Journal of the American Psychiatric Nurses Association
2020, Vol. 26(5) 447–457

DOI: 10.1177/1078390320929410
journals.sagepub.com/home/jap
SAGE

Cannabidiol or CBD Oil: Help, Hope, and Hype for Psychiatric and Neurologic Conditions

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Abstract

OBJECTIVE: This article presents proven, promising, and potential therapeutic uses for cannabidiol (CBD) in the treatment of psychiatric and neurologic conditions and diseases. It presents popular, but scientifically unproven health and therapeutic claims of CBD supporting the beneficial homeostatic effects of the intrinsic or endogenous cannabinoid system. It includes a review of cannabinoid pharmacology; it compares properties and the legal status of CBD and THC (delta 9-tetrahydrocannabinol) as well as the hemp and marijuana varieties of *Cannabis*, and it reviews the historic 2018 U.S. Food and Drug Administration approval of Epidiolex, an oral solution of cannabidiol for two rare treatment-resistant childhood epilepsies, as the first *Cannabis*-derived drug. **METHOD:** We reviewed literature on cannabidiol, CBD, the endocannabinoid neuropharmacology system, and hemp and marijuana varieties of *Cannabis sativa*. **RESULTS:** The proven and promising medical uses and deficiencies of unproven health claims for CBD, legal implications for *Cannabis*-derived drugs, and comparisons of CBD and THC and hemp and marijuana are summarized objectively with pertinent references. **CONCLUSION:** CBD and CBD and THC combinations have potential to provide safe, effective therapy for several psychiatric and neurologic conditions and diseases. However, such achievement will require a uniform standard of CBD purity and strength, and corroboration from adequately large and rigorously controlled clinical research studies.

Keywords

cannabidiol, cannabis, CBD, endocannabinoids, hemp

Introduction

The spring 2019 national marketing surge of retail CBD oil products for multiple mental and neurologic health claims (e.g., anxiety, insomnia; pain) resulted from three coincidental factors. First, was the June 2018 U.S. Food and Drug Administration (FDA) approval of Epidiolex, an oral solution of CBD for two rare and devastating childhood epilepsies, as the first *Cannabis*-derived new drug, followed by its U.S. marketing in November (Drugs.com, 2018; GW Pharmaceuticals, 2018; U.S. FDA, 2018). Second, was passage of the Agricultural Improvement Act of 2018, or 2018 Farm Bill, which removed the *Cannabis sativa* variety of hemp from scheduling under the Controlled Substances Act (CSA), when the content of THC, delta 9-tetrahydrocannabinol, is less than 0.3% (Americans for Safe Access, 2019; Cadena, 2019a; Congressional Research Service, 2019; Petkovic, 2019; Tesséra Naturals, 2019; U.S. Senate, 2018). Third, is continuing federal deference to individual states passing their own *Cannabis* medical and recreational use laws, including individual states' regulation or nonregulation of retail CBD oil (Cadena, 2019a; Hararr, 2019; Nichols, 2019).

Two early sources that heralded the therapeutic efficacy of CBD for childhood seizures were a 2013 television documentary by Dr. Sanjay Gupta on CNN (Gupta, 2013), and an article by Sides and Johnson in the June 2015 issue of *National Geographic*, the cover of which states, "WEED: The New Science of Marijuana" beneath green *Cannabis* leaves. Dr. Gupta's September 2019 "Weed 5: the CBD craze" documentary concisely captures the overall hopes and hypes of the 2019 retail CBD boom (Gupta, 2019).

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Figure 1. Vial of cannabidiol (CBD) oil (left) and *Cannabis sativa* leaf (right)
Image retrieved from https://cbdoilreview.org/cbd-cannabidiol/what-is-cbd-oil.

This article reviews main scientific facts, hopes, and popular claims for CBD oil, which is illustrated in Figure 1 with a leaf of *Cannabis sativa* or marijuana. Because the 2018 FDA approval and U.S. marketing of Epidiolex is a contributor to the current retail sales boom of CBD oil products, Table 1 contains a condensation of the Epidiolex full prescribing information (Drugs.com, 2018; GW Pharmaceuticals, 2018; U.S. FDA, 2018). Both Epidiolex and oral nonprescription CBD products are solutions in vegetable oil, which provide approximately nine fat calories per milliliter (mL).

