

# APA Resource Document

## Resource Document on Cannabidiol (CBD) in Psychiatry

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Prepared by the Council on Addiction Psychiatry

### Introduction

With the increasing legalization of cannabis, cannabidiol's (or CBD) traction towards popularity has grown substantially. Companies have marketed CBD as helpful for anxiety, depression, pain and more without clear evidence of benefits in literature. This document summarizes the evidence-base related to over-the-counter CBD products in response to growing interest in the topic especially as it pertains to mental health. The purpose of this resource document is to help educate psychiatrists, physicians, other providers and the community about the current literature of CBD and how to approach psychoeducation in a tactful and nonjudgmental manner. The document details CBD's pharmacology, FDA-approved indications, marketing, regulation, use and perception data, risks, clinical practice approaches, and recommendations for future research.

### Pharmacology of CBD

CBD is one of many cannabinoids in the cannabis plant and is most popularly known in addition to  $\Delta$ 9-tetrahydrocannabinol (THC). THC is commonly cited as the psychoactive component of cannabis via activation of CB1 and CB2 receptors, influencing appetite, mood, memory and motor responses through effects in hippocampus, basal ganglia, basolateral amygdala, hypothalamus, and cerebellum. Activation of the receptors leads to the inhibition of adenylyl cyclase activity and a cascade of effects thereafter. Acute THC intoxication is reported to induce euphoria which can be referred to as a "rush" or "buzz" or a "high" and very high levels can be associated with panic attacks, paranoid thoughts, and hallucinations.<sup>1</sup>

CBD on the other hand acts as a negative allosteric modulator at CB1 cannabinoid receptors and an antagonist at CB2 cannabinoid receptors, while also inhibiting endocannabinoid signaling.<sup>2</sup> As a result, CBD can interfere with deactivating the endocannabinoid anandamide which may indirectly activate CB1 receptors. (Endocannabinoids are endogenous molecules, made by our bodies.) CBD reduces neuronal excitability through the inhibition of adenosine transport, the modulation of TRPV (Transient Receptor Potential Vanilloid) receptor, potassium channels, NMDA (N-methyl-D-aspartate) receptors, and the interaction with the GPR55 (cannabinoid) receptor,<sup>3,4</sup> It is also possible that CBD may increase the effect of antiepileptic medications it is co-administered with through modulation of cytochrome p450s. Drug interaction data suggests a strong risk of drug interaction with CYP and UGT substrates (especially CYP2C19 substrates), CYP inducers, and CYP3A inhibitors.<sup>5</sup> (More information to follow in "Risks"

section.) CBD also serves as an agonist of the serotonin 5HT1A receptor and thus may have psychoactive properties. Other potential effects of CBD include pain/inflammation impacts (through enhanced adenosine receptor signaling by inhibiting adenosine inactivation), and subsequent antioxidant, anti-inflammatory, neuroprotective potential, for example as demonstrated with the application of seizures.

### **FDA status**

The only United States Food and Drug Administration (FDA) approved formulation of CBD is a synthetic pharmaceutical known as Epidiolex. It is for adjunctive treatment for two rare pediatric-onset, drug-resistant epilepsies, Lennox-Gastaut and Dravet Syndrome. It is also approved for treatment of epilepsy related to tuberous sclerosis complex in patients one year of age or older. Possible adverse event include somnolence, diarrhea, fatigue, vomiting, pyrexia, and lethargy. Elevations in the liver enzyme alanine transaminase (ALT) are dose dependent on increases in CBD, and liver enzymes should be monitored at the first, third, and sixth months of use.<sup>6</sup>

In 2018, the Drug Enforcement Administration gave Epidiolex a Schedule V classification, designating it a drug with a relatively low risk of abuse. By contrast, delta-9 tetrahydrocannabinol (THC) containing cannabinoid products were still given a Schedule I classification as THC is a psychoactive substance.

There are no breakthrough statuses from the FDA for CBD products, though there are other cannabinoid drugs approved by the FDA for various indications. Dronabinol, a synthetic THC analogue is approved for treatment of chemotherapy-induced nausea and treatment of anorexia associated with AIDS-related weight loss. Nabilone, another synthetic cannabinoid is an anti-emetic for those receiving chemotherapy and is prescribed off-label for neuropathic pain in the United States.

