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The Safety and Efficacy of CBD—A Pharmacist's Perspective

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Abstract

Here in the United States Cannabidiol (CBD) is legal in all 50 states if the Tetrahydrocannabinol (THC) concentration of the product is no more than 0.3%. The largest retailers of CBD in 2019 were located in California, Florida, and New York, which sold $730 million, $291 million, and $215 million, respectively. Of the patients who use CBD, the most common reasons for their use were pain, anxiety, and insomnia. As the use of CBD for the relief of different issues increases, it is important to assess the safety and efficacy of CBD as it pertains to drug-drug interactions, lab interactions, and its actual benefits. This subject of safety and efficacy is increasingly important as the use of CBD has increased, with approximately 64 million Americans having tried CBD between 2017 and 2019. In this article, we will discuss these different aspects of CBD use from the point of view of a pharmacist. Not only do pharmacists commonly get questions on different aspects of CBD use, but they are also drug experts in areas including drug-drug interactions, drug toxicities, pharmacokinetics and pharmacodynamic profiles of medications, and guideline-recommended therapeutic options. Although there is a limited amount of data, there is still accessible data that may serve to inform pharmacists to become aware of the safety and efficacy of CBD. This information will serve pharmacists to educate patients that CBD contains properties to be used in a variety of conditions such as Lennox-Gastaut Syndrome, Dravet Syndrome, pain, and sports enhancement.

Keywords

CBD, Cannabidiol, Cannabinoid

1. Introduction

On April 27, 2021, an electronic systematic search was conducted on a variety of databases, which consists of Web of Science, Cochrane Controlled Register of

Trials (CENTRAL), as well as PubMed. Search terms included "cannabidiol", "CBD", and "cannabinoid" were combined with "epidemiology", "safety", "efficacy", "drug interactions", "interactions", "adverse effects", "adverse reactions", "side effects", "Lennox Gastuat Syndrome", "LGS", "Dravet Syndrome", "epilepsy", "seizures", "pain", "inflammation", "anti-inflammatory", "opioids", "THC", "sports enhancement", "sports", "athletes", "anxiety", and "depression". The eligibility of identified articles was evaluated based on title and abstracts. The reference lists of included articles were also individually examined to determine whether further citations would be required.

2. What Is CBD?

To begin our discussion, we need to understand what exactly CBD is. CBD is one of the main active ingredients found in cannabis plants [1]. Though it is an active ingredient in cannabis, it does not contribute to the "high" that users get when smoking marijuana. CBD can be directly extracted from both hemp plants and marijuana [1]. Many CBD providers prefer to extract from hemp plants due to their natural low THC profile [1]. Unlike the potential for addiction with smoking marijuana, CBD has not been shown to cause addiction or dependence with its use according to the World Health Organization (WHO) [2]. CBD is a 21-carbon compound that is the product of decarboxylation of a cannabidiolic acid precursor [2]. CBD is typically consumed via inhalation, but can also be delivered to the body using various delivery methods such as topical oils, chewing gums, and more [2].

3. Safety Considerations?

The safety of CBD is important to discuss as it has the potential to interact with the metabolism of multiple chronic and acutely prescribed medications. It also carries the potential for its own adverse effects that consumers can experience. In the controlled clinical trials of Epidiolex, common adverse events which occurred in at least 10% of patients when compared to placebo include the following: fatigue, reduced appetite, sleep disturbances, gastrointestinal intolerances, transaminase enzyme elevations, infections, decreased energy, and rash [3]. These doses ranged from 10 mg/kg/day to 20 mg/kg/day for the treatment of Lennox-Gastaut syndrome and Dravet Syndrome, with elevations in transaminase enzymes being the common reason for discontinuation [3]. In higher doses of 25 mg/kg/day, adverse reactions that occurred in at least 10% of patients in comparison to placebo include somnolence, diarrhea, transaminase enzyme elevations, vomiting, decreased appetite, and fever, while other adverse events include anemia and serum creatinine increase seen at doses varying from 10 mg/kg/day to 25 mg/kg/day [3]. In other clinical studies investigating the safety profile of CBD derived from Cannabis sativa did not find significant acute or chronic adverse reactions with doses up to 1500 mg/day in some patients [4]. In animal models, monkeys exposed to high doses up to 300 mg/kg experienced tremors, sedation,

hyperpnea, and bradycardia which ultimately lead to cardiac arrest and death [4]. Currently, clinical studies show that CBD remains relatively safe in humans, but the effects seen in higher doses still remain unclear in humans.

