CANNABIDIOL: Navigating the Evidence

EBONY ISIS EVANS, PHARMD
JESSICA HONG, PHARMD
MELISSA MATTISON, PHARMD
KAM CAPOCCIA, PHARMD, BCPS, CDCES

Cannabidiol, also known as CBD, currently has a ubiquitous presence in our society. According to a 2019 Gallup survey, 1 in 7 Americans (14%) said they personally use CBD-containing products.[1] Although the exact mechanism of action of CBD is currently unknown, many of the potential benefits of use are evident. In the Gallup survey, CBD users cited relief from pain (40%), anxiety (20%), insomnia (18%), and arthritis (8%) as their top reasons for using it. Another 4% and 7% cited "general health" and "other" as their respective reasons for using CBD; it is possible that some were using it to manage their diabetes and the associated complications.[1] People with diabetes may have questions and need guidance from diabetes care and education specialists (DCES) when contemplating CBD use.

The purpose of this article is to assess the evidence regarding the effects of CBD in people with diabetes. A literature search of PubMed using the terms *cannabidiol*, *CBD*, *marijuana*, *diabetes*, and any combination of these words resulted in 213 articles after limiting the results to English and full-text availability. Articles published before 2015 and those that were not human studies were excluded. The remainder were then assessed for relevance based on the objective, resulting in 10 articles for review (Figure 1). When discussing the articles, it is necessary to provide the relevance of the data, hence some animal model information is provided as background.

What Is CBD?

CBD is the nonpsychoactive constituent of cannabis. The psychoactive component is Δ^9-tetrahydrocannabinol, commonly known as THC. Both CBD and THC can be extracted from cannabis and taken into the body in various forms, including inhalation, aerosol spray, topically, and orally. See Table 1 for a glossary of cannabis terms.

CBD can be derived from either marijuana or hemp—each a form of *Cannabis sativa* L., an herbaceous species originating from Central Asia that has been used in folk medicine for hundreds of years[2] (see Figure 2). Hemp is defined by the US federal government as having less than 0.3% of THC.[3] The 2018 Farm Bill exempted hemp, and thus CBD extracted from it, from the Controlled

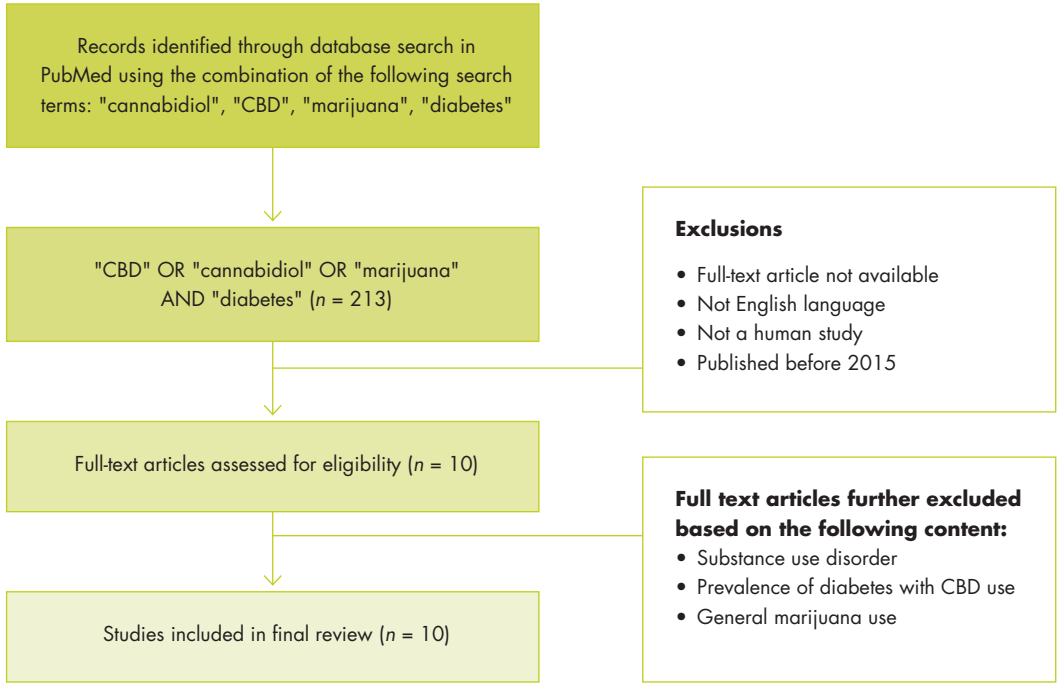

Figure 1. Literature search method.