Comparison of CBD With THC, Delta 9-Tetrahydrocannibinol, and Hemp With Marijuana

In brief, CBD does and THC does not prevent seizures, and THC does and CBD does not cause a "high," euphoria or other psychoactivity and dependence. Table 2 lists some main differences and similarities of CBD and THC, which are the two primary phytocannabinoids of some 100 in *Cannabis sativa* (Atakan, 2012; Howlett & Abood, 2017; Lafaye et al., 2017; Perucca, 2017; Project CBD, 2019; Royal Society of Chemistry, 2019a and 2019b; Rudd, 2018). Despite *Cannabis* being the most common worldwide illicit drug consumed by ingestion and smoking in highly variable qualities and quantities (World Health Organization [WHO], 2016), there were no reports of death from *Cannabis* overdose in 2015 (United Nations Office on Drugs and Crime, 2017). That finding contrasts starkly with more than 130 U.S. deaths daily from opioids (National Institute on Drug Abuse, 2019), and it verifies the safety of CBD and THC specifically with regard to acute toxicity. This great safety difference results from lack of cannabinoid receptors and abundance of opioid receptors in the brainstem respiratory center.

Some main differences between the hemp and marijuana varieties of *Cannabis* are listed in Table 3 (Cadena, 2019b; Congressional Research Service, 2019; Rawls, 2019; Sanders, 2019). Although the U.S. Agricultural Improvement Act of 2018, or 2018 Farm Bill, made hemp with less than 0.3% dry weight THC nonscheduled under the CSA, that is, not regulated by the U.S. Drug Enforcement Administration marijuana remains Schedule I. As noted in Table 3 hemp has naturally large CBD and small THC, but that is *vice versa* for marijuana. Industrial hemp is typically grown outdoors in natural conditions to maximize crop yield, whereas marijuana is cultivated in enclosures under controlled environmental conditions to produce profusely budding unfertilized female plants with particular CBD and THC content (Cadena, 2019b; Sadock et al., 2017).

Hemp oil and CBD oil are not the same. Hemp oil is expressed from hemp seeds, and it does not contain CBD and THC. CBD oil is extracted from the buds, leaves, and stalks of either hemp or marijuana, and; thus, it always contains at least some small amount of THC (Natural Force, 2019; Petkovic, 2019; Tesséra Naturals, 2019). Hemp-derived commercial products of CBD may cause blood and urine drug screening failures, because of the THC content. The results of such screenings will depend primarily on (a) the specificity and sensitivity of the assay detection method and (b) the THC concentration in the specimen. A positive result is more likely to occur when the hemp source is not verified to conform to the less than 0.3% THC limit specified in the 2018 Farm Bill. Because of this possibility, some U.S. military branches, government agencies, and nongovernmental employers are prohibiting or warning members and employees from using CBD oil (Jaeger, 2019).

Besides efficacy in treating two rare pediatric-onset seizures, the FDA approval of Epidiolex also required proof of the absence of psychoactivity and dependence from the very small THC content (Table 1). Approximately 3 milligrams (mg) of THC must enter the bloodstream rapidly from smoking marijuana to cause a mild, brief high (Sadock et al., 2017). Using the Table 1 maximum THC content of 0.01% or 0.1 mg per mL, it would require 30 mL of Epidiolex to provide 3 mg of THC, and that 30 mL contains 3000 mg of CBD. When administered at

Table 1. Epitome of Epidiolex Full Prescribing Information.[a]

