

Clinicians' Guide to Cannabidiol and Hemp Oils

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Abstract

Cannabidiol (CBD) oils are low tetrahydrocannabinol products derived from *Cannabis sativa* that have become very popular over the past few years. Patients report relief for a variety of conditions, particularly pain, without the intoxicating adverse effects of medical marijuana. In June 2018, the first CBD-based drug, Epidiolex, was approved by the US Food and Drug Administration for treatment of rare, severe epilepsy, further putting the spotlight on CBD and hemp oils. There is a growing body of preclinical and clinical evidence to support use of CBD oils for many conditions, suggesting its potential role as another option for treating challenging chronic pain or opioid addiction. Care must be taken when directing patients toward CBD products because there is little regulation, and studies have found inaccurate labeling of CBD and tetrahydrocannabinol quantities. This article provides an overview of the scientific work on cannabinoids, CBD, and hemp oil and the distinction between marijuana, hemp, and the different components of CBD and hemp oil products. We summarize the current legal status of CBD and hemp oils in the United States and provide a guide to identifying higher-quality products so that clinicians can advise their patients on the safest and most evidence-based formulations. This review is based on a PubMed search using the terms *CBD*, *cannabidiol*, *hemp oil*, and *medical marijuana*. Articles were screened for relevance, and those with the most up-to-date information were selected for inclusion.

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One of the biggest challenges facing health care today is combatting opioid abuse, with medical and nonmedical overuse of opioids exacting a huge toll on society in recent years.¹ Although there has been a larger focus on reducing opioid prescriptions and preventing nonmedical use of opioids, there is an increasing interest in finding more treatment options for patients in pain,² and the diverse field of integrative medicine has been finding an increasing role in this area.^{3,4} One promising area has been use of the plant *Cannabis sativa*, both in medical marijuana as well as hemp and cannabidiol (CBD) oils, with some evidence that access to medical marijuana is correlated with a decrease in opioid use, although there has been controversy about the risks and benefits of encouraging poorly regulated medical use of a known substance of abuse.^{5,6} Cannabidiol and hemp oils have become especially popular

because of their low tetrahydrocannabinol (THC) levels, resulting in attributed medical benefits without the “high” of marijuana.⁷ However, clinicians have concerns about whether these treatment options are legal, safe, and effective and are largely unfamiliar with these products.^{8,9} Therefore, we provide an overview of the scientific work on cannabinoids, CBD, and hemp oil and clarify the distinction between marijuana, hemp, and the different components of CBD and hemp oil products so that clinicians may be able to direct their patients to the safest and most evidence-based products.

Cannabis sativa has long been utilized by human populations across the world for its therapeutic properties, from pain relief to treatment of epilepsy.¹⁰ Marijuana and hemp are 2 strains of the same plant, *C sativa*, with marijuana being cultivated over the years for its THC content and hemp for its myriad other uses including paper, clothing,

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ARTICLE HIGHLIGHTS

- Cannabidiol (CBD) is a nonintoxicating compound extracted from *Cannabis sativa* plants that has gained popularity for medical uses ranging from epilepsy to pain control and addiction treatment because of its differing mechanism of action from marijuana and its safety profile.
- Although important preclinical and pilot human studies have suggested a potential role for CBD in numerous clinical situations, thorough clinical studies have only been performed on intractable epilepsy syndromes for which Epidiolex, a CBD drug, was approved by the US Food and Drug Administration for use.
- The legal landscape of CBD remains complex because of differing state and federal laws giving access to medical hemp and marijuana products.
- The CBD and hemp oil product market remains a concerning one because of noted variability in CBD and tetrahydrocannabinol levels in products, as well as lack of regulation in production and distribution.
- Although CBD and hemp oils remain an unproven therapeutic option, physicians should remain open to the possible future role these products may play in the management of a variety of difficult to treat diseases, in particular pain and addiction treatment in the context of the opioid crisis.

and food.¹¹ Despite considerable sociopolitical obstacles, scientific understanding of *C sativa* has progressed substantially in the past 30 years as the many active ingredients of the *C sativa* strains were isolated and major discoveries were made regarding the body's own *endogenous* cannabinoids and the endocannabinoid system (ECS).¹²

