AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Discuss cannabidiol's known pharmacologic profile
- Identify FDA-approved indications for prescription cannabidiol and other indications in which research is promising
- Distinguish the FDA-approved cannabidiol from various nonprescription products in terms of quality and risk/benefit profile
- Maximize the pharmacist's role in helping patients who are good candidates for prescription cannabidiol or use nonprescription cannabidiol products either with or without other prescription drug therapies

After completing the continuing education activity, pharmacy technicians will be able to

- Discuss the basic facts about cannabidiol products
- Acquire reputable sources for patients who have an interest in cannabidiol to find information
- Distinguish between nonprescription and prescription cannabidiols
- Infer when to refer patients to the pharmacist for recommendations or referral

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE UAN: 0009-0000-22-043-H01-P
0009-0000-22-043-H01-T

Grant funding: Jazz Pharmaceuticals
Cost: FREE

INITIAL RELEASE DATE: June 15, 2022
EXPIRATION DATE: June 15, 2025

To obtain CPE credit, visit the UConn Online CE Center https://pharmacyce.uconn.edu/login.php. Use your NABP E-profile ID and the **session code 22YC43-XYZ92 for pharmacists or 22YC43-CBA84 for pharmacy technicians** to access the online quiz and evaluation. First-time users must pre-register in the Online CE Center. Test results will be displayed immediately and your participation will be recorded with CPE Monitor within 72 hours of completing the requirements.

For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

TO RECEIVE CREDIT FOR THIS CE,
go to
https://pharmacyce.uconn.edu/login.php

You Asked for It! CE

Cannabidiol: When is Similar Different?

ABSTRACT: The U.S. Food and Drug Administration (FDA) approved a highly purified cannabidiol (CBD) product called Epidiolex (hereafter referred to as CBD-Rx) for the treatment of seizure disorders in Dravet and Lennox-Gastaut syndromes and for patients with tuberous sclerosis complex (an indication that was FDA-approved in August 2020). Patients with epilepsy are sensitive to small changes in antiepileptic drug concentrations. Due to CBD products' tendency to deviate from the dose on the label with the dose actually delivered, the medical evidence highly discourages use of non-FDA-approved CBD products in people with epilepsy. CBD is well tolerated but like all drugs, poses risks to the consumer. CBD has benefits, adverse events, and drug interactions that the pharmacy team must assess; careful counseling is critical for optimal use. While the lay press and various sites on the Internet tout CBD to treat or alleviate many ailments, the evidence for benefit is limited. The pharmacy team, with their high accessibility and deep respect in the community, should be an unbiased information source on the possible benefits and risks of CBD for various ailments.

FACULTY: C. Michael White, Pharm.D., FCP, FCCP; Distinguished Professor and Chair, Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, CT and Director, HOPES Collaborative Group, University of Connecticut and Hartford Hospital, Hartford, CT.

FACULTY DISCLOSURE: Dr. White has no financial relationships with an ineligible company.

DISCLOSURE OF DISCUSSIONS of OFF-LABEL and INVESTIGATIONAL DRUG USE: This activity may contain discussion of off label/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of the University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

INTRODUCTION

Sales of Epidiolex, the prescription oral solution version of cannabadiol (CBD) and known hereafter as CBD-Rx, grew from $296 million in 2019 to $464 million by the end of 2021 in the U.S.[1,2] Nonprescription CBD products, hereafter known simply as CBD, also grew from $0.8 billion in 2018 to $1.6 by the end of 2021.[3] Continuing robust sales growth is expected for both CBD-Rx and CBD through at least the year 2025.[3] Both types of CBD products took very different legal routes from a Drug Enforcement Agency (DEA) Schedule I designation to allowing legal

sales in the U.S. These legal differences yield important clinical differences. What are prescription and nonprescription CBD products' similarities and differences? How should they impact the pharmacy team's advice to health professionals and consumers?

This continuing education activity will help pharmacists and pharmacy technicians understand the different legal frameworks for CBD-Rx and other CBD products while elucidating the patient care implications. It will explore the evidence supporting the benefits and safety of CBD-Rx and CBD products in important diseases from seizures and anxiety to sleep disorders and pain, inflammation, and other diseases. To start, the **SIDEBAR** dispels some common myths.

Legal Status: CBD-Rx and Unapproved Products

Epidiolex (CBD-Rx) was Food and Drug Administration (FDA)-approved in 2018 and remains the only approved form of CBD. It is indicated for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes or tuberous sclerosis complex in patients 1 year of age and older. It consistently delivers 100 mg/mL of CBD to patients with THC concentrations below 0.1%. The DEA placed CBD-Rx in Schedule V (drugs with a relatively low risk of abuse).[4,5]

Health professionals and consumers see CBD products in beer, oil, coffee, creams and ointments, gummies, lip balm, and seltzer on store shelves across the country. These CBD products are not FDA approved—they are over the counter products and do not meet the definition of dietary supplements either. As stipulated in the 2018 U.S. Farm Bill, the Department of Agriculture regulates some hemp-derived CBD products that have THC concentrations of less than 0.3%, and are not DEA Schedule I (high risk of abuse or harm, limited or no medicinal value, illegal to possess).[6] Manufacturers of these CBD products can sell them to consumers if they made no health claims that would place their products under the FDA's jurisdiction. If CBD products have a THC concentration at or exceeding 0.3%, whether known to the proprietor or consumer or not, they are considered marijuana-derived CBD, classified as DEA Schedule I, and illegal to sell or possess according to federal law.[6]

Common Misperceptions

Myth: CBD has all medical cannabis's beneficial effects except the tetrahydrocannabinol high.
Reality: CBD provides one of cannabis' many constituents only. No one should assume it will work the same as medical cannabis. Before people can treat medical disorders with CBD confidently, researchers must prove it's effective and safe for each indication.

Myth: CBD has been proven effective for many diseases and disorders.
Reality: CBD has been proven effective for seizure control in Lennox-Gestaut and Dravet syndromes and tuberous sclerosis complex, but there is insufficient human efficacy data for other uses. Although promising for patients with stage fright, schizophrenia, pain, inflammation, and Parkinson's disease, much more research needs to be done before the balance of benefits to harm is known.

Myth: CBD has no adverse effects or drug interactions.
Reality: In clearly defined and controlled doses, CBD is generally safe and well tolerated. But CBD has potential to cause adverse events, including severe adverse events. It also has many potentially serious drug interactions requiring oversight from a trained health professional for safe use.

Myth: All CBD products are the same.
Reality: Nonprescription CBD products (which are not FDA-approved) could be adulterated or contaminated and have CBD concentrations that frequently differ from the dose listed on the label. These variations can change the benefit to harm balance.

Myth: All CBD products are now legal to sell, possess, and use in the United States.
Reality: CBD products that intentionally or inadvertently contain more than 0.3% THC are illegal according to federal law, but some states have legalized recreational marijuana and do not prosecute. However, transporting any product with more than 0.3% THC over state lines remains illegal. If patients use non-FDA-approved CBD forms and don't have test results confirming an acceptable THC level, they could be in legal jeopardy.

COMPARING PRODUCTS: QUALITY AND PURITY DIFFERENCES, DOSAGE FLUCTUATIONS

The CBD-Rx product provides the CBD concentration specified on the label with little variation over time. That is, patients can trust that the product contains and delivers the labeled dose, and people who take the same dose consistently will have predictable blood levels. However, this may not occur with non-FDA-approved CBD products. In 2016, investigators purchased 84 non-FDA-approved CBD products from 31 different Internet-based companies. A commercial laboratory tested them in triplicate using high-performance liquid chromatography (HPLC; an analytical chemistry technique used to separate, identify, and quantify each component in a mixture).[7] The laboratory averaged and reported triplicate test results by product weight. If the average detected concentration was 90% to 110% of the labeled value, it was considered accurately labeled. With respect to CBD, manufacturers had labeled only 31% of products correctly, with most products under-labeled. The frequency of accurate labeling for CBD vaporization liquids, tinctures, and oils was 12.5%, 25%, and 45%, respectively. Products contained unlabeled THC at a mean concentration of 0.45 mg/mL (range 0 to 6.4) in 21% of samples, which would place people selling, possessing, or using these products at risk of arrest and prosecution.[7] People have failed THC drug tests despite reporting use of CBD products only.[8,9]

These quality issues persist. In 2020 the FDA assessed 102 products that indicated a specific amount of CBD.[10] Only 45% of products had dosages within 20% of that specified on the label with 18% having less than 80% of the specified amount; 37% had more than 120% of the amount of CBD indicated on the label. Additionally, 49% of products tested positive for tetrahydrocannabinol (THC, cannabis's principal psychoactive constituent and one of at least 113 cannabinoids [CB] in the plant). The U.S. is not the only country with concerns.