Product category	Description or designation
Description	100 milligrams (mg), per milliliter (mL), of not less than 98% pure cannabidiol, CBD, from *Cannabis sativa* in strawberry flavored sesame oil in 105 mL bottles
Delta 9-tetrahydrocannabinol, THC, limits[b]	Not more than 0.1% THC in CBD, and not more than 0.01% THC in the oral solution product.[c]
Indications (approved uses)	Patients 2 years and older with Dravet or Lennox-Gastaut syndrome, which is resistant to other antiepileptic drugs
Dosage	2.5-10 mg per kilogram, kg, of body mass two times daily
Pharmacology	Mechanism of anticonvulsant action is unknown, but is not via cannabinoid receptors
Pharmacokinetics	Enzymatic hepatic metabolism by CYP3A4 and CYP2C19; elimination half-life approximately 60 hours in healthy subjects; absorption increases four- to five-fold with high fat meals
Drug interactions[d]	CYP3A4 and CYP2C19 inhibitor substrates could increase CBD plasma concentrations, which could increase CBD adverse effects; CYP3A4 and CYP2C19 inducer substrates could result in subtherapeutic CBD plasma concentrations
Warnings and precautions and adverse effects	Elevated hepatic transaminases (AST, ALT); somnolence, fatigue, lethargy and tiredness; and decreased appetite and weight loss.[e] Suicidal thoughts.[f]
Dependence	No evidence of withdrawal.[g]
U.S. DEA Schedule	V

Note. CBD = cannabidiol; THC = delta 9-tetrahydrocannabinol; AST = aspartate transaminase; ALT = alanine transaminase; U.S. DEA = U.S. Drug Enforcement Administration.
[a]U.S. FDA, 2018. [b]Personal email communications June 13 and 20, 2019 from Medical Information Team of Greenwich Biosciences to coauthor. [c]This maximum 0.01% THC content in the oral solution is equivalent to 10 mg THC per 100 mL, and; thus, is much too low to elicit a marijuana "high," altered cognition, rewarding self-administration, and dependence when Epidiolex is administered in the largest approved dose. [d]Readers are referred to the Flockhart Table, http://medicine.iupui.edu/clinpharm/ddis/main-table/, for a sample of CYP3A4 and CYP2C19 inducer and inhibitor substrates. [e]The differences in rates of occurrence between Epidiolex and placebo for these three types of adverse effects were, respectively, 9% and 1%, 38% and 7%, and 18% and 3%. [f]Epidiolex may be expected to result in one case of suicidal thoughts per every 500 patients treated. Epilepsy and treatment with any antiepileptic drug are risk factors for suicidal thoughts. [g]Administration of 750 mg twice daily to adults, which is equivalent to the largest approved dosage of 20 mg/kg/day to a 75 kg (165 lb) person for 28 days, did not result in withdrawal symptoms on discontinuation.

Table 2. Comparative Properties of Cannabidiol (CBD) and Delta 9-Tetrahydrocannibinol (THC).[a]

Activity or property	CBD	THC
Psychoactive	No	Yes
Addicting	No	Yes
Overdose acute toxicity	No	No
Principle *Cannabis sativa* variety	Hemp	Marijuana
Research proven therapeutic use	Anticonvulsant[b]	Antiemetic[c]
Empirical chemical formula, molecular (mol) weight[d]	$C_{21}H_{30}O_2$, 314.5 g	$C_{21}H_{30}O_2$, 314.5 g

[a]Atakan, 2012; Perucca, 2017; Project CBD, 2019; Royal Society of Chemistry, 2019a and 2019b; Rudd, 2018. [b]Indication for Epidiolex. [c]Indication for Marinol (dronabinol), which is a synthetic chemical congener of THC, and anecdotal claims from consumers of marijuana. [d]The chemical structures may be viewed in the references in footnote a.

Table 3. Comparative Characteristics and Properties of the *Cannabis sativa* Varieties, Hemp and Marijuana.[a]

Characteristic or property	Hemp	Marijuana
Leaves[b]	Narrower and sparser at top	Broad with dense buds
Stalks[b]	Taller and slenderer	Shorter and bushier
Cannabidiol (CBD), content	up to 40%	very low[d]
Tetrahydrocannabinol (THC), content	Less than 0.3%[c,d]	up to 30%
Uses	Industrial products (e.g., food additive, paint, paper, rope)	Recreational 'high"; Food and Drug Administration nonapproved medicinal claims

[a]Cadena, 2019b; Rawls, 2019; Sanders, 2019. [b]Illustrations may be viewed in the references in footnote a. [c]As specified in the U.S. Agriculture Improvement Act of 2018 or 2018 Farm Bill. [d]The contents of THC and CBD can be varied by selective breeding or cultivars.

the largest approved 10 mg per kg of body weight dosage, 3000 mg of CBD correspond to a person weighing 300 kg or 660 lb. From such an improbably large dose, it is clear why Epidiolex lacks evidence of and potential for recreational use, psychoactive cognitive impairment, and dependence. Furthermore, the maximum 3 mg of THC in 30 mL of Epidiolex would be absorbed more slowly than would 3 mg inhaled from smoking marijuana. Similar calculations for the THC content in retail oral CBD oil products would require disclosure of THC content range or maximum by producers or vendors.