THE ENDOCANNABINOID SYSTEM

It is now known that the ECS is globally involved in maintaining homeostasis in the body, connecting all of the body's organs and systems.¹³ The ECS has been implicated in a variety of disease states and important regulatory functions, from chronic inflammatory conditions and regulation of immune homeostasis in the gut to anxiety and migraines.¹⁴⁻¹⁷ Although the body has its own endogenous cannabinoids, most notably anandamide and 2-arachidonylglycerol,

plant-derived cannabinoids (phytocannabinoids) have been researched as potential therapeutic options in a variety of areas because of their modulation of the ECS.¹⁸⁻²⁰ Figure 1 summarizes the basic molecular biology of the ECS, as well as some of the molecular effects of phytocannabinoids.

PHYTOCANNABINOIDS

Although the body contains its extensive ECS that works through endogenous cannabinoids, many plant-derived cannabinoids have been discovered that act on the ECS as well. The first ones were discovered in the context of *C sativa* research, with more than 80 phytocannabinoid compounds being discovered in the marijuana plant alone.²¹ Phytocannabinoids and other important *C sativa* components such as terpenoids have now also been documented in a variety of other plants and foodstuffs, such as carrots, cloves, black pepper, ginseng, and *Echinacea*.^{22,23} The most notable and well-understood phytocannabinoids are THC and CBD, the most common phytocannabinoids in marijuana and hemp strains, respectively.²¹ Tetrahydrocannabinol has been noted to work mostly through the CB1 receptor as an agonist, leading to its well-known intoxicating effects.²⁴ Cannabidiol, on the other hand, has been found to work through a variety of complex pharmacological actions, such as inhibition of endocannabinoid reuptake, transient receptor potential vanilloid 1 and G protein-coupled receptor 55 activation, and increasing the activity of serotonin 5-HT_{1A} receptors.²⁵⁻²⁸ Cannabidiol's minimal agonism of the CB receptors likely accounts for its negligible psychoactivity when compared with THC.²⁹

Figure 2 summarizes the different endocannabinoids, phytocannabinoids, and synthetic cannabinoids. The synthetic cannabinoids are laboratory-derived THC preparations that have been US Food and Drug Administration (FDA) approved for various usages, as well as nabiximols, which is a nonsynthetic 1:1 THC and CBD preparation that has been approved in the United Kingdom for pain and spasticity related to multiple sclerosis. Nabiximols is not approved by the FDA.³⁰ Notably, there are