In the Netherlands, for example, a laboratory assessed eight CBD products. Four were labeled correctly (less than 10% variability), two had 18% or 35% higher concentrations, and two had 74% or 98% lower CBD concentrations than the label stated, respectively.[10] ConsumerLabs is a third-party laboratory that differs from most labs. Instead of being paid to do their analysis by product manufacturers, it conducts its testing without the manufacturers consent and then charges consumers to see the results. They assessed multiple CBD products for CBD content and found the labeled CBD dosages had little correlation with the products' actual CBD concentrations.[11] It is simply impossible to know the exact CBD dose patients take if they buy products that are not FDA approved or independently tested by outside laboratories.

Inaccurately labeled CBD concentration or variability in CBD concentrations create potentially dangerous implications.[12] For example, in a systematic review of non-CBD antiepileptic drugs, the University of Connecticut Evidence-Based Practice Center found that small changes in drug concentration impacted seizure control. While brand and generic antiepileptic drugs were equally effective when started *de novo*, risk of emergency medical services or hospitalization increased when patients switched from a brand to a generic or vice versa.[12] This suggests that for seizure control, using CBD products with differing CBD content or products in which CBD concentrations vary over time could harm patients. This is especially risky since the FDA-approved indications for CBD-Rx include use in children as young as 1 year old.

Adulteration and Contamination

Adulteration and contamination pose additional risks to patients using non-FDA-approved CBD products. In 2017, five patients in Utah who used CBD reported adverse events (e.g., seizures, confusion, unconsciousness, and hallucinations).[13] An in-depth investigation found that a CBD product included a synthetic CB. From 2017 to May 2018, the specific product's contamination harmed 52 people in that region.[13]

The International Cannabis and Cannabinoid Institute in the Czech Republic assessed 29 CBD products and found 69% of them exceeded recommended levels of polycyclic aromatic hydrocarbons. The International Agency for Research on Cancer classifies polycyclic aromatic hydrocarbons as class IIa carcinogens and genotoxic mutagens.[10,14]

Additionally, pesticide or heavy metal contamination in unregulated CBD products is possible.[10] The Florida Department of Agriculture and Consumer Services tested a random sample of a CBD product and found lead levels at 4.7 ppm. When informed, the manufacturer conducted an internal investigation and instituted a recall of one batch of their product.[15] Another assessment of CBD oil and hemp oil products found detectable levels of arsenic, cadmium, and lead. A large assessment of 240 CBD products was conducted by Ellipse Analytics, an independent laboratory.[16] It found that 70% of CBD products tested positive for heavy metals like lead and arsenic, concentrated chemical pesticides, or toxic mold.[17] Without independent third-party laboratory testing, there is no way to know if any product is adulterated or contaminated. See the Tech Talk **SIDEBAR** for some product verification tips and tricks.

SIDEBAR: Understanding CBD Product Verification Absent FDA Approval[18,19]

CBD products have flooded the market, but don't require FDA approval. The FDA takes no responsibility for ensuring that the CBD concentration on the label matches the product content.

Monitoring CBD products is especially important as "cannabis plants readily absorb heavy metals, pesticides, and other potentially harmful chemicals that may be in the soil or water."[18] Therefore, consumers—and the pharmacists and technicians who advise them—need to investigate available CBD products. Consumers can request CBD products' Certificate of Analysis (CoA) from the manufacturer, which provides information about testing for contaminants and THC and CBD levels. If the retailer cannot provide it, consumers should avoid that product.

States and retailers are starting to take the initiative to ensure consumers have needed information. In Indiana, CBD products must have a Quick Response (QR) code that consumers can use to obtain the product's CoA on a smartphone. Some states require dispensaries to make CoAs available to consumers. CVS has stated that it will work with a third-party laboratory to test the CBD products available in its stores in 20 states at this time for contaminants and THC and CBD concentrations.

When looking at the CoA, consumers can be more confident in quality if the CoA states that the lab meets "ISO 17025" standards. Consumers can also look to see if the CoA states that the lab complied with the standards set by one of three organizations: the Association of Official Agricultural Chemists (AOAC), the American Herbal Pharmacopoeia (AHP), or the U.S. Pharmacopeia (USP).

Consumers should beware of products that list the total cannabinoid concentration in the product and not the CBD concentration. Of course, products should clearly define a "dose," and list the amount of CBD in a dose and not in the entire product.

CBD Alone or CBD + Other Cannabis Constituents

CBD isolate products, including CBD-Rx, contain virtually no cannabinoids, terpenes, or other compounds in cannabis sativa except for CBD. In contrast, broad or full-spectrum CBD contains the cannabis plant's naturally available compounds and differ only in the amount of THC. Broad-spectrum products have very low THC concentrations, while hemp-based full-spectrum products contain between 0.1% and 0.29% THC.[17] Other constituents in the cannabis sativa plant may accentuate or attenuate the effects of CBD alone through the "entourage effect." For each disease or disorder, researchers need to determine whether broader administration of the other cannabis sativa constituents impacts efficacy or safety.

Pharmacokinetic Profile Comparison

The CBD-Rx product demonstrates a less than dose-proportional increase in concentration over the range of 5 to 20 mg/kg/day doses in patients. At steady state, the time to maximal concentration (T_{max}) is 2.5 to 5 hours, the volume of distribution is high at 20963 to 42849 liters (showing very high penetration into fat and other body tissues like the brain), and the elimination half-life is long at 56 to 61 hours. High fat/high calorie meals dramatically increase the maximum concentration (C_{max}) and the area under the curve (AUC) by 5- and 4-fold, respectively, but the prescribing information does not address timing with food.[17] However, the labeling recommends taking CBD-Rx consistently with regards to food. Following a single CBD 1500 mg dose (1.1 times the maximum recommended daily dosage), plasma clearance is 1111 L/hour.[4]

Unapproved CBD products lack similar pharmacokinetic data and could differ from that of the CBD-Rx product as the formulation changes. For instance, topical application of one CBD product may penetrate the skin and enter the bloodstream very differently than another. Additionally, edible products with CBD might not be absorbed as readily as other oral delivery methods, and vaporized CBD could have faster onsets of action.

CBD, when given as the CBD-Rx product or not, has many potential drug interactions as a substrate and as an inhibitor and inducer of metabolic enzymes. CBD is primarily metabolized by hepatic cytochrome P450 (CYP2C19 and CYP3A4) and uridine 5'-diphospho-glucuronosyltransferase (UGT1A7, UGT1A9, and UGT2B7).[4] Researchers have explored the impact of CYP3A4 and CYP2C19 inducers and inhibitors on CBD for a combined CBD/THC product.[20] The C_{max} and AUC decreased 52% and 59% with concomitant rifampin (CYP enzyme inducer), increased 89% and 165% with concomitant ketoconazole (CYP3A4 inhibitor), and was unchanged with omeprazole (CYP2C19 inhibitor).[20]

CBD's main metabolite is 7-OH-CBD which subsequently converts into the 7-COOH-CBD metabolite, both of which may have anticonvulsant properties. After repeat dosing, the 7-OH-CBD and 7-COOH-CBD metabolites' AUCs are 38% lower and 40-fold higher respectively than CBD's AUC.[4,21] Protein binding of CBD and its metabolites was found to be 94% *in vitro*.[4]

CBD inactivates some CYP enzymes in the short term but like other anticonvulsants, induces them with chronic dosing.[21] Upregulation of CYP3A4 and CYP2B10 mRNA have occurred in mice and induction of CYP1A1 occurred in vivo.[21] In contrast, CBD seems to inhibit UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 metabolism.[4]

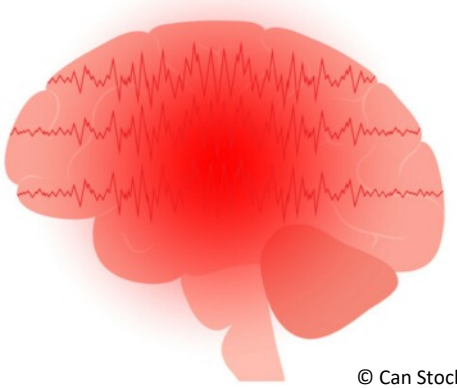
To test CBD's enzyme inhibition and induction effects, researchers assessed CBD-Rx's impact on clobazam and its N-desmethylclobazam metabolite in 13 subjects (age range 4 to 19 years) with refractory epilepsy. The mean increase in clobazam and N-desmethylclobazam levels was 60% and 500% after four weeks of concomitant therapy. CBD-Rx was determined to be a CYP2C19 inhibitor.[22] The prescribing information suggests clinicians consider reducing the dose of sensitive CYP2C19 substrates such as diazepam and clobazam, as clinically appropriate, when coadministered with CBD-Rx.[4]

Taken together, the pharmacokinetic and drug interaction data suggests a strong risk of drug interactions with many CYP and UGT substrates (especially CYP2C19 substrates), CYP inducers, and CYP 3A4 inhibitors.[4,21] Much more research is needed to determine how to manage patients—especially those with refractory seizures—who take multiple drugs that impact the CYP enzyme system. The potential for multiple drug interactions makes patient CBD use without input from a health care professional risky.