### **Regulation of CBD**

With the 2018 Farm Bill, the FDA defined hemp as *Cannabis Sativa L* with no more than 0.3% THC. This law allowed for hemp (which often includes CBD products) to be removed from the Controlled Substances Act. As noted above, the FDA has approved one drug, Epidiolex for treatment of seizures. Likewise, CBD cannot be marketed as a dietary supplement under the Federal Food, Drug, and Cosmetic Act.<sup>7</sup> However, given lack of systemic regulation, including specific policy on other THC strains such as delta-8 and delta-10 THC, and variable enforcement, there exists uncertainty regarding appropriate commerce.

While Epidiolex provides a uniform concentration of CBD, this is often not the case with unregulated CBD products. In fact, one study in *JAMA* found that 26% of products had less CBD content than labeled, while 42% of products had a higher CBD content than labeled and THC is also found in many products.<sup>8,9</sup> Another concern is that the THC content is variable in unregulated products, placing children and adolescents who consume these products at risk of cannabis intoxication or adults unknowingly having detectable THC in their systems. Purity may also be a concern as non-FDA regulated THC products may have contaminants including synthetic cannabinoids, heavy metals, pesticides, and carcinogenic polycyclic aromatic hydrocarbons.

The FDA was recently asked to issue a regulation that would allow cannabidiol (CBD) products to be marketed as dietary supplements which they denied "because in light of the available scientific evidence, it is not apparent how CBD products could meet the applicable safety standard for dietary supplements." So as of 2023, the FDA is recommending a new pathway that is yet to be determined.<sup>10</sup> They cite concerns with long term use, potential harm to the liver, potential harm to the male

reproductive system, interaction with medication, exposure to vulnerable groups like children, people who are pregnant and animals.

### **Marketing of CBD**

With the recent legalization of recreational cannabis use in certain states, there has been a rise of businesses selling CBD in the forms of tinctures, pills, creams, and lotions as well as in supplements. Although CBD does not have the psychoactive properties as THC, it is not without risks. CBD can cause liver injury, drug interactions can make it potentially cause serious side effects, interactions between other substances may cause increased sedation and drowsiness, and male reproductive toxicity although unclear in humans has been observed in rodent studies.<sup>11,12,13</sup> (See more in Risks section.)

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, any product claiming to have therapeutic or medicinal use (other than food) is considered a drug.<sup>14</sup> Drugs must receive premarket approval by FDA through the New Drug Application (NDA) process or conform to a “monograph” for a particular drug category as established by FDA’s OTC drug review. Since CBD was not an ingredient considered under the OTC (over-the-counter) drug review, CBD cannot be distributed or sold in interstate commerce as a drug.

Even with FDA’s strict regulation, there have been a multitude of companies that have made unsubstantiated claims of CBD diagnosing, curing, mitigating, treating, or preventing diseases.<sup>15</sup> Some even going further claiming that CBD was effective in treating teething and ear pain in infants, autism, ADHD, and dementia (i.e. Parkinson’s and Alzheimer’s).<sup>16</sup> This has potentially harmful effects to consumers and vulnerable populations as they may be influenced not to use approved therapies to treat serious and even fatal diseases that may otherwise be treatable. As of January 22, 2021, the FDA has not approved a marketing application for cannabis for the treatment of any disease or condition.

Alongside false claims of indications for CBD, another important facet of marketing that should be addressed is dosing. Due to the lack of convincing clinical trials of CBD and labeling inconsistencies in formulations, there are currently no guidelines or dosage recommendations for specific indications.<sup>17</sup> Even though little is known for the safe and effective dose of CBD, there are companies claiming to have a set amount of CBD in their products for various medicinal or therapeutic uses. However, upon examining the percentage of CBD, these claims appeared to be false. Thus, it would be apt for industry or business entities to review the FDA’s “Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research” prior to submitting approval of their CBD product of medicinal or therapeutic use.<sup>18</sup>