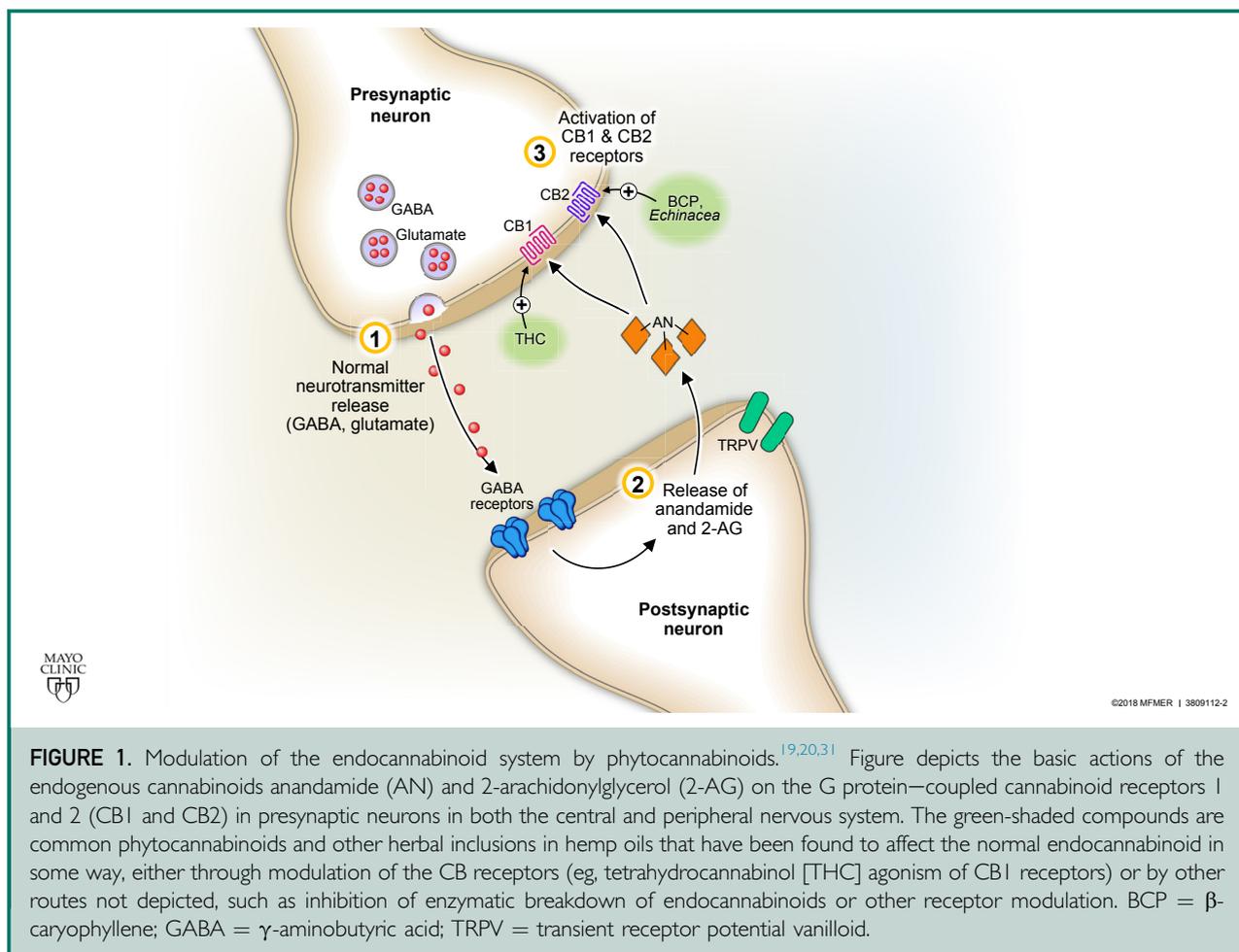


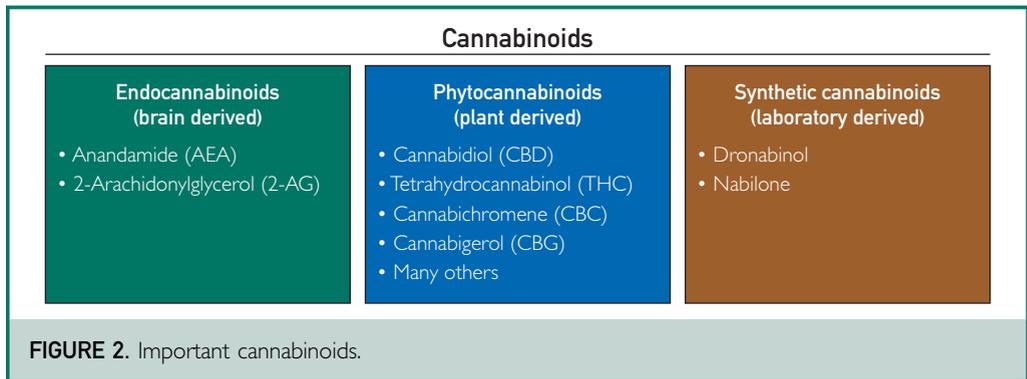
FIGURE 1. Modulation of the endocannabinoid system by phytocannabinoids.^{19,20,31} Figure depicts the basic actions of the endogenous cannabinoids anandamide (AN) and 2-arachidonylglycerol (2-AG) on the G protein–coupled cannabinoid receptors 1 and 2 (CB1 and CB2) in presynaptic neurons in both the central and peripheral nervous system. The green-shaded compounds are common phytocannabinoids and other herbal inclusions in hemp oils that have been found to affect the normal endocannabinoid in some way, either through modulation of the CB receptors (eg, tetrahydrocannabinol [THC] agonism of CB1 receptors) or by other routes not depicted, such as inhibition of enzymatic breakdown of endocannabinoids or other receptor modulation. BCP = β -caryophyllene; GABA = γ -aminobutyric acid; TRPV = transient receptor potential vanilloid.