CBD-RX'S EFFICACY IN REFRACTORY RARE SEIZURE DISORDERS

Five major randomized trials were instrumental to the FDA's decision to approve CBD-Rx, involving patients with rare seizure disorders – for more information about these conditions, see the **SIDEBAR** (next page).

PAUSE AND PONDER: How can the pharmacist proactively ensure that CBD products are not interacting with a patient's prescribed therapy if patients purchase CBD products from a smoke shop or over the Internet?



© Can Stock Photo/Pikovit

What are Lennox-Gestaut and Dravet Syndromes and Tuberous Sclerosis Complex? [23-25]

Lennox-Gestaut syndrome affects roughly one in 3,800 people, making it rare. Its many different causes include inflammation of the brain or brain covering, brain malformations, decreased blood and oxygen to the brain, or injuries to the brain's frontal lobes that create a constellation of childhood epilepsy disorders. In 25% of cases, clinicians can't find a cause. On electroencephalogram when the person is awake, patients with Lennox-Gestaut syndrome have similar presentations characterized by slow spike and wave epileptiform activity. Multiple seizure types can occur (tonic, atonic or drop attacks, atypical absence, myoclonic, and generalized tonic-clonic) and Lennox-Gestaut syndrome is associated with cognitive impairment. Although rare, Lennox-Gestaut syndrome comprises 10% of children with epilepsy appearing before 5 years of age.

Dravet syndrome is a rare genetic defect (affecting 1 in 20,000 to 40,000 children) arising from new genetic polymorphisms rather than genetic heritage. It usually begins in the first year of life in an otherwise healthy infant and causes seizures throughout life. Infants have normal development when the seizures begin but as seizures continue, most children develop some level of developmental disability.

Tuberous sclerosis complex, also a rare genetic disorder, affects 1 in 6,000 children. Mutations in the tuberous sclerosis complex 1 or 2 gene cause benign tumors in different parts (e.g., brain, skin, lung, kidney, heart, and eye). When the tumors impinge on the brain, seizures can result. Tumors in other organs can cause respiratory, kidney, heart, or vision disorders.

In the first study, researchers randomized 120 children and young adults with Dravet syndrome and drug-resistant seizures to receive adjunctive CBD-Rx oral solution (20 mg/kg CBD per day) or placebo.[26] The median frequency of convulsive seizures per month decreased from 12 to six with CBD-Rx versus a decrease from 15 to 14 with placebo (p = 0.01). The CBD-Rx patients' overall condition improved by at least one category on the 7-category Caregiver Global Impression of Change scale (62% versus 34%, p = 0.02) with CBD-Rx versus placebo. The trends toward at least a 50% reduction in seizure frequency (43% versus 27%, p = 0.08) and being entirely seizure free (5% versus 0%, p = 0.08) with CBD-Rx versus placebo were strong.[26]

Adverse events occurred more frequently in the CBD-Rx group than in the placebo group including somnolence (36% versus 10%), diarrhea (31% versus 10%), fatigue (20% versus 3%), vomiting (15% versus 5%), pyrexia (15% versus 8%), and lethargy (13% versus 5%).[26] A drug interaction between CBD and clobazam likely accentuated the somnolence since 18 of the 22 sleepy patients in the CBD-Rx group took both drugs. More patients had increased aminotransferase levels with CBD than placebo (12 versus 1) and more patients in the CBD-Rx group withdrew from the trial (8 versus 1).[26]

Since the FDA approved CBD-Rx, a randomized, double-blind, placebo-controlled trial of 199 patients compared CBD-Rx 10 mg/kg/day and 20 mg/kg/day to placebo.[27] Patients were aged 2 to 18 years with a confirmed diagnosis of Dravet syndrome and at least four convulsive seizures during the 4-week baseline period while receiving at least one antiepileptic drug. The percentage reduction compared to placebo was 29.8% (p = 0.01) for CBD-Rx-10 group and 25.7% (p = 0.03) for the CBD-Rx-20 group. The most common adverse events were decreased appetite, diarrhea, somnolence, pyrexia, and fatigue. Five patients in the CBD-Rx-20 group discontinued treatment owing to adverse events but no patients in other groups discontinued treatment. Three patients in the CBD-Rx-10 and 13 in the CBD-Rx-20 groups experienced elevated liver transaminase levels, with all affected patients on concomitant valproate sodium. Overall, this trial found similar efficacy and better potential safety with a lower initial CBD dosage.[27]

A multicenter, double-blind, placebo-controlled trial conducted in patients with Lennox-Gastaut syndrome enrolled 225 patients (aged 2 to 55 years) who were resistant to other therapy and experienced two or more seizures per week.[28] Researchers randomized them to receive CBD-Rx oral solution at a dose of either 10 mg/kg CBD twice daily (high dose CBD), 5 mg/kg twice daily (low dose CBD), or matching placebo for 14 weeks. The median percent reduction from baseline in drop-seizure frequency with CBD-Rx was 41.9% in the CBD-Rx-10 group (p = 0.005) and 37.2% in the CBD-Rx-5 group (p = 0.002) compared with 17.2% in the placebo group. Most common CBD-Rx-related adverse events (occurring more frequently in the higher-dose group) were somnolence, decreased appetite, and diarrhea. Six patients in the high-dose CBD group and one patient in the low-dose CBD group discontinued therapy because of adverse events. Fourteen patients who received CBD (9%) had elevated liver aminotransferase concentrations.[28]

In a second randomized, double-blind, placebo-controlled trial in patients (N = 171) with treatment-resistant Lennox-Gastaut syndrome, researchers investigated CBD-Rx's efficacy as add-on therapy.[29] Eligible patients (aged 2-55 years) had Lennox-Gastaut syndrome, at least two drop seizures per week during the 4-week baseline period and had not responded to treatment with at least two antiepileptic drugs. Patients randomly received CBD-Rx 20 mg/kg/day or matched placebo for 14 weeks.[29]

The median percentage reduction in seizure frequency from baseline was 43.9% (IQR -69.6 to -1.9) in the CBD-Rx group and 21.8% (IQR -45.7 to 1.7) in the placebo group for an estimated median difference between the groups of -17.21 (95% CI -30.32 to -4.09; p = 0·0135) over 14 weeks.[29] Adverse events occurred in 86% of patients (n = 86) in the cannabidiol group and 69% of patients in the placebo group (n = 85). The most common treatment-related adverse events were diarrhea, somnolence, pyrexia, decreased appetite, and vomiting. Fourteen percent of

patients in the cannabidiol group and 1% of patients in the placebo group withdrew because of adverse events.[29]

In a recent randomized, double-blind, placebo-controlled trial of 224 patients with tuberous sclerosis complex, researchers compared the efficacy and safety of CBD-Rx oral solution (CBD-Rx-25: 25 mg/kg/day and CBD-Rx 50: 50 -mg/kg/day) to placebo over 16 weeks.[30] Eligible patients were aged 1 to 65 years with medication-resistant epilepsy and had experienced at least 8 seizures during the 4-week baseline period. The percentage of seizure reduction versus placebo was 30.1% ($p < 0.001$) for the CBD-Rx-25 group and 28.5% ($p = 0.002$) for the CBD-Rx-50 group. The most common adverse events were diarrhea (25%, 31%, and 56%) and somnolence (9%, 13%, and 26%) in the placebo, CBD-Rx-25 and CBD-Rx-50 groups, respectively. Two, 8, and 10 patients in the placebo, CBD-Rx-25, and CBD-Rx-50 groups discontinued treatment because of adverse events. Twenty-eight patients taking cannabidiol (18.9%) had elevated liver transaminase levels compared to none taking placebo.[30]

Since CBD-Rx is an effective anti-convulsant therapy, the FDA is concerned that it might cause suicidal ideation.[4] Currently, long-term data is insufficient, or study populations have been too small to fully assess for suicidal ideation or suicides.[4] The literature and the FDA have not reported suicide or suicidal ideation associated specifically with the use of CBD-Rx. Counseling patients and/or their parents/caregivers on the risk of suicidal ideation so they can seek early intervention if problems arise is critical.