Pharmacology of Endocannabinoids and CBD

Just as there are endogenous opioid peptides, that is, enkephalins and endorphins, which act on μ, δ and κ receptors (Yakish & Wallace, 2011), so there are endogenous cannabinoids, endocannabinoids or eCBs, which act on cannabinoid receptors CB1 and CB2. The opioid receptors and CB1 and CB2 belong to a large family of guanine protein-coupled receptors, that wind through cell membranes like a spring with seven helical coils. The CB1 and CB2 GPCRs (guanine protein-coupled receptors) are located, respectively, mostly in the central nervous and immune systems and they mediate complex mental and physical interactions and effects. The two main eCBs are anandamide (*ananda* in Sanskrit means *bliss*) or *N*-arachidonoylethanolamine or AEA, and 2-arachidonyl glycerol or 2-AG (Atakan, 2012; Donvito et al., 2018; Howlett & Abood, 2017; Lu & Mackie, 2016; Pacher et al., 2006; Pertwee, 2009; Perucca, 2017; WHO; 2017; Zou & Kumar, 2018).

Both AEA and 2-AG are eicosanoid products of cell membrane arachidonic acid, which is best known for its inflammatory leukotriene, prostaglandin, and thromboxane metabolites (Samuelsson, 2000). AEA and 2-AG provide homeostatic protective effects, which include reducing stress response and neuropathic pain, and stabilizing appetite, mood, and memory. Deficiency of eCBs is associated with inflammation (e.g., fibromyalgia and irritable bowel syndrome), mental illness (e.g., depression, schizophrenia), and diseases of the nervous system (e.g., multiple sclerosis, Parkinson's disease; Atakan, 2012; Donvito et al., 2018; Lu & Mackie, 2016; Pacher et al., 2006; Pertwee, 2009; Perucca, 2017; WHO, 2017; Zou & Kumar, 2018).

Despite the close chemical similarity of CBD and THC (Atakan, 2012; Project CBD, 2019; Royal Society of Chemistry, 2019a and 2019b; Rudd, 2018), CBD is not an agonist at either the CB1 or CB2 receptor, but THC is an agonist at both. CBD is a negative allosteric modulator, which binds to a secondary site and alters the shape of the primary orthosteric site on CB1 receptors, and; thus, reduces THC binding thereto (Laprarie et al 2015). This negative allosteric modulator effect explains why CBD is a partial antagonist of CB1 receptors (Atakan, 2012; Bridgeman & Abazia, 2017; Donvito et al., 2018; Laprarie et al., 2015; Lu & Mackie, 2016; Pacher et al., 2006; Pertwee, 2009; Perucca, 2017; WHO, 2017), and suggests research on CBD as a potential treatment for or inhibitor of the adverse psychoactive effects of THC. The Epidiolex prescribing information (U.S. FDA, 2018) states that the anticonvulsant action of CBD does not result from interaction with cannabinoid receptors and is otherwise unknown.

Claims Are Many and Proofs Are Few for Health Benefits of CBD Oil

The claim "hemp-derived cannabinoids support the Endocannabinoid System" in Figure 2, which is an excerpt from a pharmacy's 2019 over-the-counter (OTC) or nonprescription CBD oil sales flyer, is typical for retail CBD products. Such unproven "support" could result from CBD inhibiting neuronal reuptake or metabolism of eCBs (WHO, 2017). It is not possible to determine predictable dose-response relationships from popular health claims for CBD oil products, because of the following deficiencies (Americans for Safe Access, 2019; Bonn-Miller et al., 2017; Bridgeman & Abazia, 2017; Harrar, 2019; Nichols, 2019; Pierre, 2019):

