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Current state of knowledge on the use of cannabidiol (CBD) in various medical conditions

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Abstract

INTRODUCTION AND PURPOSE

Cannabis sativa contains hundreds of compounds, referred to as cannabinoids. Two most prevalent are delta-9-tetrahydrocannabinol and cannabidiol (CBD). CBD is non-psychoactive substance that has recently gained attention in lay press and in medical research. Aim of this study is to review evidence-based data on safety, effectiveness and applicability of CBD in various medical conditions in order to provide healthcare professionals with information that may be useful in their practice.

MATERIALS AND METHODS

In April 2023, PubMed and Google Scholar databases were searched for studies that included phrases “CBD” or “cannabidiol”, and related phrases. In the review, only studies that used well-established research methods were included.

RESULTS

CBD is an effective novel treatment option in Lennox–Gastaut syndrome, tuberous sclerosis complex and Dravet syndrome. Data supporting CBD’s applicability in anxiety, Parkinson’s Disease, schizophrenia, insomnia, pain, autoimmune diseases, osteoporosis and as an anti-

aging agent is promising, but more research on bigger groups of patients is needed to establish its role in modern medicine.

CONCLUSIONS

The use of CBD is associated with risks of variable dosage, contamination and adulteration. At present, there is a need of more research to establish effective and safe doses of CBD. Clinicians need to monitor new data from ongoing CBD trials, but at present there is no hard evidence supporting effectiveness of CBD in various medical conditions, apart from epilepsy.

INTRODUCTION

Cannabis sativa is one of the longest-cultivated plants in the history of human agriculture. It is known to contain hundreds of chemical compounds, referred to as cannabinoids or phytocannabinoids[1],[2]. For hundreds of years, *cannabis sativa* was used for the production of fabrics, ropes and paper[3] and in ancient medicine it was known as a panaceum for various medical conditions[4].

Two most prevalent components derived from *cannabis sativa* are delta-9-tetrahydrocannabinol (delta-9-THC; often referred to as “marijuana”) and cannabidiol (CBD)[5]. Those compounds differ in their psychoactive potential, and the use of delta-9-THC is limited due to its effect on perception (“high”)[5]. In most European countries, delta-9-THC use, production and distribution both for personal use and for medical purposes is a subject to strict regulations. For instance, production and use of medical marihuana is not allowed in Latvia and Bulgaria, whereas in France and Spain medical marihuana is registered for cultivation and use under specific circumstances[6]. In Poland, marihuana was legalized for medical uses in 2017, and at present is used mainly as a component of pain management program in palliative care[7].

As opposed to delta-9-THC, cannabidiol (CBD) is the non-psychoactive compound of *Cannabis sativa*. Of late, CBD has been gaining a lot of attention both in lay press and in medical research[5]. A multitude of CBD-containing products is now available in Poland, both in topical and oral preparations. Media coverage is leaning towards idealizing CBD as a panaceum for many medical conditions. Hence, healthcare professionals should be able to

provide their patients with evidence-based information on the effectiveness, safety and applicability of CBD in various medical conditions.

AIM OF STUDY

The aim of this study is to review and summarize evidence-based data on safety, effectiveness and applicability of cannabidiol (CBD) in various medical conditions in order to provide healthcare professionals with information that may be used in their everyday practice. We aimed to describe well-established clinical applications of CBD, as well as outline novel results and directions of research on CBD in other medical conditions.

MATERIALS AND METHODS

In April 2023, PubMed and Google Scholar databases were searched for studies that included phrases “CBD” or “cannabidiol”, “CBD sleep disorder”, “CBD anxiety”, “CBD schizophrenia”, “CBD epilepsy”, “CBD Parkinson’s Disease”, “CBD skin”, “CBD pain”, “CBD osteoporosis”, “CBD autoimmune diseases”. In the review, only studies that used well-established research methods were included. We reviewed and synthesized data on various applications of CBD in modern medicine.

RESULTS

I. GENERAL INFORMATION

Endocannabinoid system. Unlike in some animals, in the human body CBD does not convert to delta-9-THC[8]. Nevertheless, it is suggested that CBD, like delta-9-THC acts through the endocannabinoid system (ECS), which consists of various receptors, such as cannabinoid receptor 1 and 2 (CB1, CB2), serotonin 1a receptor (5HT1-alpha), G-coupled protein receptor (GPR55) and Adenosine A2A receptor. Inhibition or activation of those receptors by CBD may induce various effects, such as anti-inflammatory effect, anticancer activity, anxiolytic effect and analgesic effect[8],[9]. What is more, ECS is involved in modulation of appetite and cognition, and endogenous cannabinoids are known to modulate neuronal plasticity and synaptic signaling[10]. Thus, CBD is widely researched as a potential treatment for various neurodegenerative disorders, such as Alzheimer’s Disease and Parkinson’s Disease[10].