Table 1. Glossary of Cannabis Terms.[23-25]

Cannabidiol (CBD)	One of the major cannabinoids derived from cannabis or synthesized. Synthetic cannabidiol, brand name Epidiolex, received FDA approval for the treatment of 2 types of seizures. CBD is not believed to be psychoactive due to its very low affinity for CB1 and CB2 receptors. It is found in a variety of formulations (inhaled, topical, edible).
Cannabinoids	Chemicals found in cannabis that activate specific receptors throughout the body to produce pharmacologic effects, particularly in the central nervous system and the immune system.
Cannabis	The generic term for products of the plant *Cannabis sativa* L. Federally, the possession of *Cannabis* is illegal in the United States except within approved research settings; however, a growing number of states have enacted laws to legalize its medical and/or recreational use.
Endocannabinoids	Chemicals produced by the body that target cannabinoid receptors. The endocannabinoid system (ECS) is an innate complex cell-signaling system that is active in the human body. In the ECS, there are 2 main endocannabinoid receptors, cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors. CB1 is found mostly in the central nervous system. CB2 is found mostly in the peripheral nervous system. Examples of endogenous endocannabinoids found in the body include 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine (AEA) or anandamide.
Hemp	Strains of the *Cannabis sativa* L. plant grown for fibrous materials found in the stalks and seeds, used to produce clothing, rope, paper, fuel, insulation, etc. The flowering portion of the hemp variety may be used to extract nonpsychoactive cannabidiol.
Marijuana	The dried mixture of cannabis leaves and flowers that are consumed in a variety of formulations (edible, inhaled, topical).
Phytocannabinoids	The more than 100 naturally occurring chemicals found in the cannabis plant. These compounds are capable of either directly interacting with the ECS, sharing chemical similarity with cannabinoids, or both.
Synthetic cannabinoids	Cannabinoids produced in a laboratory. Examples include dronabinol and nabilone, which are FDA-approved drugs for the treatment of cancer-related side effects.
Δ^9-Tetrahydrocannabinol (THC)	The most active pharmacologic cannabinoid derived from cannabis. The psychoactive properties are due to its agonist properties at the CB1 that produce behavioral, cognitive, and psychotropic effects.