many other components in hemp extracts, and many products boast of being “full-spectrum” in retaining these other components, each with their own attributed effects that are theorized to synergize through what is termed the *entourage effect*—essentially that the whole plant is greater than the sum of its parts.²²

LEGAL AND REGULATORY CONSIDERATIONS

Since the 1970 Controlled Substances Act outlawed growing and selling of both hemp and marijuana, hemp continued to remain illegal to grow in the United States until passage of the 2014 Agricultural Act, which distinguished between hemp and marijuana legality for the first time. The law defined “industrial hemp” as “*Cannabis sativa L.*

and any part of such plant, whether growing or not, with a delta-9-THC content of no more than 0.3% on dry weight basis,” and this allowed industrial hemp to be grown for “research purposes.”³² However, it is technically illegal to introduce any supplement or food containing CBD into interstate commerce (as would be the case when ordering online), so most products are imported from Europe and then processed and distributed in the United States.³³ Additionally, 3 states—Idaho, South Dakota, and Nebraska—still do not have any *C sativa* access laws, and CBD and hemp oils are therefore illegal to sell or consume there. For all other states, CBD and hemp oils are legal as long as the THC content is below the 0.3% threshold. It is also important to note that patients using CBD products may test



positive for marijuana on drug screening, as was noted in the Epidiolex drug trials.³⁴

Figure 3 lists the current laws regarding CBD oils and medical marijuana in the United States available from the National Conference of State Legislatures website, which has helpful information on medical marijuana and CBD laws on a state-by-state basis.³⁵ Importantly, although many states have allowed use of medical marijuana, physicians may only “certify” or “recommend” that their patients may use medical marijuana for a certain condition and cannot

issue a prescription for specific cannabis products because they are not approved by the FDA or Drug Enforcement Administration (DEA).³³ Notably, because CBD and hemp oils do not contain intoxicating amounts of THC, they do not require a certification or recommendation from a physician to be purchased and consumed. However, there have been numerous warning letters sent by the FDA to companies about inconsistent ingredients in their products, with many products containing higher amounts of THC than legally allowed while