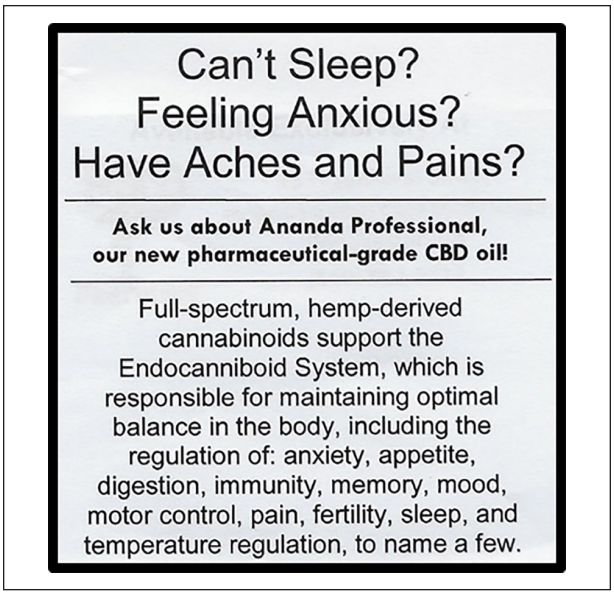

Figure 2. Excerpt from a pharmacy's 2019 over-the-counter cannabidiol (CBD) oil sales flyer. Ananda Professional identifies the product source.

1. Lack of corroborated rigorously controlled and statistically powerful clinical studies.
2. Studies use(d) CBD oil with variable or non-quantitatively assayed content of CBD and THC; thus, dosage accuracy is assumed from the labeled strength of CBD and effects are attributed to only CBD.
3. Analytical assays of CBD content have identified products containing much greater or less than (e.g., 10% or more) to almost no CBD compared to labeled strengths.
4. Dose measurement was or is performed and responses interpreted by consumers; not health care providers.

The 1 to 10 list below features some of the disease and health conditions for which appropriate clinical research studies could potentially lead to FDA approvals for safer therapy with new prescription CBD products than with existing drugs (American for Safe Access, 2019; Bergamaschi et al., 2011; Boggs et al., 2018; Bridgeman & Abazia, 2017; Crippa et al., 2011; Daley, 2019; Donvito et al., 2018; Elms et al., 2019; Fraser, 2009; Giuffrida et al., 2004; Grinspoon, 2018; Harrar, 2019; Hollander, 2019; Kubala, 2018; Lafaye et al., 2017; Leweke, 2012; Leweke et al., 2012; McGuire et al., 2018; Minichino et al., 2019; National Cancer Institute, 2019; Natural Force, 2019; Neumeister et al., 2013; Nichols, 2019; Petkovic, 2019; Pierre, 2019; Project CBD, 2019; Rawls, 2019; Sanders, 2019; Tesséra Naturals, 2019; Urits et al., 2019; Wong, 2019; Zuardi et al., 2017). For example, somnolence and appetite suppression, which are the most common dose-related adverse effects of Epidiolex (Table 1; U.S. FDA, 2018), could lead to approval of CBD to treat insomnia and cause healthy weight loss. To earn FDA approval for any use in this list would require rigorous controls on CBD content strength and purity, dosage regimens, and patient assessment as well as large quantities of subjects for statistically significant results.

1. Anxiety
2. Autism spectrum (The Hollander, 2019 study uses non-psychoactive cannabidivarin or CBDV, which differs from CBD by a 3-carbon instead of 5-carbon side chain on the dihydroxy, i.e., diol, benzene ring)
3. Tobacco dependency
4. Psychosis and schizophrenia
5. Posttraumatic stress disorder (PTSD)
6. Opioid addiction
7. Seizures and spasticity (Huntington's and Parkinson's diseases, and multiple sclerosis)
8. Chronic inflammatory and neuropathic pain
9. Insomnia
10. Appetite suppression and weight loss

