannabinol (delta-9-tetrahydrocannabinol, THC), the most psychoactive cannabinoid; delta-8-tetrahydrocannabinol; cannabidiol (CBD); cannabinol (CBN); cannabicyclol (CBL); cannabichromene (CBC) and cannabigerol (CBG) with less psychotropic effects than THC. The most studied are THC and CBD. Primary cannabinoid receptors are: CB1, responsible for psychoactive effects of cannabinoids found in the brain, and CB2 found peripherally throughout the body are thought to modulate pain and inflammation.

Medical and recreational use of cannabis dates from the ancient civilization almost 5000 years ago in Chinese medicine and after that is described also in Egyptian, Greek, Indian and Middle Eastern cultures.

Medical cannabis (or medical marijuana) refers to the use of *cannabis* and its compounds, to treat disease or improve symptoms. Preliminary evidence suggests that Cannabis has potential beneficial effects in chronic pain and muscle spasms, in reduction of nausea during chemotherapy, improving appetite in HIV/AIDS, improving sleeping and improving tics in Tourette syndrome and treating severe forms of epilepsy including treatment resistant epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS).

Synthetic cannabinoids are available for prescription use in many countries. Food and Drug administration (FDA) has approved two oral cannabinoids for use as medicine: dronabinol and nabilone, the only current cannabinoids available by physician prescription. Dronabinol is a synthetic THC listed as Schedule II, while, Nabilone, is a synthetic cannabinoid listed also Schedule II, indicating high potential for side effects and addiction.

The objective of this paper is to make overview of the current scientific papers for medicinal cannabis use in pediatric population.

METHODS

Conducted was a systematic and literature review of the literature on the use of medical cannabis in children and adolescents. PubMed, Medline, and Google Scholar were searched for scientific papers published during the last five years, including systematic reviews, clinical trials, clinical studies, meta-analysis, multicenter studies, observational studies, randomized controlled trials and case reports by using the following medical terms and keywords: "cannabinoids", "cannabis", "cannabidiol" (CBD), "medical marijuana", "dronabinol", "nabilone", "tetrahydrocannabinol" (THC).

Filters were managed by inclusion of publications in the last 5 years, published in English language, studies conducted in humans and age from birth to 18 years.

RESULTS

PubMed, Medline, and Google Scholar searches yielded 2843 published articles and citations published from year 2015 to 2019. Included were case reports, clinical studies, clinical trials, meta-analysis, multicenter studies, observational studies, randomized controlled studies and systematic reviews and reviews and the search result were decreased to 598 published papers. After adjusting the search results, excluded were articles with the sample being older than 18 years, those about drug abuse or intoxication and effects of cannabis consumption, exposure and addiction, cannabis withdrawal and cannabis use disorders. The remaining citations were identified for final inclusion, describing 13 reviews; 9 clinical trials of which 3 randomized controlled trials, 1 prospective study, 1 retrospective study; 3 clinical studies and 5 case reports. Of the all medical conditions studied in these papers, the most common indication was for seizures; motor disorders; chemotherapy induced nausea and vomiting (CINV); neurodevelopmental and behavioral conditions and posttraumatic stress.

Articles about the use of cannabis in seizures included studies of treatment-resistant epilepsy (TRE), LGS and DS. Epilepsy is one of the most common chronic disorders of the brain affecting around 70 million people worldwide, 30% of which are resistant to antiepileptic therapy. LGS and DS are severe, refractory epilepsy syndromes with onset in early childhood and in most of the cases currently available treatments fail to control seizures, therefore remains the need to identify new treatments. An open label, large prospective study that was conducted to characterize the changes in response to a pharmaceutical formulation of highly purified CBD, included 72 children with TRE who used CBD during 48 weeks, reports significant improvements in adverse events, seizure severity and seizure frequency. Another study of a phase 1 trial of CBD in children with treatment-resistant epileptic encephalopathy where 28 children were included reports that CBD Cannabis extracts is safe and well tolerated for pediatric patients with refractory epilepsy and improves the frequency and duration of seizures. Double-blind placebo controlled trial conducted at 30 clinical centers that included 225 patients with LGS who used CBD reported a great reduction in the frequency of drop seizures. Another double blind placebo controlled trial conducted at 24 clinical sites with included 171 patients with LGS reported that add-on CBD is efficacious for the treatment of patients with drop seizures associated with LGS and is generally well tolerated. Double-blind placebo controlled trial, which included 120 children with Dravet syndrome who received CBD, or placebo concluded that CBD resulted in greater reduction in seizure frequency than placebo (*Devinsky et al. 2017*).

Another study suggests that CBD might reduce seizure frequency and might have an adequate safety profile in children and adolescents with treatment-resistant epilepsy (Devinsky *et al.* 2016). An observational longitudinal study conducted in 57 patients with epilepsy of different etiology treated with CBD-THC suggests that adding CBD enriched cannabis extract to the treatment regimen may result in significant reduction in seizure frequency according to parental reports. An observational study conducted by a survey that included 15 patients with refractory epilepsy, suggests a possible beneficial effect of CBD on the control of seizures and on the improvement of neurocognitive aspects in patients with refractory epilepsy.