### **Use and Perception of CBD**

Related to marketing, the availability and popularity of CBD has increased. CBD in a variety of formulations is now widely available not only through cannabis dispensaries but also in many typical retail outlets such as convenience stores and drug stores as well as for purchase online. Data on the extent of and reasons for its use are just beginning to accrue. Consumer sales show a ten-fold increase between 2014 and 2020 (from \$108 million to \$1.2 billion) with a projected further increase to \$1.6 billion in 2021.<sup>19</sup> Most recent data shows the CBD industry to be valued at 4.6 billion with an estimate to quadruple by 2026.<sup>20</sup> From April 1, 2019 to March 31, 2020, the first year in which CBD was identified uniquely as a substance in the National Poison Data System, poison control centers handled 1581 cases

involving exposures to CBD-containing products.<sup>21</sup> There was a significant trend of over 5 additional cases related to this substance per month, suggesting continually increasing usage. Patients under age 13 years made up 44.0% of reported exposures. Mild CNS depression (10.3%), tachycardia (5.7%), dizziness/vertigo (5.3%), vomiting (4.9%), nausea (4.5%), and agitation (4.4%) were the most frequently reported symptoms. 13% of cases were coded as having "moderate" or "severe" medical outcomes. There were no fatalities.

The remaining information on CBD usage comes primarily from surveys. Such surveys are likely to attract respondents who have an interest in CBD or other cannabis products, and this selection bias likely reflects rates of usage far higher than what actually occurs in the general population. One of the largest cross sectional surveys is from 2018, of n=2409 self identified CBD users noted that 62% were using for a medical condition, the top three being pain, anxiety, depression.<sup>22</sup> 36% reported CBD treats a medical condition "very well by itself" while 4.3% reported "not very well" and one of three reported a non-serious adverse effect. CBD use was higher among regular cannabis users. In a later anonymous survey distributed via social media from November 2018 to January 2019 had 340 respondents of whom 242 (71%) had heard of CBD, and 135 (39.7%) reported using it.<sup>23</sup> CBD users were primarily white, female, without children, made less than \$25,000 per year, and unmarried. Most commonly used CBD products were edibles (56.30%), tinctures (54.07%), and vape (38.52%). Top reasons for use included stress relief (65.39%), relaxation (54.81%), and sleep improvement (42.22%). Many respondents reported using guesswork to determine dosage, and over half of respondents reported at least one unanticipated side effect. Another anonymous survey queried 2701 individuals with fibromyalgia from around the U.S. with 38.1% reporting never using CBD, 29.4% past CBD use, and 32.4% current CBD use.<sup>24</sup> Those using CBD typically did so due to inadequate symptom relief, while those not using CBD typically cited safety concerns as their reason for not using CBD. Two-thirds of participants disclosed CBD use to their physician, although only 33% asked for physician advice on using CBD. Participants used CBD for numerous symptoms (most commonly pain), and generally reported slight to much improvement across symptom domains. Around half of participants reported side effects, which were typically minor. A fourth survey conducted in 2018 and 2019 included 253 patients recruited from 7 pain clinics in Southern California.<sup>25</sup> A majority (62%) endorsed use of CBD products, although for 56.3% these products also contained THC. When asked what type of products they have used, the most frequent responses were inhaled/smoked (62.9%), edibles (54.3%), and oral tinctures (52.3%). Most found that CBD products helped with pain and helped them to reduce their other pain medications and did not believe that CBD is harmful or addictive. A final survey included 1050 respondents in the U.S. in 2019.<sup>26</sup> CBD only was used by 9.24% and CBD and THC by 14.19%. More than half perceived CBD as having medical use and perceived potential for misuse as much lower than for commonly prescribed anti-anxiety and pain medications. Reasons for use among CBD only users included sleep, pain reduction, and stress reduction with a very small minority using only for recreational purposes.

Based on a recent meta-analysis, in 2022 usage length of time can range between 1 to 16 weeks. Similarly, the dose being used can also vary from 300 to 800 mg/day or 20 to 50 mg/kg/day. The median age was 62 with a wide range noted from 1.1 years old to 56.8 years old.<sup>27</sup>

Overall, rates of CBD usage are climbing with use common among regular cannabis users and people with chronic pain conditions. People who do use CBD believe it helps their pain to some extent and that it may help with anxiety, depression, sleep and stress.