CBD and Schizophrenia

Several studies have found higher concentrations of the endocannabinoid, anandamide, in blood and cerebrospinal fluid of nondrug-treated psychotic patients than in controls, suggesting that anandamide elevation in persons with schizophrenia may be a compensatory disease response. CBD may benefit persons with schizophrenia by partially inhibiting anandamide metabolism (Giuffrida et al., 2004; Leweke, 2012; Leweke et al., 2012; Minichino et al., 2019). One study of 43 persons with schizophrenia and 45 placebo control subjects found that 1000 mg of CBD daily in addition to prescribed antipsychotic drugs for 6 weeks resulted in mild improvement of positive psychotic symptoms and similar adverse events in the two groups (McGuire et al., 2018). Another placebo controlled randomized crossover study in 36 persons with schizophrenia treated with antipsychotic drugs plus 600 mg CBD daily for 6 weeks found no psychosis improvement, but increased sedation with CBD (Boggs et al., 2018). Those studies of few patients with variable designs and dosing, which used CBD as an adjunct to antipsychotic drug therapy justify the following opinion of CBD in the professional treatment of psychiatric diseases and mental conditions:

> In psychiatry, there have not yet been enough robust clinical studies to support broad therapeutic claims for CBD as a treatment for any mental disorder. Unreliability of product labeling [strength and purity] makes it difficult to predict the effects of CBD products that are not subject to FDA purity standards for medications or dietary supplements. It should

> now be possible to prescribe FDA-approved CBD [Epidiolex] for off-label [FDA unapproved] purposes, including the treatment of schizophrenia and other psychiatric disorders. There is not yet adequate evidence to support an FDA indication for CBD in schizophrenia. Additional studies of CBD for schizophrenia are ongoing. (Pierre, 2019, p. 19)

The conclusion, "There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework." in the more recent analysis of 83 studies by Black et al (2019), corroborates Dr. Pierre's foregoing opinion.

CBD and Anxiety

Sedation was the most common dose-related adverse effect reported in clinical trials leading to the 2018 FDA approval of Epidiolex (Table 1; U.S. FDA, 2018), which implies CBD use in treating anxiety disorders, and that preceded Epidiolex. In a study of 60 normal subjects of which three groups of 12 were treated with a CBD single dose of 100 mg, 300 mg, or 900 mg, only the 300 mg group members showed reduced anxiety when speaking before the other 48 subjects (Zuardi et al., 2017). Simulated public speaking is a standard stimulus to induce anxiety in persons to test the effectiveness of anxiolytic drugs (Bergamaschi et al., 2011). A trial in which 12 subjects received a single 600 mg CBD dose and 12 others received placebo, and a crossover trial in which 10 subjects received a single 400 mg CBD dose found reduced anxiety to public speaking in only the CBD-treated subjects (Bergamaschi et al., 2011; Crippa et al., 2011). The effectiveness of CBD was proposed to result from CBD inhibition of anandamide metabolism and neuronal reuptake (Crippa et al., 2011).

One noncontrolled study of CBD to treat posttraumatic stress disorder (PTSD) showed symptom improvement after 8 weeks in the 11 completing patients, but the trial included variable CBD doses administered by different methods (Elms et al., 2019). In a study comparing 25 untreated persons with PTSD to 12 persons with non-PTSD trauma and 13 nontrauma subjects, only the persons with PTSD had significantly lower anandamide plasma concentrations (Neumeister et al., 2013), which further suggests the involvement of the endocannabinoid system in, at least, the psychiatric conditions of anxiety, schizophrenia, and traumatic stress.

A noncontrolled study of 47 persons with PTSD treated with nabilone at up to 6 mg daily until improvement resulted in reduced frequency or absence of nightmares in 34 of them (Fraser, 2009). In the U.S., nabilone is marketed as Cesamet, a CSA Schedule II substance (U.S. FDA, 2006). Chemically, nabilone is more like THC with an intact pyran ring than CBD in which the oxygen atom of the opened pyran ring is reduced to an alcohol or -OH group, that is, one of two such groups on CBD in which the D for diol means di-alcohol. A study that began in March 2019 of 136 military veterans with PTSD is comparing the effects of prolonged exposure therapy with CDB to prolonged exposure with placebo. This randomized double blind crossover trial at the San Diego, CA Veterans Affairs Medical Center will extend to September 2023 (VA Office of Research and Development, 2019).