Proper Use: CBD-Rx in Seizure Disorders

The recommended starting dosage of CBD-Rx for Lennox-Gastaut or Dravet Syndrome is 2.5 mg/kg twice daily (5 mg/kg/day).[4] After one week, the dosage can be increased to the usual maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). If the individual clinical response is insufficient and tolerated, CBD-Rx can be increased in 2.5mg/kg increments each week up to a maximum maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).[4]

The recommended starting dosage for tuberous sclerosis complex is 2.5 mg/kg twice daily (5 mg/kg/day).[4] Prescribers can increase the dose weekly by 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a usual maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day).[4]

Using the highest recommended maintenance dose of 10 mg/kg twice daily or 12.5mg/kg twice daily can provide better seizure protection but increases the severity of adverse effects, including the risk of liver damage.[4] Food may affect CBD-Rx levels, so consistent dosing with respect to meals is recommended to reduce variability in response. That means if a patient chooses to take (or a caregiver administers) CBD-Rx with food in the morning or the evening, the patient should always take or receive the drug with food. Pharmacists should be mindful that children grow quickly and CBD-Rx doses may require adjustment to maintain effectiveness and prevent breakthrough seizures. Prescribers should monitor patients' weights; weight gain of four kilograms of body weight or more requires administration of an additional 10 mg of CBD-Rx.[4]

If patients wish to discontinue CBD-Rx therapy, patients should step down the dosage in weekly intervals to prevent breakthrough seizures. Patients or their families should always consult with their prescribers before stopping therapy.

Patients with moderate hepatic impairment should receive half of the normal starting, maintenance, and maximum maintenance doses.[4] In patients with severe hepatic impairment, prescribers should start all patients at 0.5 mg/kg twice daily with a normal maintenance dose of 1 mg/kg twice daily for Dravet and Lennox-Gestaut syndromes and 2.5 mg twice daily for tuberous sclerosis complex. The maximum CBD-Rx dose should be 2 mg/kg twice

daily for Dravet and Lennox-Gestaut syndromes and 2.5 mg twice daily for tuberous sclerosis complex.[4]

CBD-Rx's manufacturer provides a calibrated 5 mL or 1 mL oral syringe for accurate dosing.[4] Patients with calculated CBD-Rx doses of 100 mg or less should receive the 1 mL syringe because the product contains 100 mg of CBD per mL. Household teaspoons or tablespoons are not proper measuring devices and patients should not use them. Patients should discard any unused CBD product remaining 12 weeks after first opening the bottle. Again, small changes in anticonvulsant drug concentrations can result in breakthrough seizures.[4]

Counseling for CBD-Rx

CBD-Rx comes with oral syringes.[4] Pharmacy staff should show patients or caregivers the oral syringe and demonstrate how to affix the syringe to the bottle and withdraw the plunger to the correct line (or mark) to achieve a proper dose.[4]

Pharmacists should remind patients with seizure disorders who are prescribed CBD-Rx to avoid non-FDA-approved CBD products due to risks from dosing variability inducing breakthrough seizures or adverse events, exposure to unneeded THC, and complications from adulteration and contamination. This is an area where technicians can be very helpful, especially in stores that sell CBD products over the counter; technicians who see patients purchasing nonprescription CBD products should invite discussion with the customer, especially if the customer or a family member is using CBD-Rx.

Pharmacists should inquire whether the prescriber has ordered liver function testing before the patient starts therapy and when follow-up monitoring of the liver is planned. Pharmacists should also counsel patients to alert their prescribers if they develop new unexplained nausea and vomiting, right upper quadrant abdominal pain, fatigue, anorexia, jaundice, and/or dark urine. These signs of liver injury indicate patients should have their liver function tested. Clinicians should routinely assess liver function before therapy and one, three, and six months after patients start therapy. Therapy should be discontinued if the AST or ALT rises more than three times the upper limit of normal or bilirubin is increased more than 2 times the upper limit of normal.

CBD-Rx can sedate patients. Sedation is usually more intense for several days after therapy initiation or a dosage increase. People should avoid driving or operating heavy machinery until they know that they can function adequately while taking the CBD-Rx. They should also avoid concomitant use of other sedating over the counter products such as alcohol, sedating antihistamines, kava, or valerian.

Pharmacists should screen patients for drug interactions and monitor patients when it's impossible to avoid the risk of adverse drug interactions. They should be vigilant, especially when patients are prescribed diazepam and clobazam.

While we do not know if CBD-Rx enhances the risk of suicidal ideation like other antiepileptic medications, patients receiving CBD-Rx almost always take other antiepileptic medications. As such, patients need to be aware that any antiepileptic medication could cause this effect. Counseling that they should monitor themselves or their children for signs of depression or suicidal ideation while taking antiepileptic medication including CBD-Rx is critical.

CBD-RX OR UNAPPROVED CBD IN OTHER DISEASES AND DISORDERS

Researchers have studied both CBD-Rx and unapproved CBD products in many other diseases and disorders. While Internet sources hype CBD's curative effects in many diseases and disorders, **Table 1**. summarizes the available—and much weaker—evidence. Confused by the statistical terms in this section? Check out the **SIDEBAR** (next page).

Anxiety

Multiple studies have assessed CBD's impact on anxiety.[31-43] All studies except one used single dose CBD so the efficacy or safety of chronic therapy is unknown. Most studies enrolled normal volunteers, so their response might be different than responses in people with social anxiety or generalized anxiety disorders.[31-43] The studies used a range of CBD doses from multiple manufacturers.

In several trials, single dose CBD was given to counteract anxiety induced by single dose THC.[31-34] While concurrent CBD use seemed beneficial as assessed using two validated anxiety scales,

Table 1. Relative Strength of Evidence Base for CBD

Condition	Evidence Base
Anxiety	
THC Induced or Opioid Withdrawal	++
Public Speaking	++
Stressor Prophylaxis	+
Chronic Anxiety	0
Psychosis/Schizophrenia	
THC Induced	++
Other	+
Pain and/or Spasticity	0
Parkinson's Disease	
Movement disorders	+
Sleep	+
Acne	
Sebum production	+
Fewer Breakouts	0
Rosacea, Eczema, Psoriasis	0
Crohn's Disease	0
Cancer	0
Legend: 0 No Evidence or no evidence of benefit, + Very weak evidence of benefit, ++ Weak evidence of benefit, +++ Moderate evidence of benefit, ++++ Strong evidence of benefit	

What do these statistical terms mean?

Strength of Evidence – The strength of evidence indicates how certain you are that the intervention you are assessing will deliver desired or feared results when used in patients. The best way to improve the strength of evidence is to use strong study methods and adequate numbers of participants; they minimize the chance that study weaknesses will cause the results. If the study methods are weak or researchers enroll too few patients, the results may be caused by chance rather than an actual difference caused by the intervention. In studies discussed in this activity, CBD is the intervention.

Extrapolation – Extrapolation means taking data from one setting or circumstance and making a guess about what would happen in another setting or circumstance. For example, when researchers breed animals to have extremely high cholesterol and treat them with lipid-lowering drugs, the animals' cholesterol levels fall, and they live longer than animals that do not receive lipid-lowering drugs. Researchers might assume that it would also provide these benefits in humans. In another example, a drug reduces blood pressure and in general, higher blood pressure increases the risk of heart attack or stroke. So, researchers might extrapolate the blood pressure reductions and assume that this means that the drug also reduces heart attack and stroke risk.