4. Drug-Drug Interactions

CBD's main drug-drug interactions are a result of its effects on CYP450 enzymes in the liver [5]. These CYP450 enzymes are used in the biotransformation and metabolism of many prescribed medications [6]. CBD has been shown to interact with several CYP450 enzymes including isoforms 3A4, 2C9, 2C19, 1A2, 2C8, 2B6, and 2E1 [7]. Potentially of no surprise, the largest interaction was found to be with the 3A4 isoform, which is involved in most of the drug-drug interactions of all the isoforms [6]. **Table 1** below illustrates a list of these common CYP450 isoforms as well as the effects they may have when involved in interactions [6]. Common drugs known to be CYP450 enzyme inhibitors such as azole antifungals, macrolide antibiotics, and amiodarone can cause an increase in CBD levels due to inhibition of the CYP450 enzyme and the ability for the enzyme to metabolize CBD [6]. Vice versa, drugs such as phenytoin, rifampin, and oxcarbazepine, that are known CYP450 inducers have the potential to decrease levels of

Table 1. Potential drug-drug interactions with CBD [5].

Enzyme	Medication Examples	Effect/Recommendation
CYP3A4 Substrates	Immunosuppressants, chemotherapeutics, antidepressants, antipsychotics, opioids, benzodiazepines, z-hypnotics, statins, calcium channel blockers, etc.	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects, and toxicity. Avoid prescribing cascade with new treatments for side effects.
CYP3A4 Inhibitors	Strong: Protease inhibitors, ketoconazole, loperamide, nefazodone. Moderate: Amiodarone, verapamil, cimetidine, aprepitant, imatinib.	Increased CBD bioavailability, possible increase in adverse effects. Reduce CBD dose.
CYP3A4 Inducers	Strong: Enzalutamide, phenytoin. Moderate: Carbamazepine, topiramate, phenobarbital, rifampicin, efavirenz, pioglitazone.	Decreased CBD dose availability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C19 Substrates	Antidepressants, antiepileptics, proton pump inhibitors, clopidogrel, propranolol, carisoprodol, cyclophosphamide, warfarin.	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.
CYP2C19 Inhibitors	Strong: Fluvoxamine, fluoxetine. Other: Proton pump inhibitors, cimetidine, ketoconazole, clopidogrel, fluconazole, efavirenz.	Increased CBD bioavailability, possible increase in risk for adverse effects. Reduce CBD dose.
CYP2C19 Inducers	Rifampin, carbamazepine, phenobarbital, phenytoin, St. John's Wort.	Decreased CBD bioavailability, possible decrease in CBD effectiveness. Increase CBD dose.
CYP2C8/9 Substrates	Rosiglitazone, buprenorphine, montelukast, celecoxib, sulfonylureas, losartan, naproxen, phenobarbital, phenytoin, rosuvastatin, valsartan, warfarin.	Increased risk of side effects related to substrate. Avoid co-administration, reduce substrate dose, monitor for adverse effects and toxicity. Avoid prescribing cascade with new treatment for side effects.

CBD [7]. Due to these interactions, it is important for pharmacists and other healthcare professionals to obtain accurate information regarding the medications that a patient is using to assess for these common drug-drug interactions. Proper information allows for possible mitigation of these interactions and a decreased risk of adverse events.

5. Uses and Clinical Efficacy

There are multiple pathways for CBD's therapeutic activity [7]. At very low concentrations it antagonizes what is known as the orphan G-protein-coupled receptor, or GPR55 [7]. It has also been shown to enhance the activity of the 5-HT1a receptor [7]. Given its effects through multiple pathways, CBD has several therapeutic uses. One major option for the use of CBD is in childhood epilepsy disorders [8]. Epilepsy is caused by abnormal electrical activity in the brain and has the potential to be life threatening [9]. This is where it has been studied the most and has some of the greatest amount of efficacy data. The CBD product, Epidiolex, is FDA approved for the treatment of seizures associated with either Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older [6]. It is not fully understood how this CBD product exerts its anticonvulsant effect in humans, however researchers do not believe that it is due to an interaction with cannabinoid receptors [6]. CBD also has the potential for alleviating pain and has various applications in other areas such as sports enhancement due to its anxiolytic effects and anti-inflammatory properties [10] [11].