Lattanzi *et al.* provide a critical review of the pharmacology of CBD and the most recent clinical studies that evaluated its efficacy and safety as an adjunctive treatment of seizures associated with LGS and DS. A review reported that CBD shows similar efficacy in the severe pediatric epilepsies to other antiepileptic drugs. Three randomized, placebo-controlled, double blind trials in DS and LGS found that CBD produced a 38% to 41% median reduction in allseizures compared to 13% to 19% on placebo. Similarly, CBD resulted in a 39% to 46% responder rate (50% convulsive or drop-seizure reduction) compared to 14% to 27% on placebo. Elliot *et al.* performed a systematic review of studies involving the use of cannabis to treat pediatric epilepsy, providing an up-to-date summary of the available evidence about the use of cannabis in children with TRE. In an open-label trial, patients with severe, childhood-onset, TRE, who were receiving stable doses of antiepileptic drugs before study entry, were enrolled in an expanded-access programme at 11 epilepsy centers across the USA. Findings suggest that CBD might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly TRE. One study estimated the efficacy and safety of CBD as adjunctive treatment in patients with epilepsy using meta-analytical techniques that included four trials involving 550 patients with LGS and DS were included.

Tuberous sclerosis complex (TSC), an autosomal-dominant genetic disorder, usually manifests with epilepsy, affecting approximately 85% of patients, 63% of whom develop TRE. Findings of a study that evaluated the efficacy, safety, and tolerability of CBD as an adjunct to current antiepileptic drugs in patients with refractory epilepsy in the setting of TSC suggest that CBD may be an effective and well-tolerated treatment.

Libzon *et al.* studied the efficacy, safety, and tolerability of medical cannabis in children with complex motor disorder, while two products of CBD enriched 5% oil formulation of cannabis were compared: one with 0.25% THC 20:1 group, the other with 0.83% THC 6:1 group in 25 children and adolescents. Significant improvement in spasticity

and dystonia, sleep difficulties, pain severity, and QOL was observed in the total study cohort, regardless of treatment assignment. Published paper of a case report of a patient suffering from treatment-resistant Tourette syndrome showed that administration of a THC-CBD showed a rapid and highly significant improvement in the Yale Global Tic Severity Scale. *Jakubovski* and *Muller* reported two cases of treatment-resistant Tourette syndrome (TS) with incapacitating stuttering-like speech disfluencies caused by vocal blocking tics and palilalia who received dronabinol, suggesting that cannabis-based medicine appears to be effective in treatment-resistant TS patients with vocal blocking tics.

Children with ASD commonly have comorbid symptoms such as aggression, hyperactivity and anxiety. It is estimated that 25% of children with treatment-resistant epilepsy have comorbid autism spectrum disorder (ASD). Based on parents' reports, findings suggest that CBD may be effective in improving ASD comorbid symptoms. A review of the scientific literature suggests that CBD has promising results in the treatment of ASD. Currently, one ongoing clinical study is assessing the tolerability and efficacy of a CBD and THC combination product in treating behavioral problems in children with ASD. Reported are cases of marijuana treatment in patients with developmental and behavioral conditions including high-functioning autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD)-combined type, anxiety, and depression, mild intellectual disability, and schizoaffective disorder. *Hadland et al.* review describes the role of the endocannabinoid system in normal neurodevelopment and discusses some of the proposed uses of cannabis in ADHD and ASD. Nausea and vomiting remain a problem for children undergoing treatment for malignancies despite new antiemetic therapies.

A review included 34 studies of randomized controlled trials (RCTs) that compared a pharmacological antiemetic, cannabinoid, or benzodiazepine with placebo or any alternative active intervention in children with cancer who were to receive chemotherapy and reported cannabinoids to be effective. One review examines the evidence for medical marijuana as a supportive care agent in pediatric oncology. A multicenter retrospective review described the safety and efficacy of nabilone given to pediatric patients to prevent acute CINV. Oral solution of both CBD and THC was investigated for safety and efficacy as adjunctive therapy to opiates in pediatric patients with Cancer-related pain in double-blind, placebo-controlled study. The European Commission for sublingual spray with THC and CBD for the treatment of glioma granted orphan designation. Most recently, researchers have reported promising *in vitro* and *in vivo* studies for use of cannabinoids in Neuroblastoma. Use of CBD either as single agent or in combination with existing compounds and chemotherapy agents is a possibility to improve the antitumorigenic effects of other

treatments in Neuroblastoma. Epidermolysisbullosa is a rare blistering skin disorder that is challenging to manage because skin fragility and repeated wound healing causes itching, pain, limited mobility, and recurrent infections.

Reported are 3 cases of self-initiated topical CBD use in patients with Epidermolysis bullosa in an observational study. All 3 reported faster wound healing, less blistering, and amelioration of pain with CBD use.

One case study provides clinical data that support the use of CBD as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder. Recent evidence suggests a potential anti-inflammatory effect of cannabis. A review presents an overview of recent literature on the use of cannabis in IBD focusing on pediatric IBD patients.

Cannabinoids were investigated for possible effects in Perinatal Brain Injury and CBD is thought to have a protective effect on nerve cells due to its expected anti-inflammatory properties and prevent the permanent brain damage in newborns.

CONCLUSION

Cannabis based productsbenefithas been demonstrated through many Randomized Clinical Trials of many conditions in pediatrics.

The objective of thissystematic review was to synthesize the current state of the research onmedical cannabinoids in childrenand adolescents. The use of CBD has gainedincreasing attention regarding its lack of psychoactive propertiesand potential benefits that have been noted in certain diseases such as epilepsy, ASD, motor disorders, anorexia associated with cancer, chronic pain and spasticity; CINV, sleep disorders, Tourette syndrome, multiple sclerosis.

Cannabis-based therapies have been used to treat epilepsy for millenniabut interest in the use of cannabis as a treatment for pediatric epilepsy especially TRE has grown over the last decade exploring the potential efficacy of CBD use in children with DS and LGS.

Although supporters of medical cannabis say that it is safe, further research is required to assess the long-term safety of its use especially given increasing accessibility fromstate legalization and potential psychiatric and neurocognitive adverse effects identifiedfrom studies of recreational cannabis use.

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