Underpowered – Sometimes an intervention seems to provide benefits or harms, but the researchers haven't enrolled enough people to be able to say with 95% confidence that the results are not due to chance. For example, a study of four people per group found that no people died in group A died (0% mortality) but 1 person in group B died (25% mortality). It may be that intervention in group A prevented the death, but if the participant's death (although unfortunate) had nothing to do with the intervention. If the study had 800 people and the mortality rate was 0% vs. 25% in the two groups, you would have much more confidence that the intervention in group A could protect people from death.

© Can Stock Photo/GoodStudio

this result cannot be used as evidence of anti-anxiety effects arising from things other than THC agonism of the CB1 receptor.[31-34] However, in one study, researchers assessed people who were prone to paranoia unrelated to THC use in an anxiety-provoking virtual reality session.[44] Participants were randomized to receive a single dose of oral cannabidiol (600 mg) or placebo 130 minutes before entering virtual-reality. Immersion in the virtual-reality session elicited anxiety as indexed by the Beck's anxiety inventory ($p < 0.005$), and increased cortisol concentrations ($p = 0.05$), heart rate ($p < 0.05$), and systolic blood pressure ($p < 0.05$). Not only did CBD fail to provide any benefits on these parameters, but the researchers also noted a trend toward increasing anxiety ($p=0.09$).[44]

Other trials assessed CBD use a couple of hours before public speaking.[35-37] Overall, CBD provided positive anti-anxiety effects compared with the control. While underpowered, the 300 mg dose might provide greater benefits than smaller or larger doses, but this requires further investigation. CBD's benefits were less robust than the benzodiazepine clonazepam's in one study, but the latter induced significant sedation whereas the former did not.[35-37]

Researchers also assessed the acute use of CBD before stressful or anxiety-provoking situations other than public speaking.[38-43] Unfortunately, the results were inconsistent and it is unclear whether patients taking CBD before non-public speaking anxiety-provoking events is an effective strategy.[38-43] However, in 2021, the impact of the placebo effect on CBD anxiolysis was explored.[45] Researchers gave 43 people a CBD-free hemp oil but told them in one phase that they were receiving CBD oil and in another phase that they were not receiving CBD oil. Those with the strongest beliefs that CBD was an effective anxiolytic had the most profound anxiety reductions when they were given placebo compared with when they had the same acute stressor but were told they were not receiving CBD.[45] As such, given the current dataset, it is hard to discern whether CBD's innate pharmacology helps calm anxiety or the expectation of anxiolysis provides the benefit.

The final study in this section assessed short term anxiety caused by withdrawal symptoms.[46] In a randomized, double-blind, placebo-controlled trial, researchers enrolled drug-abstinent individuals with heroin use disorder. They assessed the acute (1 hour, 2 hours, and 24 hours), short-term (3 consecutive days), and protracted (7 days after the last of three consecutive daily administrations) effects of CBD administration (400 mg or 800 mg, once daily for 3 consecutive days) on drug cue-induced craving (exposure to stimuli associated with drug use that often causes craving and subsequent anxiety and drug-seeking behavior). Acute CBD administration reduced both craving and anxiety induced by the presentation of salient drug cues significantly more than placebo. Three days of CBD also showed significant protracted effects on these measures seven days after exposure.[46]

Taken together, short term use of CBD may provide anti-anxiety benefits to those ingesting THC who are at risk of anxiety from paranoid thoughts but those prone to paranoia not due to THC might not accrue these benefits. Researchers have been unable to determine the extent to which this CBD helps people with stage fright; such reductions could be due to its pharmacology or might be placebo effect. And while anxiety due to opioid withdrawal was reduced in one study, researchers need to repeat these studies and enroll larger numbers of participants. No data suggest that CBD is a safe, effective chronic medication for those with anxiety disorders.

Psychosis and Schizophrenia

THC is known to induce paranoia and psychosis in some individuals. Two double-blind trials assessed the impact of single doses of CBD on attenuating the acute psychotic-like effects of THC in normal volunteers.[39,47] The first trial found CBD had no impact on the Positive and Negative Syndrome Scale (PANNS) score without THC use when compared to placebo. It did find suppression of THC-induced changes at 30 minutes.[39] The second trial compared CBD to placebo 210 minutes before the researchers administered intravenous THC 1.5 mg.[47] Post-THC administration, the CBD group had lower PANSS positive scores, but the difference was statistically insignificant. However, clinically significant positive psychotic symptoms were less frequent in the CBD group compared with the placebo group. Post-THC paranoia and episodic memory, as rated with the State Social Paranoia Scale (SSPS) and the Hopkins Verbal Learning Task-revised (HVLT-R), were lower in the CBD group compared with the placebo group.[47]

Two randomized, placebo-controlled trials assessed the impact of moderate length CBD therapy on patients with schizophrenia.[48-50] The first trial found significantly greater reductions in PANNS positive scores in the CBD group versus placebo but not for the other PANNS scores (PANNS negative, total, or general).[48] The second trial found CBD therapy conferred no significant benefits for PANNS total, general, positive, or negative scores compared to placebo. The first trial allowed only one antipsychotic to be used for baseline therapy while the second trial allowed a sizeable portion of patients to receive more than one antipsychotic agent.[49]

In a double-blind, randomized, actively controlled trial, CBD was directly compared to the atypical antipsychotic amisulpride in patients (n = 39) with acute schizophrenia.[50] After three antipsychotic-free days (or greater than three months after a depot injection), the researchers randomized patients to 200 mg of CBD or amisulpride daily, which could be increased by 200 mg daily for a total of four administrations daily (total 800 mg per day) within the first week. The PANNS total, general, positive, and negative scores and the Brief Psychiatric Rating Scales scores improved significantly in both groups at 14 and 28 days but there were no significant differences between the two groups at any point. As compared to amisulpride-treated patients, CBD-treated patients had fewer extrapyramidal symptoms, approximately 3 kilograms (6.6 pounds) less weight gain at 28 days of therapy, and less prolactin release at both 14 and 28 days.[50] This improved safety profile could be an important advantage for CBD either as monotherapy or as an adjunctive therapy if it provides reasonable efficacy.[50]

Pain and Spasticity

Studies assessing CBD alone for pain relief are scant and two of three use methodologies with very weak strength of evidence.[51,52] The first two trials were open label single arm studies assessing pain relief from human papillomavirus (HPV) vaccine or renal transplant. While study participants had qualitatively lower pain scores over time after CBD use, researchers could not determine whether benefits seen in these trials were due to CBD, natural alleviation of symptoms over time, or placebo. A lack of intention-to-treat methodology with a high withdrawal rate may have confounded the first trial.[51,52] Similarly, the first trial used CBD-enriched hemp oil; hemp oil constituents (other than CBD) might have provided some of the benefits.[51]

One randomized, double-blind, multi-group crossover trial assessed pain and spasticity. This trial enrolled patients (N = 24) with multiple pain and spasticity disorders.[53] Only 12 patients, 16 patients, and eight patients completed the pain, spasm, and spasticity assessments, respectively, creating a weak dataset without the use of intention to treat analysis. The CBD group had significantly better but modest pain control (54.8 $\pm$ 22.6 versus 44.5 $\pm$ 22.7, $P < 0.05$) but no significant improvements in spasm (54.6$\pm$19.1 versus 47.3$\pm$22.6), spasticity (47.8 $\pm$ 18.5 versus 42.3 $\pm$ 18.1), bladder function (60.5 $\pm$ 28.4 versus 54.9 $\pm$ 28.8), or coordination (38.3 $\pm$ 22.9 versus 40.6 $\pm$ 21.1) compared with placebo.[53]

In one study, 29 patients with symptomatic peripheral neuropathy were randomized to a topical whole-plant-extracted CBD (250 mg CBD/3 fluid ounces) group or a matching placebo group with therapy applied up to four times daily.[54] The researchers administered the Neuropathic Pain Scale biweekly to assess the mean change from baseline to the end of the treatment period. The change from baseline was -5.55 $\pm$ 2.81 points in the CBD group and -3.33 $\pm$ 2.02 in the placebo group for a significant mean difference of −2.22 (95% CI −4.07 to −0.37). No adverse events were reported.[53]