5.1. Lennox-Gastaut Syndrome

Epidolex efficacy was established for the use in Lennox-Gastaut syndrome in two separate studies [7]. The first study contained 171 participants and compared Epidolex 20 mg/kg/day with placebo. The second study, which contained 225 participants, compared two different doses of Epidolex, 10 mg/kg/day and 20 mg/kg/day. Ninety-four percent of the patients in the first study were also taking two or more antiepileptic medications during the study. These antiepileptic medications included clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%). Study 2 contained similar figures and ninety-four percent of participants were also taking two or more antiepileptic medications. For both studies, the primary measure of efficacy was the percent change from baseline in the frequency of drop seizures over the 14-week period that the study took place. Drop seizures included atonic, tonic, or tonic-clonic seizures. Secondary efficacy points used in the studies included change in total frequency and changes from baseline in the Subject/Caregiver Global Impression of Change, S/CGIC, score at the last visit of the study. In both these studies, the median reduction in frequency of drop seizures was significantly greater in the Epidiolex group than in the placebo group (**Table 2**). These effects were observed within 4 weeks of starting Epidiolex and were consistent over the remainder of the study period.

Table 2. Change in drop seizure frequency in Lennox-Gastaut syndrome (%).

Drop Seizure Frequency (per 28 days)	Placebo	EPIDIOLEX 10 mg/kg/day	EPIDIOLEX 20 mg/kg/day
Study 1	N = 85	N/A	N = 86
Baseline Period Median	75	N/A	71
Median Percentage Change During Treatment	−22	N/A	−44
p-value compared placebo			0.01
Study 2	N = 76	N = 73	N = 76
Baseline Period Median	80	87	86
Median Percentage Change During Treatment	−17	−37	−42
p-value compared placebo		<0.01	<0.01

5.2. Dravet Syndrome

For Dravet Syndrome, there is one randomized double-blind, placebo-controlled trial that illustrates efficacy for this type of epilepsy [8]. This trial contained 120 participants aged 2 to 18 years old. The study contained two treatment arms, 20 mg/kg/day of Epidiolex, and placebo. One of the participant characteristics for the study was that patients had a diagnosis of treatment resistant Dravet Syndrome that was inadequately controlled with one or more antiepileptic medications. The primary efficacy measure of this study was the percent change from baseline in the frequency, defined as per 28 days of convulsive seizures over a 14-week treatment period. Convulsive seizures included those classified as atonic, tonic, clonic, and tonic-clonic seizures. Just like in the Lennox-Gastaut studies, the majority (93%) of patients were taking 2 or more antiepileptic medications during the study. The study concluded that the median percent change from baseline in the frequency of convulsive seizures was significantly greater in the Epidiolex group than in the placebo group. Also like the Lennox-Gastaut studies, the reduction was observed within 4 weeks of beginning therapy and remained constant throughout the remainder of the trial. **Table 3** shows the percentage reduction in convulsive seizure frequency between the two groups.

5.3. Pain

Current treatment of chronic moderate to severe pain often includes the use of opioids [12]. Though these medications are often effective at alleviating pain, they carry risks of abuse, addiction, and overdose [13]. Due to the current opioid epidemic, practitioners need alternative safer methods. CBD is one possible alternative for these patients. It is challenging to determine if CBD by itself contains any therapeutic effect because it is always delivered with THC [8]. At this moment, appropriate clinical studies are lacking to showcase its efficacy due to the lack of pharmaceutical products that are approved for the treatment of chronic pain that only contain CBD [12]. Furthermore, CBD has not been studied

Table 3. Change in convulsive seizure frequency from baseline in Dravet syndrome.