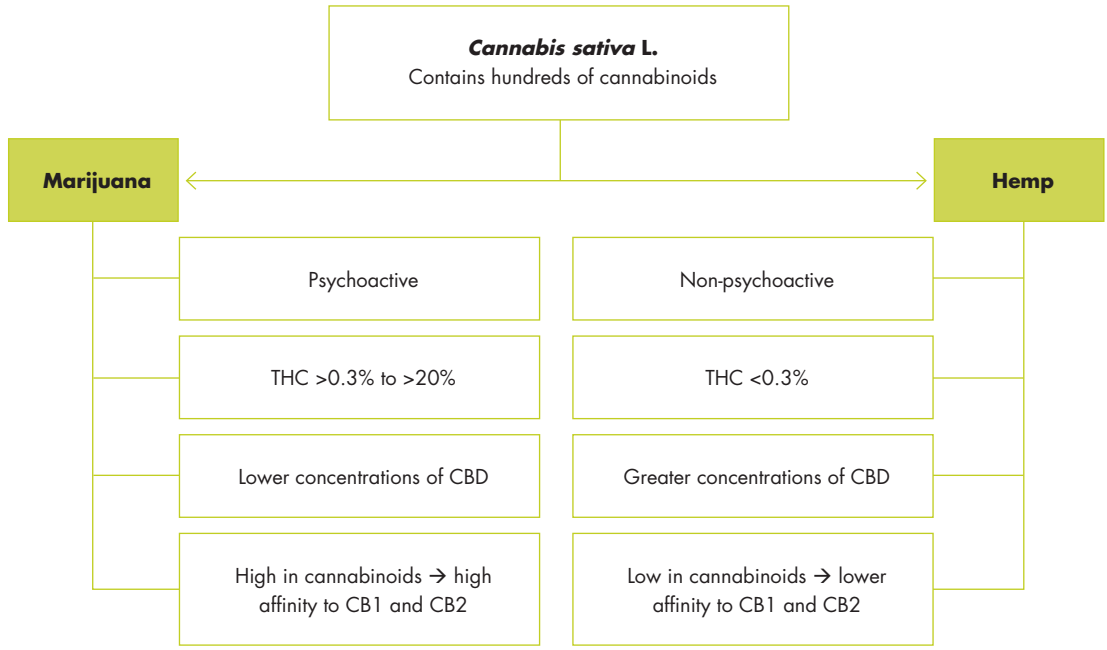

Figure 2. Difference between marijuana and hemp.

Substances Act, making it legal for sale.[4] However, CBD-containing products can only be marketed with therapeutic claims if approved by the FDA. Epidiolex, an oral solution of synthetic cannabidiol indicated for the treatment of certain types of seizure and supported by safety and efficacy studies, is the only FDA-approved product containing CBD. Still, many foods, supplements, and products containing CBD exist in the marketplace. Although all 50 states have some degree of legal restriction on CBD, these are lessening, so the use of CBD will likely continue to increase.

Even though people will try CBD for secondary complications of diabetes such as sleep disturbances and depression or diabetes distress, the literature is not sufficient at this time to make a recommendation as to the efficacy.

Safety and Efficacy in Brief

According to Natural Medicines, a well-respected database of medical information for supplements, herbals, and complementary therapies, CBD is rated as possibly safe when used orally. Some of the data supporting the safety claim are derived from studies using the prescription synthetic cannabidiol oil, Epidiolex. However, Natural Medicines maintains there is insufficient reliable information available to determine safety for CBD in other formulations, such as topical.[5]

Much like other dietary supplements and herbal medicines, CBD products are available commercially in mainstream stores and claim numerous health benefits with unfounded data to support such claims. Unfortunately, there is a scarcity of literature regarding CBD use. One small study saw an improvement in anxiety but not a sustained improvement in sleep in the general population.[6] Even though people will try CBD for secondary complications of diabetes such as sleep disturbances and depression or diabetes distress, the literature is not sufficient at this time to make a recommendation as to the efficacy.

Drug interactions cannot be overlooked. CBD is an inhibitor of cytochrome P450 and a substrate of cytochrome P450 enzymes and may have effects that either increase or decrease the levels of CBD. Common medications like omeprazole, valproate, and carisoprodol, to name just a few, may have major interactions.[6] Food may also interact with CBD, which may be a talking point for educators. Ingesting fat or fatty foods may increase the metabolism and increase plasma levels of CBD compared with taking CBD on an empty stomach or in a fasting state.[5]

Cardiovascular Effects of CBD

Specifically, in diabetes, persistent hyperglycemia triggers the expression of inflammatory molecules such as cytokines, chemokines, and cell adhesion molecules. This overexpression results in blood flow abnormalities and myocardial fibrosis,

which can present as diabetic cardiomyopathy.[7,8] Preclinical evidence suggests CBD has therapeutic potential in inflammatory conditions, and in vivo CBD treatment reduced endothelial and cardiac dysfunction in diabetic cardiomyopathy.[8]

Stanley and colleagues[7] explored the potential role of CBD in arterial vasorelaxation. Based on prior studies demonstrating endogenous, synthetic, and plant-derived cannabinoids causing vasorelaxation in animal arterial beds, this study researched the direct vascular effects of CBD in humans. By examining mesenteric tissue from 37 patients, CBD was added to viable arteries and compared to controls. The results demonstrated greater arterial vasorelaxation in the CBD-induced arteries compared to the control group.[7] Researchers believe the underlying mechanism of CBD on vasorelaxation may be attributed to its significant reduction in key pro-inflammatory pathways in human endothelial cells, likely due to the activation of the cannabinoid receptor 1 (CB1).[7] Therefore, the inflammatory features in diabetic cardiomyopathy could be reduced or prevented in the presence of CBD.