Parkinson's Disease

One available trial examined CBD in Parkinson's disease.[55,56] Twenty-one patients with Parkinson's disease without dementia or comorbid psychiatric conditions were assigned placebo, CBD 75 mg/day, or CBD 300 mg/day for six weeks.[55] The researchers found no differences in or between any group for the Unified Parkinson Disease Rating Scale, concentrations of Brain-Derived Neurotrophic Factor, or in Proton Magnetic Resonance Spectroscopy indices. The group receiving CBD 300 mg/day had signifi-

cant improvements compared with placebo in the Parkinson's Disease Questionnaire-39 ($p = 0.05$).[55] Four of the subjects had Parkinson's disease-associated rapid eye movement (REM) sleep behavior disorder, which is characterized by nightmares and loss of muscle tone or strength during REM sleep.[56] All REM sleep behavior disorder-affected patients received CBD (75 mg/day in one patient and 300 mg/day in three patients). At baseline patients had between two to four episodes of REM sleep behavior disorder per week but during the six-week study, three patients had no events, and the other patient (receiving 300 mg/day CBD) had a reduction to one episode per week.[56]

In an open-label study of 13 patients with Parkinson's disease and substantial rest tremor, CBD-Rx was titrated from 5 mg/kg/day to 20 to 25 mg/kg/day and maintained for 10 to 15 days.[57] All participants reported adverse events, including diarrhea (85%), somnolence (69%), fatigue (62%), weight gain (31%), dizziness (23%), abdominal pain (23%), and headache, weight loss, nausea, anorexia, and increased appetite (each 5%). Adverse events were mostly mild; none were serious. Elevated liver enzymes, mostly a cholestatic pattern, occurred in five (38.5%) participants on 20-25 mg/kg/day, only one symptomatic. Three (23%) dropped out due to intolerance. The 10 people who completed the study had 18% improvements ($p=0.012$) in their total and 25% improvements ($p=0.004$) in their motor Movement Disorder Society Unified Parkinson Disease Rating Scale scores. Nighttime sleep and emotional/behavioral scores also improved significantly.[57]

Finally, investigators in one study used the public speaking methodology employed in the anxiety study section above and studied CBD's impact in patients with Parkinson's disease.[58] Participants in this randomized, double-blinded, placebo-controlled, crossover clinical trial (N = 24) underwent two experimental sessions within a 15-day interval. CBD attenuated experimentally-induced anxiety assessed by the Visual Analog Mood Scales anxiety factor and reduced anxiety-provoked tremor amplitude as recorded by the accelerometer.[58]

Topical CBD for Skin Related Disorders

Despite the hype around CBD use for acne, rosacea, eczema, and other skin disorders, the data is poor. To date, only two studies have explored CBD's role in acne. In the first study, researchers administered CBD to cultured human sebocytes and human skin organ culture, which inhibited the lipogenic actions of various compounds (arachidonic acid, linoleic acid, and testosterone) and suppressed sebocyte proliferation and lipogenesis through TRPV4 activation.[59-61]

In a second study, male volunteers applied a 3% cannabis seed extract in a vehicle to one cheek or vehicle alone to the other cheek for 12 weeks. Using a sebumeter, the researchers found a significant reduction in sebum production with cannabis extract versus vehicle alone ($p < 0.05$). CBD's contribution apart from the contribution from other cannabis constituents' contribution in this study is unknown and researchers have not adequately explored its role in reducing pimples or pustules. Other CBs have potential anti-acne potential with similar effects on human sebocytes, so whether CBD alone or the CB mixture in hemp extract is more effective is unknown.[59-61]

PAUSE AND PONDER: Aside from possible adverse effects, what are some other risks of trying to self-medicate with CBD for inflammatory diseases like rheumatoid arthritis, colitis, and psoriasis?

Theoretically, CBD could impact inflammatory skin conditions. However, human data on CBD's impact on rosacea, eczema, or psoriasis is nonexistent in the biomedical literature.

Crohn's Disease

CBD is an anti-inflammatory cannabinoid shown to be beneficial in an animal model of inflammatory bowel disease. It has only been studied in one human trial. The study randomized 20 patients with refractory Crohn's disease to receive oral CBD 10 mg twice daily or placebo. After eight weeks of treatment, no differences in CBD signs and symptoms occurred. It is possible that refractory patients were not amenable to benefits, the dose was too low, or that CBD is just ineffective for this inflammatory disorder.[62]

To understand this next study, readers need to know that episodes of inflammation like those seen in inflammatory bowel disease and septic shock compromise the gut's barrier function (increase its permeability), allowing noxious material to transfer into the systemic circulation. In an initial randomized, double-blinded, placebo-controlled trial, 30 normal volunteers who had no gastrointestinal diseases received aspirin 600 mg to increase gut permeability.[63] Researchers administered oral CBD 600 mg or placebo to participants and then compared their lactulose/mannitol ratios over six hours; a larger ratio suggests greater gut permeability. The lactulose/mannitol ratio across the experimental period was increased after both CBD and placebo ($P < 0.001$ for both compared with their respective baselines) but compared with the placebo and aspirin group, the lactulose/mannitol ratio was lower in the CBD and aspirin group ($p < 0.0001$). While this is a model for inflammatory bowel diseases, whether these effects will translate to clinical benefits in patients with Crohn's disease remains to be seen.

Cancer

Some *in vitro* and animal models suggest CBD has cancer preventive or treatment effect.[64] A few case reports suggest efficacy.[65,66] However, no human trials have evaluated CBD's anticancer effects and cancer patients may be at appreciable risk due to CBD drug interactions if they self-treat without coordinating with their treatment teams.

COUNSELING:UNAPPROVED CBD PRODUCTS

All healthcare providers should caution people interested in oral CBD for non-FDA-approved indications that no human studies exist for most diseases. While preliminary trials in anxiety, local pain, psychosis or schizophrenia, and Parkinson's disease are promising, patients should not use nonprescription CBD to replace FDA-approved therapies. Patients should disclose CBD use to all healthcare clinicians so trained clinicians can assess the impact and potential adverse events. Pharmacists and pharmacy technicians can remind patients to only buy CBD products with independent laboratory verification of the CBD dosage, THC percentage, and lack of contamination and adulteration. Using substandard products in which the active ingredient varies from batch to batch for diseases or disorders is dangerous.

For all oral CBD products, instructing patients about the main risks of therapy including sedation and gastrointestinal distress is essential. Due to possible sedation, patients shouldn't operate heavy machinery until they know how CBD impacts them specifically and even then, only if they can do so safely. Patients using oral CBD shouldn't start new OTC drugs or dietary supplements without checking with their pharmacists to avoid drug interaction-induced adverse events. Here, again, the pharmacy technician's role is to watch for purchases of these products.

Patients with chronic liver disease should not use CBD products as they might worsen the degree of damage. Pharmacists should warn patients that if they develop tender upper quadrant abdominal pain, yellowing of the skin and eyes, or light-tan colored stools, they should call the doctor right away as this can indicate liver damage. Finally, pharmacists should tell patients and/or their caregivers about the risk of suicidal ideation, that this warning is not specific to oral CBD products, and it has been reported with other anticonvulsants as a class. Pharmacists should remind patients that if they notice feeling more down than usual or are thinking about harming themselves, they should consult their doctors immediately.

If patients ask about topical CBD products for acne, pharmacists can tell them limited weak data suggests a potential benefit. Whether pure CBD is better or worse than products with all of hemp extract's components is unknown. For rosacea, psoriasis, and other inflammatory skin disorders, no human studies suggest a benefit from topical CBD products.

Finally, CBD is a drug, not a trendy food or beverage additive. Pharmacists should recommend against using CBD products without healthcare provider input, especially if the patient takes other CBD products or other drugs that could interact.

CONCLUSION

If patients use non-FDA-approved forms of CBD, they risk exposure to variable CBD and THC dosages, adulteration, and contamination. If not FDA-approved, products tested by an independent laboratory are safer. CBD is an effective option for the adjunctive treatment of refractory seizures in Dravet and Lennox-Gastaut syndromes and holds promise in the treatment of other refractory seizures, but more data is needed to determine its role. Additionally, CBD is promising but not proven for pre-medicating before anxiety-inducing events such as public speaking and chronic treatment of patients with schizophrenia. CBD has not been assessed for chronic treatment of anxiety. Data in pain, spasticity, and Parkinson's disease is limited and weak. CBD is not risk free since it has both drug interaction and adverse event potential. Somnolence and fatigue coupled with gastrointestinal disturbances are not uncommon and rarer but serious events such as elevated liver function tests have been observed. CBD's impact on suicidal ideation must be explored as this is a serious but rare adverse event associated with other anti-convulsant drugs. Longer-term safety data is needed to weigh CBD's possible benefits against possible harms.