Total Convulsive Seizure Frequency (per 28 days)	Placebo	EPIDIOLEX 20 mg/kg/day
Study 3	N = 59	N = 61
Baseline Period Median	15	12
Median Percentage Change During Treatment	−13	−39
p-value compared placebo		0.01

alone for the treatment of chronic pain except for one study [14], which was uninformative due to many deficiencies in study design such as patients titrating doses themselves, as well as having a THC/CBD product to use as a rescue medication for pain.

5.4. Sports Enhancement

The use of CBD has expanded outside of healthcare and into other areas, such as sports medicine [10] [15]. Unlike THC and cannabis, CBD use is no longer prohibited by the World Anti-Doping Agency (WADA) [15]. Despite the lack of human studies investigating the beneficial effects of CBD in sports injury, animal models show that CBD contains some analgesic, anti-inflammatory, anxiolytic, and neuroprotective properties [10] [15]. Athletes may experience Exercise-Induced Muscle Damage (EIMD) as a result of high intensity and duration-dependent exercises, which leads to a cascade of pro-inflammatory markers and clinical presentations of swelling, soreness, and decreased functional ability [16]. Proposed mechanisms of the analgesic and anti-inflammatory effects from CBD include modulation of receptors to down-regulate the inflammatory process, such as CB2, TRPV1, PPARγ, or Adenosine (A2A) [10] [15] [17]. Animal studies have shown a reduction in the recruitment of immune cells, upregulation of anti-inflammatory makers, and downregulation of pro-inflammatory markers (e.g. prostaglandins) after CBD exposure [10] [15] [18] [19] [20]. Though these anti-inflammatory effects were seen in higher doses equal to or greater than 10 mg/kg, some research suggests that lower doses of about 1.5 mg/kg may share similar efficacy in ischemic perfusion injuries [10]. As seen in animal studies, CBD modulating receptors such as TRPV1 and 5-HT1A account for its analgesic properties as a result from persistent inflammation, radical oxygen species damage, or arthritis and neuropathic pain, although limited clinical studies have investigated this use [10] [11] [12] [15] [18] [23] [24]. Adding to the risk for sports-related injuries, athletes are exposed to anxiety-inducing situations that may result from unexpected injuries, performance anxiety, or concussions [10] [15] [24] [25]. CBD exerts its anxiolytic effects from direct and indirect 5-HT1A and endocannabinoid stimulation, which affects the limbic and paralimbic system that regulate anxiety [25]. In human studies, participants exposed to anxiety-inducing situations reported lower scores of perceived anxiety [10] [15] [24] [25] [26] [27] [28]. In addition sports-related injuries, concussions as known as

mild traumatic brain injuries, are also common among athletes [10] [15]. CBD has demonstrated some neuroprotective properties by stabilizing glutamate levels to prevent a glutamate-induced toxicity, as shown by the reduction of aggressive and depressive-related behaviors in rodents [10] [15]. CBD has potential advantages for athletes as evidenced by preclinical trials, yet more human studies are needed to investigate its clinical application in fields such as sports medicine.

6. Discussion

CBD is rapidly growing in popularity and use as an alternative treatment for pain, insomnia, anxiety, and seizure disorders [29]. However, it is important to realize and understand that CBD, though available over the counter, carries with it certain risks. As we learn more about CBD as a medicinal option, we continue to discover aspects such as drug-drug interactions, side effects, and efficacy. For a consumer who wishes to take CBD, it is important that they inform their primary provider as well as their pharmacist due to the safety considerations that come with CBD such as its effects on CYP450 enzymes. CBD should be treated just like any other medication or supplement a patient takes and should not be underestimated in its potential to cause problems with other concurrent medications. Evidence regarding its efficacy in childhood seizures is promising and should be considered as not all patients attain relief from seizures with non-CBD products. Epidiolex illustrates sufficient evidence for its trial in Lennox-Gastaut and Dravet syndrome when traditional antiepileptic medications are inadequate. The use of CBD for pain seems questionable due to the lack of sufficient evidence illustrating the benefit of pain relief with CBD alone. This review does not include information on THC and therefore it is difficult to assess the efficacy of CBD in chronic pain control as the available studies show combination products of CBD and THC. Regarding its use in sports medicine, CBD may benefit athletes based on its anti-inflammatory, analgesic, anxiolytic, and neuroprotective properties observed in rodent models, yet more studies are warranted to understand its clinical effects.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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