Despite this initial result, the impact of CBD-induced vasorelaxation was blunted in people with type 2 diabetes. Researchers believe possible receptor disruption and decreased expression of transient receptor potential vanilloid 1 (TRPV1) and calcitonin gene-related peptide receptor (CGRPR) in high-glucose or high-insulin environments may be the cause. Stanley and colleagues[7] also demonstrated a reduction of CBD-induced vasorelaxation in people on medications treating hypertension, dyslipidemia, and hyperglycemia, suggesting potential drug-drug interactions with CBD.The cardiovascular impact of CBD makes it a potential cardioprotective candidate. However, the limited sample size and variability in patients call for further investigation. At this time, the National Academies of Sciences, Engineering, and Medicine state the evidence is unclear whether and how cannabis is related to heart disease, stroke, and diabetes.[9]

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Metabolic Effects of CBD

The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous neurotransmitters that bind to cannabinoid receptors as well as cannabinoid receptor proteins. Two primary cannabinoid receptors have been identified, CB1 and CB2. CB1 receptors are found primarily in the brain and the central nervous system, whereas the CB2 receptors are found mostly in the peripheral nervous system, primarily in immune cells. CBD binds to both the CB1 and CB2 receptors with low affinity but is able to react with both receptors at low concentrations, evidenced by the ability to antagonize CB1/CB2 receptor agonists at low doses. CBD also behaves as a CB1 inverse agonist at low concentrations and may potentially act as an inverse agonist at CB2 receptors as well, meaning it confers a pharmacological response opposite to that of an agonist when it binds.[10] The resulting action of CBD binding to the CB1 or CB2 receptor is determined by where the receptor is located.

Borowska and colleagues[11] completed a review of the literature regarding the various effects of the ECS on the regulation of glucose homeostasis. Further evidence from both preclinical and human studies indicate that the overactivity of the ECS and CB1 are associated with metabolic obesity and associated insulin resistance, demonstrated by the fact that the pharmacological blocking of the CB1 receptor leads to reduction of appetite, weight loss, body fat reduction, and increased levels of insulin. It was also shown that antagonizing the CB1 receptor had a protective effect against the development of hyperinsulinemia and β-cell dysfunction.[11] There is literature describing the investigation of the potential benefit of CB1 receptor blockade in mitigating obesity and metabolic syndrome as well as its downstream complications such as type 2 diabetes.[12]

Experimental studies have showed that pharmacologically blocking the CB1 receptor reduces appetite and causes weight loss and body fat reduction. In vitro studies showed that stimulating CB1 receptors resulted in increased secretion of insulin, somatostatin, and glucagon, whereas stimulation of CB2 inhibits insulin secretion.[11] Various molecules antagonizing CB1 receptors peripherally have been identified and researched in genetically and diet-induced obese mice with positive benefit. Most recent in its development is TXX-522, a synthesized compound that exhibited minimal brain penetration while retaining high affinity and selectivity toward CB1, resulting in improved dyslipidemia, glucose homeostasis, and fat mass in obese mice without affecting their food intake.[13]

Rimonabant, a first-in-class synthetic CB1 receptor inverse agonist, is being studied as a therapeutic agent in limited clinical populations. Jourdan and colleagues[12] describe the endocannabinoid regulation of beta-cell function and state, "in overweight individuals with metabolic syndrome, rimonabant significantly reduced fasting blood glucose and glycated hemoglobin levels relative to placebo. In drug-naive patients with [type 2 diabetes], rimonabant treatment resulted in significant improvements in glycemic control, body weight, and metabolic profile and, in insulin-treated patients with type 2 diabetes, CB1 [receptor] blockade caused further improvements in glycemic control and cardiometabolic risk factors." Further evaluation of rimonabant demonstrated the prevention of hyperinsulinemia and β-cell dysfunction.[11] This drug was approved in Europe in June of 2006 by the European Medicines Agency under the brand name Accomplia for weight loss in individuals with obesity. However, it was withdrawn worldwide in 2008 due to serious psychiatric side effects, such as depression and suicide.