Legal status of CBD. CBD-containing products are widely accessible in Europe, and their legal status remains not fully clarified, as opposed to products containing delta-9-THC. It is assumed, that CBD oils and other preparations that are available without prescription contain

less than 0.2% delta-9-THC, and thus do not cause intoxication. Research shows, that the mean concentration of delta-9-THC in industrially cultivated hemp in Europe is lower than 0.0386%, and the concentration of CBD is approximately 0.783-1.809%[11], whereas commercially sold CBD products are claimed to contain much higher concentrations of CBD, sometimes reaching 50%[12]. At present, only one CBD-containing product (Epidiolex) is registered as an FDA-approved drug, and contains specified amount of CBD[12]. On the contrary, the concentration of CBD in other non-registered hemp products may vary. 2016 research showed, that only 31% CBD oils tested for CBD concentration by high-performance liquid chromatography contained 90-110% of the labeled concentration of CBD, while 43% of the tested products contained more CBD, and lower concentrations of CBD were detected in 26% of the products[13]. Only registration and close supervision of CBD products may regulate the amount of CBD that is actually taken by patients, and therefore allow to accurately assess benefits and risks involved in this treatment[12].

Another pressing issue is a possible risk of contamination of CBD products. In 2017-2018 a total of 54 people experienced hallucinations, seizures, confusion and loss of consciousness due to exposition to a synthetic cannabinoid added to a CBD product[14]. Moreover, International Cannabis and Cannabinoid Institute in Czech Republic analyzed 29 CBD-containing products and found that 69% of them contained an excessive amount of polycyclic aromatic hydrocarbons, which are known carcinogens and genotoxic substances[15]. Additionally, CBD products may contain heavy metals and pesticides, as there is no supervision of its' cultivation and production[14]. That said, medical professionals should be aware of risks associated with over-the counter use of non-registered CBD products, which may vary from the purified products used in medical trials and contain harmful substances that may lead to poisoning and intoxication.

II. CLINICAL APPLICATIONS

Epilepsy. Epilepsy is a chronic central nervous system disorder, which affects up to 65 million people worldwide[16]. Due to limited efficacy of known antiepileptic drugs and recurrent character of the disorder, there is a pressing need for novel drugs that may limit the amount of seizures, especially in treating rare forms of epilepsy. Epidiolex was the first cannabidiol, that was approved by US Food and Drug Administration in 2018. At present, Epidiolex is registered for treatment of severe seizures occurring in three rare forms of developmental and epileptic encephalopathy: Lennox–Gastaut syndrome, tuberous sclerosis complex and Dravet syndrome[17]. Multiple human trials proved antiepileptic activity of CBD, and the proposed mechanisms of its action include not only modulatory effect on

cannabinoid receptors, but also anti-inflammatory action[18] and neuroprotective potential[19] and facilitation of neurogenesis[20]. Further research is needed to decide upon the use of CBD to control seizures in other epileptic disorders. At present, Epidiolex was approved in Europe for a 14-week phase III trial for treatment of myoclonic atonic-associated seizures in adolescents and children[17]. Unique and multifocal activity of CBD in central nervous system makes it a promising new perspective in the treatment of refractory epilepsy.

Anxiety. Multiple human and animal trials confirm that CBD displays anxiolytic properties, but evidence is limited due to small sample sizes, lack of long-term assessment and the fact, that most trials were conducted with healthy individuals who did not beforehand suffer from anxiety disorder[5],[21],[22]. What is more, a majority of the studies examined only acute dosing of CBD[23]. A 2019 review article analyzed 6 randomized controlled trials, 1 case report, and 1 case series that examined CBD potential to reduce anxiety in healthy individuals, in social anxiety disorder (SAD), in generalized anxiety disorder (GAD) and the anxiety component of posttraumatic stress disorder. Authors of this review found that CBD was effective as an anxiolytic drug, especially in GAD and SAD, and underlined CBD unique advantage of minimal adverse effects as compared to other anxiolytic drugs[24]. On the other hand, Spinella et al. found, that strong belief that CBD has anxiolytic properties led to more pronounced subjective and physiological responses in a placebo group, as compared to individuals who also did not receive CBD, but did not believe it to have anxiolytic properties initially[25]. Given that anxiety is a subjective and individual response, results of this study indicate that further and more objective research is needed to evaluate clinical importance of CBD, alongside with regulations of exact concentrations of cannabidiol in CBD preparations. Most recent review by Narayan et al. found that CBD has anxiolytic effect in healthy individuals with no prior history of cannabis use, with an inverted U-shaped dose relationship, and the minimum therapeutic single-administration dose was 300 mg[26]. As results of the 58 studies analyzed in this review were likely moderated by CBD - THC ratio and choice of healthy individuals, further research using only pre-established doses of CBD and examining effects on individuals suffering from anxiety is needed.