CBD Legal Regulation and Quality Standards

Federal deference to individual states passing their own *Cannabis* medical and recreational use laws (Bridgeman & Abazia, 2017; Fiorillo, 2019; Harrar, 2019; United Nations Office on Drugs and Crime, 2017), the 2018 Farm Bill hemp with less than 0.3% THC exemption from the CSA (Congressional Research Service, 2019; U.S. Senate, 2018), and nonregulation of hemp-derived retail CBD products compared with prescription Epidiolex are confusing and appear contradictory (Cadena, 2019a; Fiorillo, 2019; Harrar, 2019; Nichols, 2019). Individual states may prohibit sale of CBD derived from hemp that meets the 2018 Farm Bill THC requirement for CSA exemption (Cadena, 2019a; Fiorillo, 2019; Hudak, 2018).

Because *Cannabis*-derived CBD is an active pharmaceutical ingredient in an approved product, the addition of an approved drug, that is, CBD, into food products or as a dietary supplement is prohibited under FDA rules (U.S. FDA, 2019). Retail CBD oil products labeling and promotion cannot claim "use in the diagnosis, cure, mitigation, treatment, or prevention of disease," because those terms define "drug" in the 1938 U.S. Food, Drug and Cosmetic Act (U.S. Code, 2018).

On its June 25, 2018 FDA approval, Epidiolex was assigned to CSA Schedule I by the U.S. Drug Enforcement Administration. On September 28, that was reduced to Schedule V by a regulation stating, "Specifically, this order places FDA-approved drugs that contain CBD derived from cannabis and no more than 0.1 percent tetrahydrocannabinols in Schedule V" (U.S. Drug Enforcement Administration, 2018).

Epidiolex is the only current source of CBD with a federally ensured standard of CBD drug identity, THC content limit, and strength and purity plus predictable therapeutic efficacy from a specific dosage range. It would benefit consumers, health care providers, researchers, and vendors to have a CBD oil national standard of identity, strength, purity, and THC limit. Such standard could be analogous, for example, to the U.S. Pharmacopeia, USP, monograph for Digoxin obtained from *Digitalis lanata*, which specifies a digoxin-specific chemical assay range of 95.0% to 101.0%. It also limits two closely similar cardiac glycosides to 0.5% each and total impurities to 3.5% (U.S. Pharmacopeial Convention, 2019). The categories of purity standards for Digoxin, USP are notably similar to

those for CBD in Epidiolex (Table 1). Monographs for USP articles, that is, specific drug substances and their dosage forms, and dietary supplements are enforceable by FDA and U.S. courts under the U.S 1906 Pure Food and Drug Act, which named the nongovernmental USP as an official compendium.

Marketing and Medical Prospects

Retail sales of hemp-derived CBD oil products have been predicted to increase from about $350 million in 2019 to $600 million in 2022, or an average increase of $83 million per year (Sanders, 2019). Another source predicts an increase for all CBD consumer products; not just CBD oil, from a 2018 high of $2 billion to $16 billion is 2025, or an annual $2 billion increase (Dorbian, 2019). Either of those estimates is a lot of money for products that lack federal standards for CBD identity and strength, limits on THC and other chemical and microbial contaminants, and assurance of efficacy.

On May 31, 2019, the FDA hosted a public hearing titled, "Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds" (Kaplan, 2019; U.S. FDA, 2019; Wan, 2019). Undoubtedly, that hearing was a sequel to FDA approval of Epidiolex 11 months earlier. The Epidiolex manufacturer, GW Pharmaceuticals, has non-U.S. approval of Sativex in multiple countries to treat muscle spasticity and neuropathic pain caused by multiple sclerosis, and neuropathic pain from cancer "during the highest tolerated dose of strong opioid therapy . . ." and is seeking use of Sativex for "schizophrenia and other neurological conditions" (GW Pharmaceuticals, 2019, GW Pharma, Ltd., 2015; Urits et al., 2019). In the U.S., Sativex is investigational under the name, Nabiximols. Sativex is an oral or buccal spray that contains THC 2.7 mg and CBD 2.5 mg in each 100 microliters (μL), or 0.1 mL of spray actuation. GW is also testing Sativex to treat agitation and aggression in patients with Alzheimer's disease (Jones, 2019).

The first of its kind FDA hearing on Cannabis-Derived Compounds signals hope for possible future *Cannabis* formulations of CBD or CBD and THC combinations that may contain greater than 0.1% THC. Perhaps such products when proven safe and effective in rigorously controlled clinical trials could lead to their being reassigned from CSA Schedule I to II.