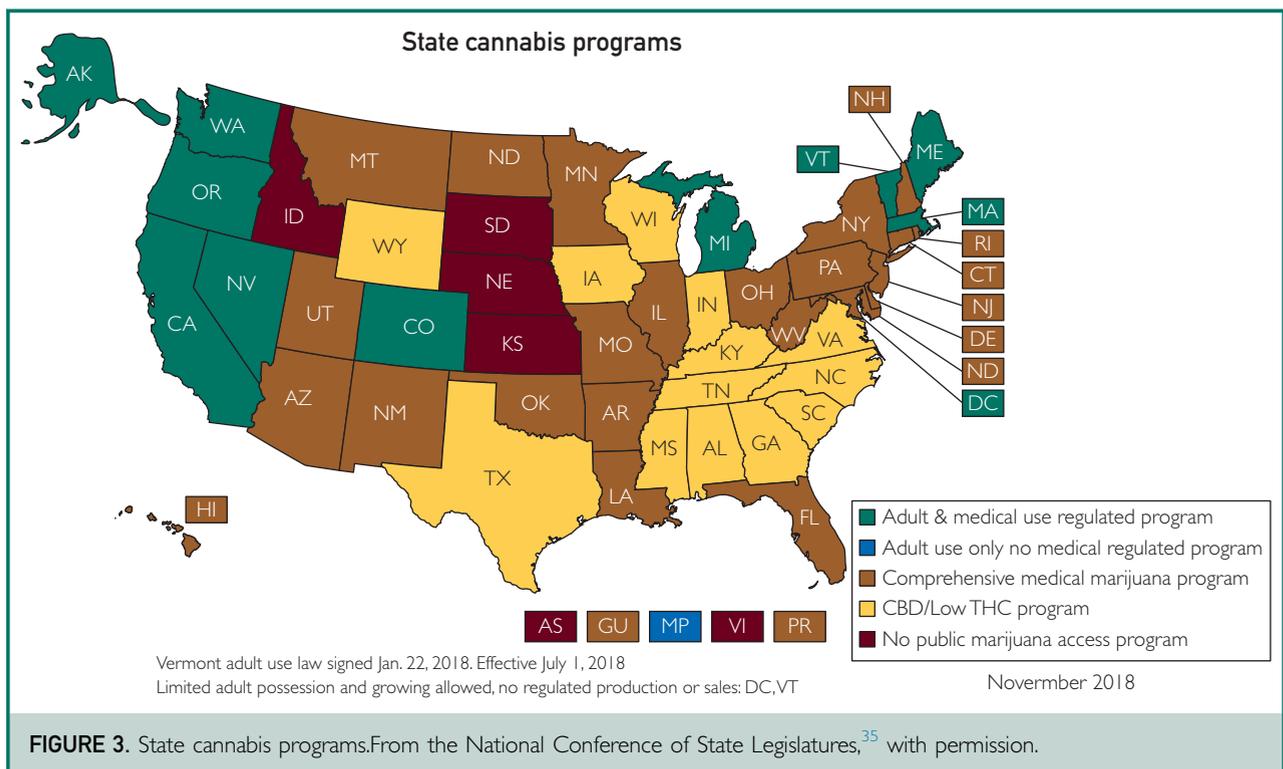


TABLE 1. Hemp Seed, CBD, and Cannabis Oils

Variable	Hemp seed oils ⁴⁰	Hemp/CBD oils ²²	Cannabis oils ^{22,41}
Part of plant extracted	Seeds	Flowers and leaves of hemp plant	Flowers and leaves of marijuana plant
Main components	Omega-6 and omega-3 fatty acids, γ -linolenic acid, nutritious antioxidants	Mostly CBD and BCP with other smaller-quantity phytocannabinoids and terpenoids	Mostly THC with some CBD and other phytocannabinoids and terpenoids
THC levels	None	<0.3% Dry weight	>0.3% Dry weight (often very high amounts such as 80%)
CBD levels	Little to none	More than average cannabis plants (12%-18% CBD, often higher due to postextraction enrichment)	Lower levels (10%-15%)
Uses	Nutritional supplement, other uses of hemp such as clothing and fibers	Medicinal uses of CBD and full-spectrum hemp oils	Medicinal uses of THC

BCP = β -caryophyllene; CBD = cannabidiol; THC = tetrahydrocannabinol.

also containing less CBD than labeled.³⁶ Additionally, now that CBD is the subject of an investigational new drug authorization for Epidiolex, it is no longer considered legal by the FDA to use it in dietary supplement products and foodstuffs.³⁷

Finally, although nearly all states have passed some sort of *C sativa* access laws, the federal government and the DEA still consider CBD and hemp oils to be schedule I substances. Although the DEA did reduce Epidiolex, the pure CBD drug recently approved by the FDA for intractable epilepsy conditions, Dravet syndrome, and Lennox-Gastaut syndrome, to a schedule V classification, they still remain “concerned about the proliferation and illegal marketing of unapproved CBD-containing products with unproven medical claims.”³⁸

CBD AND HEMP OILS

Definitions

Because of variation in the legislation regarding the *C sativa* plant as well as the tremendous increase of new products being marketed, there has been an accompanying lack of clarity about the different types of hemp and CBD oils. Depending on what part of the plant is being extracted, there will be different components present. The phytocannabinoids such as THC and CBD, as well as terpenoids like β -caryophyllene

(BCP) and limonene, collect in the flowers and leaves.³⁹ Conversely, the seeds of the *C sativa* contain little to no phytocannabinoids, instead being rich in omega-6 and omega-3 essential fatty acids, substantial amounts of γ -linolenic acid, and other nutritious antioxidants.⁴⁰ Additionally, there are “cannabis oil” products as well, which are oils derived from the marijuana plant that have high levels of THC.⁴¹ Table 1 summarizes these differences.