Schizophrenia. There are a few trials that assessed CBD use in in the treatment of schizophrenia[27],[28]. A 6-week exploratory double-blind parallel-group trial randomized patients to receive 1000 mg/day CBD or placebo alongside their existing anti-psychotic medication, and found that patients who received CBD experienced less positive psychotic symptoms, and their health was more likely to be described as improved. What is more, authors of this study found that CBD was well tolerated and the number of adverse effects in

CBD group was comparable to the placebo group[27]. What is important, CBD does not exert its anti-psychotic activity through dopamine receptor antagonism, which may be an useful asset as currently used drugs have multiple adverse effects which may limit their clinical application. On the other hand, Boggs et al. analyzed the impact of add-on CBD therapy (600mg/day) or placebo in a group of 41 patients with chronic schizophrenia and found no statistical difference in positive, negative and cognitive symptoms of schizophrenia[28], which may indicate that the dose of CBD is crucial for its effectiveness in treating psychotic disorders. A most recent study by Leweke et al. revealed that 800mg/day CBD therapy in patients with schizophrenia or schizophreniform psychosis improved neurocognitive functioning[29]. To sum, existing data on the efficacy of CBD in schizophrenic patients is promising, although the analyzed studies were conducted on small groups of patients and used different dose of CBD, and more research is needed to establish the role of CBD in alleviating the symptoms of acute psychosis and improving cognitive functions in schizophrenic patients.

Parkinson's Disease. Data on the efficacy of CBD in patients with Parkinson's disease (PD) in human models is scarce. In a 6-week exploratory double-blind trial on patients with Parkinson disease without other coexisting psychiatric conditions and without dementia, CBD was found not effective in improving motor functions, as measured by Unified Parkinson Disease Rating Scale[30]. Similarly, no significant differences were found in the concentrations of brain-derived neurotrophic factor in the placebo and CBD group. However, patients who received 300mg of CBD per day reported significantly higher scores of well-being and quality of life than the control group[30]. Results of this study, however promising, have a limited significance due to a small (n=21) size of the study. Of other trials that studied impact of CBD in PD patients, none showed a significant reduction of dystonia[31],[32],[33], but one study found that CBD significantly reduced levodopa-induced dyskinesia[34]. As results of the beforementioned studies indicate, that patients suffering from PD may benefit from CBD administration, more research is needed to establish the needed dose and profile of patients, that may benefit from CBD therapy.

Sleep disorders. One of the most popular applications of CBD is its use in the management of insomnia, and multiple studies have been conducted either using only CBD, or various CBD:delta-9-THC ratio. Some of the studied recruited individuals with pre-existing history of chronic or substantial recreational cannabis use[35],[36], which makes it difficult to assess the role of CBD, as sleep disorders are common in patients with history of delta-9-THC use[37]. Rylea et al. analysed nineteen trials that studied the influence of predominant CBD therapy on the improvement of insomnia symptoms. 7 of those studies performed hypothesis testing and

4 of them have reported a significant reduction of sleep disorder symptoms. Even though results of this analysis are promising, authors underline that more studies on patients with diagnosed insomnia and more objective comparison methods are vital for better understanding of the applicability of CBD therapy in sleep disorders[38].

Pain. CBD was found effective as an analgesic agent in multiple preclinical studies[39]. Most of the human studies examining the role of CBD in treating pain use weak methodology and small investigation groups[5]. What is more, CBD was often administered alongside delta-9-THC, hence exact analgesic properties of CBD could not be established. An open-label, single-arm trial studied the effect of CBD oil for relieving pain and improving quality of life in 12 young girls with major chronic pain due to the administration of the human papillomavirus vaccine[40]. Due to lack of initial improvement and adverse effects, only 8 girls completed the study and in those patients there was a significant reduction of body pain compared to baseline the physical component score, vitality, and social role functioning using the SF-36 questionnaire. Results of this study are promising, but of limited importance due to a small size of the studied group, and the use of CBD-enriched oil may have confounded the results, as other components of the oil may have been important for the observed pain relief. More research is needed to establish the role of CBD in treating pain.