Figure 1 summarizes key considerations when addressing the use of CBD in the clinical setting and in the setting of self-care.

Figure 1. Safety and Counseling Related to CBD Use

Best

❶ **Be COMMUNITY CHAMPIONS** and whenever possible, attend community events and state hearings about medical marijuana and CBD (or follow them in the news)

❷ **Encourage discussion** with patients about OTC and prescription CBD use stressing that these products are not interchangeable

❸ **Show patients how to measure CBD,** using the syringe for the prescription product, and by reading the labels of nonprescription products, calculating the dose, and providing the dose in writing

Better

❶ **Post information about CBD on bulletin boards in patient waiting areas** using patient-friendly language

❷ **Report adverse events related to any CBD product** through the United States Food and Drug Administration Adverse Event Reporting System (FAERS)

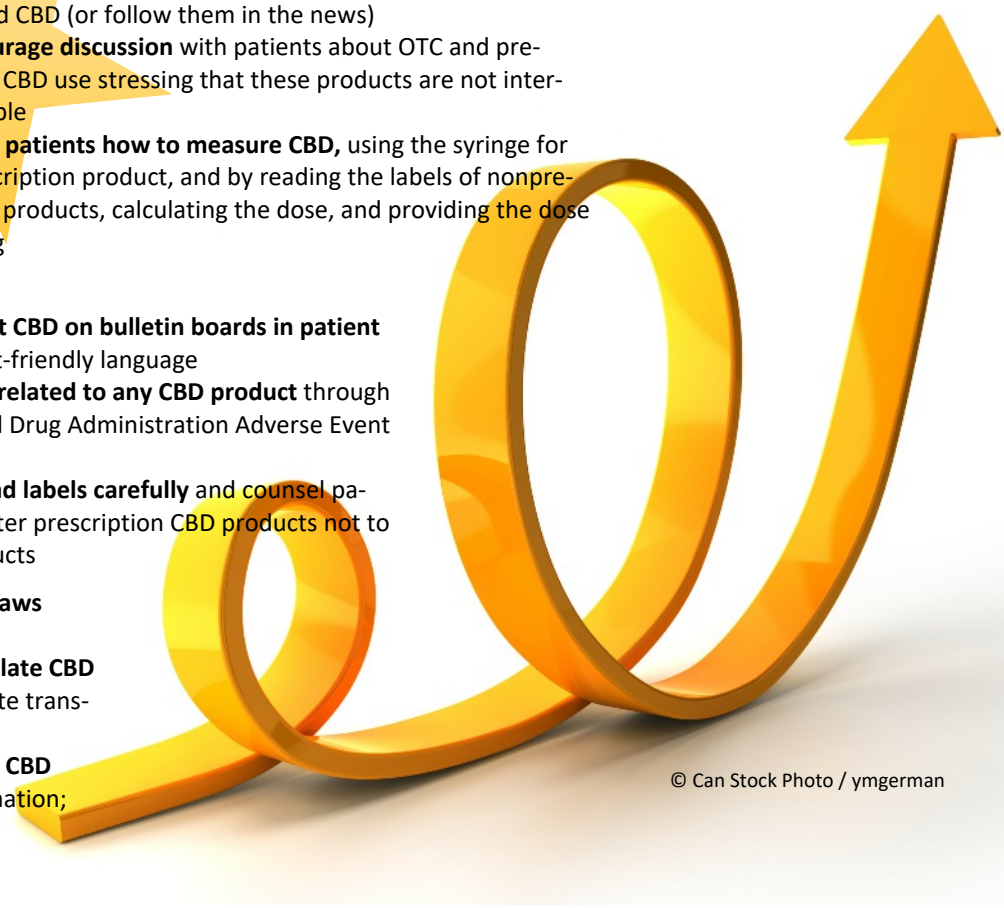
❸ **Remind patients to read labels carefully** and counsel patients who take or administer prescription CBD products not to use unapproved CBD products

Good

❶ **Be familiar with federal and state laws** concerning CBD use in your state

❷ **Know how neighboring states regulate CBD** and how your state deals with interstate transfer of these products

❸ **Understand that many people use CBD products** and may need reliable information; avoid judging them



REFERENCES

1. Clifford T. FDA-backed CBD drug brings in $296 million in 'incredible launch year,' GW Pharma CEO says. January 16, 2020. Accessed May 4, 2022. https://www.cnbc.com/2020/01/16/cbd-epilepsy-drug-does-incredible-296-million-in-sales-gw-pharma-ceo.html
2. Jazz Pharmaceuticals announces full year and fourth quarter 2021 financial results. March 1, 2022. Accessed May 4, 2022. https://investor.jazzpharma.com/news-releases/news-release-details/jazz-pharmaceuticals-announces-full-year-and-fourth-quarter-2021#:~:text=Epidiolex%2FEpidyolex%20net%20product%20sales,to%202020%20and%204Q20%20respectively
3. Total U.S. cannabidiol (CBD) product sales from 2014 to 2022. Statista. Accessed May 4, 2022. https://www.statista.com/statistics/760498/total-us-cbd-sales/
4. Epidiolex® (Cannabidiol) Prescribing Information. Greenwich Biosciences, Inc. 2022.
5. Drug Enforcement Administration. Schedules of controlled substances: placement in schedule V of certain FDA-approved drugs containing cannabidiol; corresponding change to permit requirements. 21 CFR Parts 1308, 1312 [Docket No. DEA–486]. September 28, 2018. Federal Register 2018;vol 83, No. 189. Accessed at https://www.gpo.gov/fdsys/pkg/FR-2018-09-28/pdf/2018-21121.pdf, accessed April 10, 2019.
6. Hudak J. The Farm Bill, hemp legalization and the status of CBD: An explainer. December 14, 2018. Accessed May 4, 2022. https://www.brookings.edu/blog/fixgov/2018/12/14/the-farm-bill-hemp-and-cbd-explainer/
7. Bonn-Miller MO, Loflin MJ, Thomas BF, et al. Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*. 2017;318:1708-1709.
8. Segall B. CBD oil poses risk for failed drug tests. WTHR TV. May 12, 2018. Accessed at https://www.wthr.com/article/cbd-oil-poses-risk-for-failed-drug-tests, April 10, 2019.
9. Regan T. Woman says she failed drug test after taking CBD oil. WSB-TV. October 3, 2018. Accessed at https://www.wsbtv.com/news/local/atlanta/woman-says-she-failed-drug-test-after-taking-cbd-oil/846083743, April 10, 2019.
10. Hazekamp A. The trouble with CBD oil. *Med Cannabis Cannabinoids*. 2018;1:65-72. https://doi.org/10.1159/000489287.
11. ConsumerLab. CBD & Hemp Extract Supplements, Lotions, and Balms Review. Accessed May 4, 2022. https://www.consumerlab.com/reviews/cbd-oil-hemp-review/cbd-oil/
12. Talati R, Scholle JM, Phung OJ, et al. Effectiveness and safety of antiepileptic medications in patients with epilepsy. AHRQ Publication No. 11(12)-EHC082-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2011. Accessed May 4, 2022. www.effectivehealthcare.ahrq.gov/reports/final.cfm
13. Horth RZ, Crouch B, Horowitz BZ, et al. Notes from the field: acute poisonings from a synthetic cannabinoid sold as cannabidiol – Utah 2017-2018. *MMWR*. 2018;67:587-588.
14. International Cannabis and Cannabinoids Institute. Warning for consumers of CBD and cannabis oils sold on the EU market. February 16, 2018. Accessed at https://www.icci.science/en/article/news/warning-for-consumers-of-cbd-and-cannabis-oils-sold-on-the-eu-market/, April 10, 2019.
15. Summitt Labs Issues Voluntary Nationwide Recall of KORE ORGANIC Watermelon CBD Oil Due to High Lead Results. July 28, 2020. U.S. Food and Drug Administration. Accessed May 5, 2022. https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/summitt-labs-issues-voluntary-nationwide-recall-kore-organic-watermelon-cbd-oil-due-high-lead
16. Heavy metals and cannabis. NewFood.com. Accessed May 4, 2022. https://www.newfoodmagazine.com/article/109084/heavy-metals-and-cannabis/
17. Compounds, isolate, full-spectrum, or broad-spectrum: What's the difference? healthlone.com Accessed May 4, 2022. https://www.healthline.com/health/reading-a-cbd-label#terminology
18. Gill LL. How to Shop for CBD. Consumer Reports. September 27, 2018. Accessed May 4, 2022. https://www.consumerreports.org/marijuana/how-to-shop-for-cbd/
19. Charles S. CVS To sell CBD products in 800 stores in 8 states. NBC News. March 21, 2019. Accessed May 4, 2020. https://www.nbcnews.com/health/health-news/cvs-sell-cbd-products-800-stores-8-states-n986016
20. Stott C, White L, Wright S, et al. A phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of rifampin, ketoconazole, and omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *SpringerPlus*. 2013;2:236.
21. Iffland K, Grotenherman F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis and Cannabinoid Res*. 2017;2:139-154.
22. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clozabam and cannabadiol in children with refractory epilepsy. *Epilepsia*. 2015;56:1246-1251.
23. Epilepsy Foundation. Types of epilepsy syndromes. Accessed May 4, 2022. https://www.epilepsy.com/learn/types-epilepsy-syndromes
24. Overview: Tuberous sclerosis. NHS website. Accessed May 4, 2022. https://www.nhs.uk/conditions/tuberous-sclerosis/#:~:text=Tuberous%20sclerosis%2C%20also%20known%20as,%2C%20heart%2C%20eyes%20and%20lungs.
25. Franz DN, Bissler JJ, McCormack FX. Tuberous sclerosis complex: neurological, renal and pulmonary manifestations. *Neuropediatrics*. 2010;41(5):199-208. doi:10.1055/s-0030-1269906
26. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med*. 2017;376:2011-2020.
27. Miller I, Scheffer IE, Gunning B, et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial [published correction appears in JAMA Neurol. 2020 May 1;77(5):655]. *JAMA Neurol*. 2020;77(5):613-621. doi:10.1001/jamaneurol.2020.0073
28. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. *N Engl J Med*. 2018;378:1888-1897.
29. Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391(10125):1085-1096. doi:10.1016/S0140-6736(18)30136-3
30. Thiele EA, Bebin EM, Bhathal H, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: A placebo-controlled randomized clinical trial. *JAMA Neurol*. 2021;78(3):285-292. doi:10.1001/jamaneurol.2020.4607
31. Zuardi AW, Shirakawa I, Finkelfarb E, et al. Action of cannabidiol on the anxiety and other effects produced by delt 9-THC in normal subjects. *Psychopharmacol*. 1982;76:245-250.
32. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta 9-tetrahydrocannabidiol in man. *Eur J Pharmacol*. 1974;28:172-177.
33. Zuardi AW, Cosme RA, Graeff FG, et al. Effects of ipsapirone and cannabadiol on human experimental anxiety. *J Psychopharmacol*. 1993;7:82-88.
34. Martin-Santos R, Crippa JA, Batalla A, et al. Acute effects of a single, oral dose of d-9-tetrahydrocannabidiol (THC) and cannabidiol (CBD) administration in healthy volunteers. *Curr Pharm Design*. 2012;18:4966-4979.
35. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naıve