Products may be marketed as “full-spectrum” formulas, dietary supplements, hemp oils, or CBD-enriched products, coming in the forms of oils, balms, sprays, capsules, soft gels, oral applicators, foodstuffs such as gummy bears, and even chew toys for pets. The most popular products contain a diverse array of phytocannabinoids from *C sativa* as well as other phytocannabinoids and terpenoids derived from other plants and foodstuffs such as clove, hops, ashwagandha, and turmeric. These products are being marketed for a variety of uses such as sleep aids, pain relief, or stress reduction. Because of this inconsistency in ingredient choices, as well as amounts and method of administration, it is difficult to know which ingredient accounts for a specific symptom relief. Cannabidiol is the most well-studied phytocannabinoid and will be the primary focus in this article because it is also the main ingredient in most products. Table 2

TABLE 2. Common Components and Added Ingredients in CBD and Hemp Oil Products

Ingredient	Chemical classification	Approximate concentration in hemp ³⁹	Other sources	Mechanism of action	Potential therapeutic actions
Cannabidiol	Phytocannabinoid	Up to 40%	None known	Anandamide uptake inhibitor; TRPV1 receptor activation, GPR55 receptor activation, 5-HT _{1A} activation ^{27,28,31}	Antiepileptic, antinociceptive, anti-inflammatory, anxiolytic, antidepressive, addiction management/treatment, inflammatory dermatologic conditions, neuroprotective, others ⁴²⁻⁶²
Tetrahydrocannabinol	Phytocannabinoid	<0.3%	None known	Binds to CB1 receptors ³¹	Antiemetic, antinociceptive, others ³¹
β-Caryophyllene	Sesquiterpenoid	Less than 1%	Black pepper, clove, rosemary, hops	Binds to CB2 receptors ⁶³	Anxiolytic, anti-nociceptive ⁶⁴⁻⁶⁷
Limonene	Terpenoid	Less than 1%	Citrus fruits, rosemary	Induction of glutathione	Antioxidant, antitumor activity ⁶⁸
Cannabichromene	Phytocannabinoid	Varies considerably with strain	None known	Anandamide uptake inhibitor ⁶⁹	Antinociceptive ⁷⁰
Cannabigerol	Phytocannabinoid	Varies considerably with strain	None known	Anandamide uptake inhibitor ⁷⁰	Anti-inflammatory, neuroprotective ^{71,72}
<i>Echinacea</i>	Alkylamides	None	<i>Zanthoxylum</i> (Sichuan pepper)	Binds to CB2 receptors ⁷³⁻⁷⁵	Anti-inflammatory, antioxidant, antimicrobial ⁷⁵⁻⁷⁸
<i>Boswellia</i>	Triterpenes	None	Also known as frankincense	Inhibition of prostaglandin E ₂ synthase ⁷⁹	Anti-inflammatory ⁷⁹
Tumeric	Curcuminoids (eg, diferuloylmethane, demethoxycurcumin)	None	None known	May bind to CB1 receptors ⁸⁰	Unclear in preclinical, purported antinociceptive and anti-inflammatory properties ⁸¹
Ashwaganda	Steroidal alkaloids and lactones	None	Also known as <i>Withania somnifera</i>	Possible mimicry of GABA ⁸²	Stress reduction, anxiolytic, immuno-modulatory ⁸²
Magnolia	Polyphenols	None	Also known as magnolia bark	Binds to CB2 receptors ⁸³	Antioxidant, anti-inflammatory ⁸⁴

GABA = γ-aminobutyric acid; GPR55 = G protein-coupled receptor 55; TRPV1 = transient receptor potential vanilloid 1.

is provided for reference on the most common ingredients included in CBD and hemp oils when looking at potential products.