## Risks

In a meta-analysis, the most common adverse effects were gastrointestinal symptoms (59.5%). Other adverse effects in order of decreasing incidence include somnolence (16.7%), loss of appetite (16.5%), increased ALT/AST (12.8%), and fatigue (11.4%).<sup>28</sup> Most common side effects overall include drowsiness, sedation, fatigue, dizziness, headache, diarrhea, nausea, decreased appetite, and abdominal discomfort. Other common adverse drug effects include sleep disturbances, infection and anemia.<sup>29</sup>

Pharmacokinetic drug-drug interactions can occur at multiple stages of the drug cycle: absorption, distribution, and elimination stages. This can result in varying changes in drug plasma concentrations. CBD is used at times for those with seizures. However, when CBD was used in conjunction with clobazam and valproate, reports of hypertransaminasemia greater than three times of the upper limit, seizures, and rash were observed.<sup>30</sup>

CBD is metabolized by CYP 450 isoforms 3A4, and to a lesser extent CYP2c19. Of particular interest to mental health providers, certain inhibitors of CYP3A4 include grapefruit juice, fluvoxamine, nefazodone, and can inadvertently increase levels of CBD.<sup>31</sup> Common inducers of CYP3A4 include (but is not limited to) Oxcarbazepine, St. John's Wart, Modafanil, which may decrease CBD levels. Further, CBD may act as an inhibitor of CYP2c19, CYP2D6, and CYP3A4. For this reason, metabolism of multiple psychotropic medications such as benzodiazepines, some SSRIs, TCAs, opioids, and beta blockers, are often affected by CBD.<sup>32</sup> Overall CBD is implicated as both a substrate and product of CYP, and alternative therapy should be considered for patients who are on known medications that interact with CYP.

Conversion of CBD to delta-8-THC has become a more common product, being marketed, –without evidence, for stress relief and an anxiolytic. Such products can be sold in convenience stores, in the form of gummies, vape cartridges, or other products. Given lack of regulation and laboratory testing, multiple products sold as delta-8-THC are not pure. Often, compounds labeled as delta-8-THC can have multiple different isomers including delta-9-THC (psychoactive component of marijuana). Delta-8-THC is more common in Europe, but more than a dozen states have banned delta-8-THC.<sup>33</sup>

In the pregnant population, FDA has discussed lack of [high-quality](#) studies that explore effects of CBD on developing [fetuses](#).<sup>34</sup> There is a dearth of information regarding risks or benefits in pregnant women, and no direct conclusion can be drawn regarding risks or benefits of CBD in the peripartum period. Overall, CBD can readily cross the placental barrier. Some potential effects could be improper development of immune system and microbiome of fetus.<sup>35</sup> Likewise, ex vivo models suggest that CBD could impact certain placental proteins leading to alterations in transporters that deliver crucial compounds to fetus, especially during first trimester.<sup>36</sup>

Other populations to be considered include the pediatric and geriatric populations. In young people, adverse effects were documented in a previously mentioned report of National Poison Data System data; Of the over 1500 cases in one year, almost half involved people under 14 years old with effects including from mild CNS depression (10.3%) and with 13% of cases coded as having "moderate" or "severe" medical outcomes.<sup>37</sup> Given lack of procedure in regulation and screening of CBD products, exact composition is often unknown. In certain studies, THC can be detected in 21.43% of the products.<sup>38</sup> CBD interacts with endocannabinoid system, which can lead to altered brain maturation. Similarly, safety of CBD in the geriatric population has not been fully clarified. However, since hepatic function reduces with age and

older individuals are likely to be on medications that could interact with CYP 2C19 or 3A4, there are drug-drug interactions to be expected with CBD.<sup>39</sup>

### **Clinical practice approaches**

Patients using CBD should be approached in an open, non-judgmental manner as with any other substance use or mental health concern. Clinicians should be aware, and inform their patients of, any documentation and reporting requirements specific to their state or institution, as such regulations can vary tremendously<sup>40</sup> and may affect patients' willingness to further discuss use. In discussing use, physicians can inquire whether patients are experiencing any adverse impacts of use such as side effects or foregoing evidence-based treatment approaches due to investments in CBD use. In addition to inquiring about patterns of use, clinicians may consider a motivational interviewing (MI)-informed approach, which has proven efficacy among patients seeking to change behavior around use of cannabis products.<sup>41</sup> Patients who report ongoing use despite negative consequences, have transitioned to cannabis via CBD, or who appear to meet criteria for a cannabis use disorder, may benefit from a referral to specialty treatment.<sup>42</sup>