Autoimmune diseases. Studies suggest, that endocannabinoid system may be a promising target in treating autoimmune diseases. CBD is a potent immunomodulatory agent, as it suppresses the infiltration of immune cells into the tissue and inhibits the secretion of inflammatory cytokines (IFN- γ , TNF- α , IL-12, IL-17 and IL-6)[41]. Multiple studies suggest that CBD may display anti-inflammatory and antiarthritic activity in rheumatoid arthritis[42],[43] and in inflammatory bowel diseases such as Crohn's disease[44], where it was shown to improve colitis activity index[45]. What is more, it is suggested that patients suffering from multiple sclerosis may benefit from the use of CBD, as it leads to reduction of T-cell infiltration[46] and decreases the velocity of demyelination, muscle spasticity and axonal loss[47], as well as improves the quality of life as decreases neuropathic pain index[48]. That said, more data and research on wider groups of patients is needed to establish the role of CBD in treating autoimmune diseases.

Osteoporosis. Cannabinoid receptors CB1 and CB2 are expressed in the bone tissue and modulate bone formation and healing in rodents and in humans, mainly by preserving bone from resorption[49]. Multiple preclinical and clinical trials studies suggest that CBD may improve bone density and be an effective additional treatment for osteoporosis[50], but further research is needed to establish the role of endocannabinoid system in the prevention

and treatment of osteoporosis, especially since most of the studies were conducted on rat models.

Skin applications. Of late, CBD has been widely investigated also for the topical use in dermatology and cosmetology. The endocannabinoid system has been identified in the skin, and although it's main functions remain to be fully elucidated, it is suggested to modulate hair growth, improve wound healing, and act as a sebostating, antipuritic and antimicrobial agent[51]. A recent review on therapeutic applications of CBD in dermatology suggests that it may be effective in multiple diseases such as ATD, psoriasis, acne, epidermolysis bullosa, systemic sclerosis, seborrheic dermatitis, scalp psoriasis, androgenetic alopecia and melanoma[51]. However, as CBD has an extremely hydrophobic structure, there is a need of special preparations that will allow it to be absorbed throughout the topical administration[52].

New directions of research. At present, there is a multitude of research on CBD applications in various medical conditions, and describing all of it exceeds the scope of this review.

DISCUSSION

The use of non-FDA approved CBD is associated with major risks of variable dosage, contamination and adulteration. CBD is a potent, biologically active substance, that may interact with various cell pathways and modulate response to medications and lead to unpredicted clinical outcomes[53]. Medical professionals should inform their patients of risks associated with the use of CBD and recommend only the use of products that have been FDA-approved or at least tested by an independent laboratory. Due to lack of strict regulations regarding concentration of CBD in widely accessible products, as well as the lack of supervision of production of CBD products, it is of utmost importance to remain vary of possible negative outcomes of this treatment. Even though many preliminary studies suggest that patients may benefit from CBD use in alleviating symptoms of many conditions, many of those studies use non-objective methods or were conducted on small groups of individuals. There is need for large-sample studies examining the effect of exact concentrations of CBD in various medical conditions.

CONCLUSIONS

To conclude, CBD is an effective novel treatment option in Lennox–Gastaut syndrome, tuberous sclerosis complex and Dravet syndrome, and may also be effective in other refractory epilepsies, but more research is needed to support this treatment.

Data supporting CBD applicability in anxiety is promising, but more research on bigger groups of patients suffering from anxiety is needed. Furthermore, the studies conducted used

mainly subjective methods to determine efficacy of CBD, and often combined CBD treatment with THC administration. Patients suffering from schizophrenia may benefit from adding CBD to their anti-psychotic therapy, but there is a need of large studies and establishing the dosage of CBD that may be effective.

CBD may be a promising new agent in treatment of Parkinson's Disease, but existing human trials present non-conclusive data and more research is needed in this field. Patients suffering from insomnia may benefit from CBD therapy, but at present there is no conclusion as to the dose and time of CBD therapy that is needed to observe those effects. CBD was proven to be an effective analgesic agent in animal models, but there is not enough evidence from human trails to establish it's role as an analgesic agent. Novel directions of research on CBD include autoimmune diseases, osteoporosis and as an anti-aging agent, as well as many other fields that exceed the scope of this article. To conclude, clinicians need to monitor new data from ongoing CBD trials and wisely decide upon recommending CBD to their patients.

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