There appears to be a link between insulin resistance and the ECS, likely due to increased levels of endocannabinoids. A local increase in 2-arachidonoylglycerol (2-AG), an endocannabinoid, caused an increase in the activity of the CB1 receptors, which eventually led to a reduction of glucose consumption by skeletal muscles, transfer of free fatty acids from adipose tissue to the liver, and eventual tissue resistance to insulin action.[11]

A randomized control trial was conducted by Jadoon and colleagues[14] to examine the effects of CBD and Δ9-tetrahydrocannabivarin (THCV) in people with type 2 diabetes. In the trial, 62 participants with non-insulin-treated diabetes were randomized to 5 treatment arms: CBD (100 mg twice daily), THCV (5 mg twice daily), 1:1 ratio of CBD and THCV (5 mg/5 mg twice daily), 20:1 ratio of CBD and THCV (100 mg/5 mg twice daily), or matched placebo. The primary endpoint was a change in HDL-cholesterol concentrations from baseline. Secondary/tertiary endpoints included changes in glycemic control, lipid profile, insulin sensitivity, body weight, liver triglyceride content, adipose tissue distribution, appetite, markers of inflammation, markers of vascular function, gut hormones, circulating endocannabinoids, and adipokine concentrations. After 13 weeks, CBD alone did not produce any significant effects on primary and secondary efficacy outcomes. However, a reduction from baseline of circulating resistin concentrations and an increase in circulating gastric inhibitory polypeptide (GIP) were noted. Increased concentrations of resistin are associated with obesity and insulin resistance, whereas GIP is known to have insulinotropic and pancreatic β-cell–preserving properties.[14]

The preliminary data regarding the metabolic effects of CBD is not strong enough to impact decision-making in the management of diabetes. We will need to wait for more robust, human clinical trials before recommending CBD in reducing metabolic risk.

Analgesic Effects of CBD

Cannabinoids have a diverse range of effects on the central nervous system (CNS), mediated by

the activation of the CB1 and CB2 receptors by endogenous ligands, the endocannabinoids. The endogenous cannabinoid system, consisting of the CB1 and CB2 receptors and the endocannabinoids that innervate them, are present throughout the body and are thus linked to several pathological and therapeutic processes. CB2 receptors are highly associated with immune cells, microglia, and the peripheral nervous system, evidenced by agonists at these receptors having the ability to modulate inflammatory responses.[15] CB1 receptors are expressed at very high levels in the CNS.[16] Although it is not yet certain whether ongoing inflammation or inflammatory mediators are what maintain chronic neuropathic pain, it is clear that there is some sort of inflammatory component to neuropathic pain.

Although CBD has a very low affinity to both CB1 and CB2, it has been shown to inhibit the reuptake and degradation of endogenous cannabinoids, such as arachidonoylethanolamide (AEA) and 2-AG. This, along with its ability to scavenge reactive oxygen species, may be the mechanism attributable to CBD's neuroprotective and anti-inflammatory effects because the release of AEA and 2-AG occurs in damaged regions to modulate nociceptive response.[17,18]

Glia cells are pro-inflammatory, and their actions are involved in neuropathic hypersensitivity. The association of CB2 receptors with microglia likely attribute to the anti-inflammatory effects CB2 agonists had in preventing the development of neuropathic pain in diabetic rats.[15] Selective CB2 agonists modulate tactile allodynia in nerve injured rats and mice. A CB2 agonist was found to be of benefit in a model of chronic diabetes and diabetic peripheral neuropathy. CB2-mediated antinociception also occurs in inflammatory hyperalgesia.[11] A review by Gruden and colleagues[16] reinforces the antinociceptive effects of CB2 agonists mediated through inhibition of microglia-driven inflammation. In 2009, Selvarajah and colleagues[19] randomized 30 human participants with painful diabetic neuropathy to receive either placebo or Sativex, an extract of Δ9-tetrahydrocannabinol (THC) and cannabidiol. The primary outcome measure was change in mean daily pain scores, and secondary outcome measures included quality-of-life assessments. This trial failed to show any benefit. At baseline, patients with depression had greater pain scores, and this may have been a confounding factor in this trial.[19]

Experimental studies with CBD have shown that there is a decrease in the expression of CB1 cannabinoid receptors in diabetic neuropathy.[11] This insinuates a potential benefit of CB1 receptor agonists in the treatment and management of diabetic neuropathy, whereas previous studies with CB2 agonists have demonstrated its involvement in the development of antinociception. However, more robust, randomized clinical trials are needed to definitively support CBD use in people with diabetic neuropathy.