Since CBD is marketed for a broad range of indications despite the lack of robust studies supporting its clinical, clinicians should inquire what effects the patient is attempting to achieve, or what symptoms they may be attempting to alleviate. Diagnostic interviewing around underlying conditions and gathering a history of medical and psychiatric diagnoses may be helpful, as might discussions of more evidence-based treatment alternatives. Vulnerable patients, including adolescents and those with a family or personal history of addiction and psychotic disorders, should be educated about the potential adverse effects of THC contained in many CBD products.<sup>43</sup>

As noted, the purity and accuracy of labeling of CBD products varies greatly, so clinicians should educate patients about this level of variation, and attain a current list of medications to reduce the risk of interactions between CBD and anticoagulants, antiarrhythmics, and anti-seizure medications among others.<sup>44</sup> Dose adjustments or additional safety monitoring may be required related to the current regimen.

Patients who plan to continue using CBD products may benefit from a harm-reduction approach, for which several guidelines are available.<sup>45,46</sup> Such management may include monitoring of amount and effects of use over time, associated health conditions, educating patients to use products which meet basic quality standards, are organically farmed, or lab-tested to reduce exposure to THC, pesticides, and heavy metals. For those who choose to reduce use over time, education and management of cannabis withdrawal may also be clinically appropriate.<sup>47</sup>

### **Recommendations & Closing**

In summary, there is no robust efficacy data for over-the-counter CBD as it relates to mental health conditions. As of the writing of this statement position (2023), there are no randomized control trials in humans about the safety of over-the-counter CBD; thus, it is difficult to substantiate complete safety of use in humans.

The pharmacology of CBD has been mostly studied in animal models, while promising, the dosing, efficacy, and tolerability is unknown in humans. In terms of FDA indication of CBD, Epidiolex is approved for Lennox-Gastaut and Dravet's Syndrome. Adverse effects can include dose-dependent transaminitis.

Two other cannabinoid drugs, which are FDA-approved, include Dronabinol and Nabilone. Unlike current FDA-approved cannabinoid medications (i.e. Epidiolex, Dronabinol, Nabilone), over-the-counter CBD is unregulated, and purity cannot be guaranteed. As of the publication of the APA position statement, there is currently no breakthrough status from the FDA. The marketing of over-the-counter CBD is concerning as the FDA has not approved any marketing application for cannabis or CBD. Psychiatrists and physicians should be aware that there are claims being made of CBD's therapeutic effects and that psychoeducation will be necessary to counteract misinformation.

With knowledge of the current literature of CBD, physicians will likely need to educate patients in context to the differences of FDA-approved CBD and over-the-counter CBD. This will often involve educating about current data and safety concerns of over-the-counter CBD. With this information known to both parties, patients and physicians can make informed shared decision-making in regard to the use of over-the-counter CBD. Offering evidence based solutions for reasons a patient is interested in or taking CBD can benefit the patient in outcomes and costs.

As previously mentioned, there is still a need for more research to understand dosing, efficacy, tolerability in humans regarding cannabinoid products not FDA-approved. As CBD can be stored in breastmilk, special consideration for dosing, efficacy, and tolerability is required for pregnant women and breast-feeding infants.<sup>48, 49</sup> Special consideration also extends to other vulnerable patients (i.e. adolescents, have a family history of substance use disorders, having psychotic-spectrum disorders). The APA recommends motivational interviewing be used for substance use and referral to a specialty treatment center if the patient has a substance use disorder. If the patient is taking CBD supplements, the prescriber should be keenly aware of interactions between CBD and medications (i.e. anticoagulants, antiarrhythmics, anti-epileptic medications).

In conclusion, RCTs and more research to ascertain safety of over-the-counter CBD, with a focus on vulnerable populations. This will inform future regulation with more clearcut and defined guidelines. For the reasons listed in this position statement, the APA cannot give an estimate or "safe" dosing guide to practitioners.

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