Conclusion

The 2018 debut of Epidiolex created prospects for more new prescription *Cannabis* therapies and their appropriate regulation. As this nascent CBD era evolves, a three-part blend of new FDA approvals, information from off-label uses of approved products, and quality improvement from competition between hemp-derived retail products will gradually, but incompletely, distinguish objective evidence, or help, from subjective claims, or hype, for the effectiveness of CBD.

In June 2019, there appeared a news headline questioning the possible first U.S. death from a THC or *Cannabis* overdose (Paton, 2019). However, on studying the report it appears the victim died not from THC per se, but from vaping THC or *Cannabis* oil, which may have premiered the e-cigarette severe lung damage epidemic that emerged nationwide in August 2019 (CDC Health Alert Network, 2019). *Cannabis* overdose acute toxicity is essentially nonexistent despite its enormous daily consumption by millions of U.S. and worldwide users (WHO, 2016). Compared with an estimated 130 deaths daily in part from some CSA Schedule II FDA approved opioids (National Institute on Drug Abuse, 2019), that is a strong argument for the relative safety of *Cannabis*, that is, CBD and THC, from acute overdose. A 2017 survey found that 46% of 2,776 patients reported using medical *Cannabis* instead of their prescribed opioids, anxiolytics, and antidepressants (Corroon et al., 2017). It is compelling; therefore, to wonder how many thousands of deaths and injuries could be and have been prevented by the availability of FDA approved *Cannabis*-derived drugs that are effective in treating, for example, neuropathic pain, phobic anxiety, traumatic stress, and chronic insomnia much more safely than CNS depressant opioids, anxiolytics, and sedative hypnotic drugs.

Appendix

Definitions of Abbreviations and Acronyms.

Abbreviation or acronym	Definition
APA	American Psychological Association
CBD	Cannabidiol
CB1	cannabinoid receptors predominantly in the central nervous system
CB2	cannabinoid receptors predominantly in the peripheral immune system
CNS	central nervous system
CSA	U.S. Controlled Substances Act (1970)
DEA	U.S. Drug Enforcement Administration
eCBs	endogenous (natural) cannabinoids[a]
FDA	U.S. Food and Drug Administration
GPCRs	guanine protein-coupled receptors
MS	multiple sclerosis
OTC	over-the-counter or nonprescription
PE	prolonged exposure therapy[b]
PTSD	posttraumatic stress disorder
THC	tetrahydrocannabinol, delta 9-tetrahydrocannabinol
VA	U.S. Department of Veterans Affairs
WHO	World Health Organization

[a]Metabolites of dietary arachidonic acid and arachidonic acid resulting from metabolism of dietary omega-6 or ω-6, fatty acids. [b]American Psychological Association (2017).

Acknowledgments

This article was adapted from Dr. Marian Newton's podium presentation, *Therapeutic Marijuana: Spotlight on CBD Oil*, presented in Concurrent Session 30 at the International Society of Psychiatric-Mental Health Nurses (ISPN) Annual Conference in Charlotte, NC on June 1, 2019.

Author Roles

MN conceived the idea for this article, began its literature research, and wrote the initial draft. DWN extended the literature research, organized the paper in sections, elaborated the text, and created the tables and figures. Both MN and DWN reviewed and approved all manuscript content before submitting it for publication.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Nursing Continuing Professional Development

Disclosures: The authors and planners have no conflict of interest to disclose. Off-label medication use will not be discussed.

Target Audience: APRN

Learning Outcomes:

Upon completion of this article, the participant will be able to:

1. Identify the difference between the therapeutic effects of cannabidiol (CBD) that have been proven from controlled clinical research studies and those that derive from anecdotes, uncontrolled studies and proprietary promotional claims.
2. Identify specific pharmacologic agonists and receptors in the endocannabinoid system.
3. Identify the differences in pharmacologic effects between cannabidiol (CBD) and tetrahydrocannibinol (THC).
4. Identify psychiatric and neurologic conditions for which cannabidiol (CBD) is under investigation in controlled clinical studies for potential new approved therapeutic uses.

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