In the general population for people without diabetes, there is evidence that cannabinoids are effective analgesics in pain, including forms of acute pain, inflammatory pain, and neuropathic pain. The National Academies of Sciences, Engineering, and Medicine state that although the use of cannabis for the treatment of pain is supported by well-controlled clinical trials, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.[9] Many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

Ophthalmologic Effects of CBD

Diabetes-related retinopathy, a common complication of diabetes, is caused by damage to the blood vessels in the eye, mediated by oxidative stress and proinflammatory cytokines like tumor necrosis factor-α (TNF-α) and vascular endothelial growth factor (VEGF). Breakdown of the blood-retinal barrier is a clinical hallmark of early diabetic retinopathy.[20] There is currently conflicting evidence on the benefit of CBD use in diabetes-related retinopathy. Based on evidence from an animal model, El-Remessy and colleagues[20] report that CBD use has been shown to reduce vascular inflammation and have a protective role in diabetes-related retinopathy. El-Remessy found that treatment with CBD reduced reactive oxygen species formation and TNF-α and VEGF expression, which attenuated blood-retinal barrier breakdown and prevented 2 functional components of diabetes-related retinopathy, vascular permeability and neural cell death.[21] Gruden and colleagues believe that peripheral CB1 inhibition by restricted antagonists or inverse agonists may be a treatment option for diabetes-related retinopathy.[16] They cited evidence from El-Remessy et al[21] that showed CB1 receptor inhibition limited the vascular inflammation and cell death in a human retinal cell line exposed to high glucose, similar to Horvath and colleagues,[22] who demonstrated attenuated hyperglycemia-induced apoptosis in retinal pigment epithelial cells. The role of CB1 receptors in diabetes-related retinopathy needs further investigation in human participants. At this time, there is no evidence to support recommending CBD use for diabetes-related retinopathy.

The Role of the Diabetes Care and Education Specialist

The counseling approach to CBD use is similar to the use of dietary supplements or herbal medicines. It is not up to the DCES to endorse or condemn the use of CBD or cannabis products; rather, it is critical for us to obtain an accurate history of use in a nonjudgmental manner. Opening the door of communication using verbiage that neutralizes the environment invites honesty and eliminates personal bias. An example of initiating the conversation could be as follows: "CBD is widely available for use. What type of CBD products have you tried?" When the DCES uses open-ended questions, the person with diabetes is able to discuss his or her practices, personal beliefs, and experiences with CBD. This allows us to focus on the health and safety of the people with diabetes that we counsel. See Table 2 for discussion points regarding the pros and cons of cannabidiol use.

Table 2. Pros and Cons of Cannabidiol Use.

Pros	Cons
Three national organizations, the Association of Official Agricultural Chemists (AOAC), the American Herbal Pharmacopoeia (AHP), and U.S. Pharmacopeia (USP), set standards for validated, quality testing methods for CBD companies. Although this testing is optional, consumers should seek companies that utilize these standards.	The FDA does not regulate CBD products, so the quality of individual products varies. Labeling of strength and contents is not consistent.
Possibly effective for chronic pain. Additional clinical trials are needed.	Lack of scientific evidence in the management of diabetes, heart disease, and stroke
Widely available in retail stores and online.	Must screen for drug interactions. Possible drug interactions with other drugs metabolized by the cytochrome P450 system. Concentrated products further exacerbate the potential to interact.
Available in a variety of formulations (inhaled, edible, topical).	No long-term studies to determine safety.