Social phobia patients. *Neuropsychopharmacology*. 2011;36:1219-1226.
36. Linares IM, Zuardi AW, Pereira LC, et al. Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. *Braz J of Psychiat*. 2019 Jan-Feb;41(1):9-14.
37. Zuardi AW, Rodrigues NP, Silva AL, et al. Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. *Front Pharmacol*. 2017;May 11;8:259.
38. Crippa JA, Zuardi AW, Garrido GE. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29:417-426.
39. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35:764-774.
40. Das RK, Kamboj SK, Ramadas M, et al. Cannabidiol enhances consolidation of explicit fear extinction in humans. *Psychopharmacology (Berl)*. 2013;226:781-792.
41. Arndt, DL, Harriet de Wit H. Cannabidiol does not dampen responses to emotional stimuli in healthy adults. *Cannabis and Cannabinoid Res*. 2017 Jun 1;2(1):105-113.
42. Hundal H, Lister R, Evans N, et al. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *J Psychopharmacol*. 2018;32:276-282.
43. Hindocha C, Freeman TP, Schafer G, et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *Eur Neuropsychopharmacol*. 2015;25:325-334.
44. Hundal H, Lister R, Evans N, et al. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *J Psychopharmacol*. 2018;32(3):276-282. doi:10.1177/0269881117737400
45. Spinella TC, Stewart SH, Naugler J, Yakovenko I, Barrett SP. Evaluating cannabidiol (CBD) expectancy effects on acute stress and anxiety in healthy adults: a randomized crossover study. *Psychopharmacology (Berl)*. 2021;238(7):1965-1977. Doi:10.1007/s00213-021-05823-w
46. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial
47. Englund A, Morrison PD, Nottage J, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol*. 2013;27(1):19-27.
48. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *Am J Psychiatry*. 2018;175:225-231.
49. Boggs DL, Surti T, Gupta A, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo-controlled trial. *Psychopharmacol*. 2018;235:1923-1932.
50. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry*. 2012 Mar 20;2:e94.
51. Palmieri B, Laurino C, Vadalà M. Short-term Efficacy of CBD-enriched hemp oil in girls with dysautonomic syndrome after human papillomavirus vaccination. *IMAJ*. 2017;19:79-84.
52. Cuñettia L, Manzoa L, Peyraubeb R, et al. Chronic pain treatment with cannabidiol in kidney transplant patients in Uruguay. *Transplantation Proc*. 2018;50(2):461-464.
53. Wade DT, Robson P, House H, et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 2003;17:21-9.
54. Xu DH, Cullen BD, Tang M, Fang Y. The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. *Curr Pharm Biotechnol*. 2020;21(5):390-402. Doi:10.2174/1389201020666191202111534
55. Chagas MH, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. *J Psychopharmacol*. 2014;28:1088-1098.
56. Chagas MH, Eckeli AL, Zuardi AW, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther*. 2014 Oct;39(5):564-566.
57. Leehey MA, Liu Y, Hart F, et al. Safety and Tolerability of Cannabidiol in Parkinson Disease: An Open Label, Dose-Escalation Study. *Cannabis Cannabinoid Res*. 2020;5(4):326-336. Published 2020 Dec 15. Doi:10.1089/can.2019.0068
58. de Faria SM, de Morais Fabrício D, Tumas V, et al. Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. *J Psychopharmacol*. 2020;34(2):189-196. Doi:10.1177/0269881119895536
59. Oláh A, Tóth BI, Borbíró I, et al. Cannabidiol exerts sebostatic and nti-inflammatory effects on human sebocytes. *J Clin Invest*. 2014;124:3713-3724.
60. Ali A, Akhtar N. The safety and efficacy of 3% cannabis seeds extract cream for reduction of human cheek skin sebum and erythema content. *Pak J Pharm Sci*. 2015;28:1389-1395.
61. Oláh A, Markovics A, Szabó-Papp J, et al. Differential effectiveness of selected non-psychotropic phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrheic skin and acne treatment. *Exp Dermatol*. 2016 Sep;25(9):701-707.
62. Naftali T, Mechulam R, Marii A, et al. Low-dose cannabidiol is safe but not effective in the treatment for Crohn's disease, a randomized controlled trial. Dig Dis Sci. 2017;62:1615-1620.
63. Couch DG, Cook H, Ortori C, Barrett D, Lund JN, O'Sullivan SE. Palmitoylethanolamide and cannabidiol prevent inflammation-induced hyperpermeability of the human gut in vitro and in vivo-a randomized, placebo-controlled, double-blind controlled trial. *Inflamm Bowel Dis*. 2019;25(6):1006-1018. Doi:10.1093/ibd/izz017
64. Hande K. Cannabidiol: The need for more information about its potential benefits and side effects. *Clin J Oncol Nurs*. 2019;23:131-134.
65. Sulé-Suso J, Watson NA, van Pittius DG, et al. Striking lung cancer response to self-administration of cannabidiol: A case report and literature review. *SAGE Open Med Case Rep*. 2019;7:2050313X19832160.
66. Dall'Stella PB1, Docema MFL1, Maldaun MVC1, et al. Case Report: Clinical Outcome and Image Response of Two Patients With Secondary High-Grade Glioma Treated With Chemoradiation, PCV, and Cannabidiol. Front Oncol. 2019;8:643. Doi: 10.3389/fonc.2018.00643.