Potential Therapeutic Actions

The chief ingredients of hemp oils are phytocannabinoids such as CBD and terpenoids such as BCP and limonene. However, there is a paucity of clinical research conducted on these important components because most research focuses on THC and CB1 receptors (the primary target of THC).²⁴ Much less data are available on CBD, which works via a variety of complex mechanisms noted previously,³¹ and BCP, which works through the less-understood CB2 receptors.⁶⁴ According to a recent systematic review on the medical uses of cannabinoids, there was moderate-quality evidence to support the use of cannabinoids for chronic pain and spasticity, and low-quality evidence to support use for nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome.³⁰ However, it is important to realize that most of the randomized controlled trials examined in this systematic review for each condition were of the 3 prescribable THC drugs dronabinol, nabilone, and nabiximols; only 4 trials were found for CBD, and none for any of the other phytocannabinoids or terpenoids present in *C sativa* oils,³⁰ again demonstrating the lack of solid scientific research conducted on them.

In June 2018, the FDA approved Epidiolex, a purified CBD oral solution that was found to provide major reductions in total seizure frequency vs placebo for patients with Dravet and Lennox-Gastaut syndromes. The research on these conditions is the most thorough clinical research that has been performed on CBD and for now should be relied on for understanding CBD's safety and adverse effects, which will be discussed subsequently in this article. Although the use of CBD has been theorized for a variety of other conditions from migraines and inflammatory conditions to depression and anxiety, only preclinical and pilot studies have been

performed for any of these uses, and therefore there is little guidance for physicians if their patient is interested in trying CBD or hemp oils for these conditions.

As for CBD and hemp oils' potential for use in the treatment of chronic pain, in the most recent review on the topic in 2018, Donvito et al⁴² wrote that "an overwhelming body of convincing preclinical evidence indicates that cannabinoids produce antinociceptive effects in inflammatory and neuropathic rodent pain models." Additionally, it has been reported that CBD may be able to treat addiction through reduced activation of the amygdala during negative emotional processing and has been found to reduce heroin-seeking behavior, likely through its modulation of dopamine and serotonin.^{43,44,85,86} Cannabidiol therefore represents an attractive option in chronic pain treatment, particularly in the context of opioid abuse, not only because of its potential efficacy but also because of its limited misuse and diversion potential as well as safety profile.⁸⁶ More research will be needed because these were pilot human studies with small sample sizes, but they represent potential future areas of cannabinoid use in the clinical treatment of pain relief and opioid abuse. Additionally, more reflection on the right political and industrial means to go about expanding access to CBD is needed in the context of controversial evidence supporting expanding access to medical marijuana as a pain control option.^{6,86}

Safety and Adverse Effects

No rigorous safety studies have been done on "full-spectrum" phytocannabinoid oils because these products are relatively new, but the separate ingredients have been examined somewhat, generally with no major adverse effects noted.^{87,88} Cannabidiol doses up to 300 mg/d have been used safely for up to 6 months,^{89,90} and doses of 1200 to 1500 mg/d were used in a study by Zuardi et al^{91,92} for up to 4 weeks. In the recent larger studies on CBD treatment for epileptic patients, CBD had associated adverse effects of somnolence, decreased appetite, and diarrhea noted in up to 36% of patients,

TABLE 3. Checklist for Finding a High-Quality Cannabidiol and Hemp Oil Product

1. Does it meet the following quality standards?
 - a. Current Good Manufacturing Practices (CGMP) certification from the US Food and Drug Administration
 - b. European Union (EU), Australian (AUS), or Canadian (CFIA) organic certification
 - c. National Science Foundation (NSF) International certification
2. Does the company have an independent adverse event reporting program?
3. Is the product certified organic or ecofarmed?
4. Have their products been laboratory tested by batch to confirm tetrahydrocannabinol levels <0.3% and no pesticides or heavy metals?