It is important for the DCES to provide reliable, accurate information to patients. This information must come from reputable, unbiased sources. Sources to consider include the following:

- The Natural Medicines database is not supported by any particular interest group, organization, or drug company; however, it does require a subscription for access. Natural Medicines includes monographs on hundreds of foods, herbs, and supplements and countless conditions as well as tools such as a drug interaction checker, adverse effects checker, and pregnancy and lactation checker to name a few. Although there have been no specific documented antihyperglycemic drug interactions, interactions with classes of drugs such as antihypertensives, opioids, antiplatelets, proton pump inhibitors, antibiotics, and others may occur. For those unable to purchase a subscription, completing a literature search in PubMed or another medical database for information may be helpful.
- Cannabinoidclinical.com is a for-profit, company-sponsored website that includes extensive medical information, patient education, research data, specific state regulations, and federal and international regulatory information. The website is supported by Greenwich Biosciences, a drug company that has been researching cannabis since 1998 and received FDA approval for Epidiolex.[23]
- Accredited continuing education programs can also be helpful in finding reliable, accurate information about CBD.

Although there is a lack of robust scientific data to support CBD use in the management of diabetes, it is important for us not to discount the personal experiences and beliefs of the individual. We can be supportive in providing evidence-based education and strategies to assist in evaluating the quality and safety of CBD products. Because the FDA does not regulate CBD products, the quality and stability cannot be guaranteed.

Dosages of CBD are typically expressed in milligrams and vary widely between products and formulations. When evaluating CBD products, the package should state the concentration of the particular formulation (ie, mg per dose or mg/mL) and not simply state the strength or total amount of CBD in the entire product. For additional information on the quality of CBD, consumers can ask to look at the certificate of analysis (COA). The COA contains information on the testing of levels of CBD, THC, and other contaminants. Some products will contain a QR code on the label that includes the COA. However, manufacturers are not required to obtain a COA. It is recommended for consumers to ask a retailer or online manufacturer for the COA and if they do not have one, to consider obtaining CBD from a different source. Similar to verifying the quality of over-the-counter dietary supplements and herbal medicines by

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looking for the US Pharmacopeia (USP) logo on the product label, look to see whether a CBD company is using testing methods validated by any of these respected national standard-setting organizations: the Association of Official Agricultural Chemists (AOAC), the American Herbal Pharmacopoeia (AHP), or USP.

CBD products that make broad health claims or claims to treat, cure, or prevent medical conditions should be viewed with caution. The FDA has recently sent warning letters to several CBD companies that have made unsubstantiated claims. As a DCES, you should illicit the purpose or intent of use and provide evidence-based education and strategies to evaluate the safety of any CBD products a person with diabetes wants to use. CBD products vary in manufacturing processes; switching among brands or changing the type of formulation should be done with caution because the response could vary greatly.

Hemp-derived CBD products sold in retail stores and online come from different sources. It is important to know where the hemp is grown. In the United States, most hemp is grown in Colorado, Oregon, and Kentucky.[23] This is important because there are state and federal agricultural programs that test the hemp for levels of THC and illegal pesticides. Hemp that is grown overseas is not subject to state or federal testing. There may also be a number of terpenes found in CBD extracts and oils. The number and types of terpenes are related to the specific strain of cannabis. Terpenes contribute to the aroma and flavor of CBD products and may impart unpredictable and unknown pharmacological activity. Encourage people with diabetes to look at the label for the origin of the CBD and for terpenes such as linalool, pinene, myrcene, limonene, and caryophyllene.

Conclusion

The decision to try or use CBD should not be taken lightly. DCES are positioned to help people with diabetes weigh the risks and benefits of CBD use. We can discuss the available evidence, provide strategies to evaluate quality, assess drug interactions, and monitor safety. With the increased consumer use of CBD and cannabis products, we must be informed and open the door to communication using nonjudgmental and open-ended questions to help people with diabetes make informed choices about using CBD-containing products. ■

Ebony Isis Evans, PharmD; Jessica Hong, PharmD; Melissa Mattison, PharmD; and Kam Capoccia, PharmD, BCPS, CDCES, are with Western New England University College of Pharmacy and Health Sciences in Springfield, MA.

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