although these adverse effects were less severe and less frequent when compared with the usual adverse effects of clobazam treatment.⁴⁵⁻⁴⁹ In addition, it was noted that a considerable number of patients in these studies had elevated liver function test results, and the FDA recommends liver function tests before beginning Epidiolex treatment, as well as 1 month and 3 months after initiation of treatment; thus, physicians should be cautious in patients with known decreased hepatic function who choose to use CBD and hemp oils. We recommend consulting the FDA label for Epidiolex for more information on safety, adverse effects, and dosing that was gathered from the Epidiolex trials.³⁴

In the context of treating pain, one study reported the safety of oral CBD administration (400-800 mg) alongside fentanyl administration, attributed to their different mechanisms of action.⁹³ However, other drug-drug interactions have been noted, or at least hypothesized, based on the metabolism of CBD by the cytochrome P450 superfamily, which includes warfarin and various epilepsy drugs.⁹⁴⁻⁹⁷ The other ingredients in CBD and hemp oils are usually at such small concentrations that they are unlikely to cause severe interactions, but care should still be taken with identifying ingredients present in a product and possible safety issues.

In addition, it is important to be aware of the presence of synthetic cannabinoids available on the market, such as “spice.” These substances have severe adverse effects and

have led to hospitalizations following ingestion.^{98,99} As to the labeling of concentrations in products, a 2017 survey reported that of 84 online CBD and hemp oil products examined, only 26 were accurately labeled for CBD and THC content, with CBD often being overlabeled and THC underlabeled, consistent with the statements made by the FDA.^{36,100} There have also been documented cases of pediatric THC intoxication related to CBD product ingestion, likely due to this noted variation in products, signaling the need for more regulation of the market.¹⁰¹

Finding a Quality Product

If patients and/or physicians choose to experiment with CBD and hemp oils, it is worthwhile to direct them toward the highest-quality product. This issue becomes all the more important when considering some of the problems noted previously. Because of the unclear regulations in the United States as well as some of the noted problems with online product labeling, it is recommended that patients utilize products imported from Europe, which actually has even more stringent requirements for low THC levels at less than 0.2% dry weight compared with the US requirement of less than 0.3% dry weight as well as a more established regulatory system for hemp.¹¹ As with other herbal supplements, ensure that the product has been extracted by carbon dioxide with no solvents, is certified by the US Department of Agriculture as organic, and has been tested for pesticides/herbicides, which have been found in some products.¹⁰² Additionally, ensure that the product is not merely hemp seed oil, which although containing nutritious omega-3 fatty acids does not contain any of the phytocannabinoids or terpenoids.⁴⁰ It is up to the discretion of the physician whether to suggest trying “full-spectrum” formulations because no research is available on their safety and efficacy outside of certain components in separate contexts, whereas pure CBD oils have been studied much more rigorously in the recent seizure studies. Table 3 provides a checklist for determining

a higher-quality product and company, based on requirements used by Mayo Clinic for collaboration with dietary supplement manufacturers.

CONCLUSIONS AND FUTURE RESEARCH

Cannabidiol and hemp oils are nonintoxicating and potentially useful phytocannabinoid substances that continue to grow in popularity. With increasing patient interest in and use of CBD and hemp oils, more research is indicated to better understand their potential efficacy and purported safety profile. Careful selection of a product is crucial for both safety and potential efficacy, and although the products do not have FDA approval for therapeutic use, patients continue to use them and physicians should inform themselves on both potential safety issues and potential therapeutic benefit. Chronic pain management continues to challenge patients and physicians alike, and investigation into potential therapies such as CBD and hemp oils is a promising area for the future of clinical pain management for both pain relief as well as addiction management. We encourage physicians to not disregard patients' interest in these therapies and instead to retain clinical curiosity as well as healthy skepticism when it comes to attempts to explore new options, especially in the context of curbing addiction and opioid overuse. Our hope is that this article will inspire physicians to continue to educate both patients and themselves about alternative therapies utilized by growing numbers of the public, with the example of CBD and hemp oils in particular as it continues to come to the forefront of public interest.

Abbreviations and Acronyms: BCP = β -caryophyllene; CBD = cannabidiol; DEA = Drug Enforcement Administration; ECS = endocannabinoid system; FDA = Food and Drug Administration; THC = tetrahydrocannabinol

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