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Cannabidiol (CBD): A Tale of Two Products

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's and Lennox-Gastaut syndromes. 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 and the dose actually delivered, use of non-FDA approved CBD products is highly discouraged 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 Internet touts 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. Pharmacists should discourage adding CBD to food and drink at this time.

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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

In the United States, the 2018 Farm Bill legalized hemp production, a move that has given products derived from hemp—products that contain cannabidiol (CBD)—a boost. A recent news article disucssed CBD's use by stressed-out parents.[1] Various companies market CBD, an extract from hemp and marijuana plants, as able to help patients' multiple ailments, including anxiety, pain, Parkinson's disease, schizophrenia, and cancer.[2,3] Consumers may be drawn to CBD as it comes in multiple forms (e.g., oils, eye serums, gummies, etc).[2,4] Even Willie Nelson has jumped on the CBD bandwagon—in July 2018, he released CBD infused-coffee beans.[2]

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EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Discuss cannabidiol and its known pharmacologic profile
- Identify FDA-approved indications for prescription cannabidiol and other indications in which research is promising
- Distinguish the FDA-approved canabidiol 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 participating in this activity pharmacists and 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

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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 quiz 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

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Pause and Ponder:
If you know that medical cannabis is effective for an ailment like nausea, why shouldn't you just assume that CBD will provide the same benefits?

Americans are increasingly consuming CBD; sales are expected to hit $22 billion by the year 2022.[1] Despite the hype, the U.S. Food and Drug Administration (FDA) has only approved CBD to treat two rare but severe seizure disorders in children. This continuing education activity will help pharmacists and pharmacy technicians understand how CBD differs from other cannabis plant-based products and the diagnoses in which evidence of CBD's effectives exists—and FDA-approved medication is available—and for which it does not.

Cannabis, Cannabinoids, and Cannabidiol

Like the autonomic nervous system, the endocannabinoid system is comprised of neurotransmitters and receptors that help the body maintain homeostasis or deal with stressors. Two endogenous cannabinoid (CB) neurotransmitters—anandamide and 2-arachidonylglycerol—interact with CB1 and CB2 receptors in the nervous system, different organs, and the immune system to produce biological effects. Sometimes, stimulation of one CB receptor type can modify the response caused by stimulating another type.[5]

Cannabis sativa (marijuana) is a complex plant with more than 60 CBs and many non-CB constituents called terpines. The constellation of effects from the mixture of CBs and terpines in cannabis—known as the entourage effect—can differ greatly from the effects caused by a single CB. Some CBs have opposing effects because they block another CB from stimulating a receptor or because they stimulate another CB receptor type with opposing effects.[5]

In traditional cannabis sativa plants (sometimes called medical or recreational cannabis), tetrahydrocannabidiol (THC) and CBD are the two most abundant CBs. In hemp plants, the THC concentration is markedly lower (less than 0.3%).[5] The THC component creates the "high" (i.e., altered sensory and time perception), but may also cause anxiety, paranoia, and impaired memory in many patients.[6] THC's effects are a barrier to wider acceptance of medical cannabis by patients, medical professionals, and society at large.[7] Depending on the state, employers and law enforcement may test workers or suspects for THC in their hair, nails, or urine; positive findings could result in suspension, termination, or prosecution even if the THC was used for medical purposes.[7-9]

Table 1 delineates CBD's potential mechanisms of action from *in vitro* and animal models.[8-16] It is inappropriate to make definitive treatment recommendations simply by extrapolating nonhuman data, there are just too many instances of where adequately conducted trials contradicts believed benefits. CBD may attenuate the high, anxiety, and paranoia induced by THC.[8] This is why high THC-containing cannabis varieties or synthetic cannabinoids that stimulate CB1 receptors without CBD's balancing effects are especially dangerous.[6]

Table 1. CBD Receptor Actions and Mediated Effects[8-16]

Potential Pharmacologic Outcome	Receptor Effects
Attenuation of THC-induced effects (anxiety, impaired learning, psychosis)	CB1 Antagonist
Anti-inflammatory effects	CB2 Inverse Agonist, TPVR-1 Agonist, Adenosine Enhancer
Pain relieving	5HT1-alpha Agonist, TVPR-1 Agonist
Decreased sebum producing effects	TVPR-1 Agonist
Anti-cancer effects	GPR55 Antagonist

Legend: CB1 Cannabinoid Receptor 1, CB2 Cannabinoid Receptor 2, GPR55 G-Coupled Protein Receptor, TPVR-1, 5HT1-alpha Serotonin 1a Receptor, Transient Receptor Potential Vanilloid Receptor.

This continuing education activity will

- empower health professionals to ensure that CBD is used properly in FDA approved indications,
- describe the state of the evidence for CBD products in other indications,
- describe quality control issues with non-prescription CBD products, and
- describe the pharmacokinetic and drug interaction data critical in risk assessment and for patient counseling.

FDA APPROVED PRODUCT
Currently Approved FDA Indications

Epidiolex (CBD-Rx) is the only FDA-approved form of CBD. It is indicated for the treatment of seizures associated with Lennox-Gastaut and Dravet's syndromes in patients two years of age and older. It consistently delivers 100mg/mL of CBD to patients with THC concentrations below 0.1%. In 2018, the Drug Enforcement Agency placed CBD-Rx in Schedule V (drugs with a relatively low risk of abuse).[17,18] However, all other CBD products extracted from cannabis sativa will remain Schedule I (high risk of abuse or harm, limited or no medicinal value, illegal to possess) until they are FDA-approved with a THC concentration of less than 0.1%.[18]

Supporting Data in Seizure Control

Two randomized trials were instrumental to FDA's decision to approve CBD-Rx. In these trials, patients had either Dravet syndrome or Lennox-Gestaut syndrome (see **Sidebar**, page 3 for defintions) and were insufficiently treated with traditional anti-seizure therapy.

SIDEBAR: Common Misperceptions

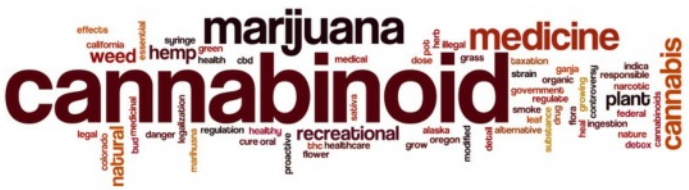
Myth: CBD has all of the beneficial effects of medical cannabis without the THC high.
Reality: CBD only provides one of cannabis' many constituents and you cannot assume it will work the same as medical cannabis. CBD has to be proven effective and safe for each indication before it is used to treat medical disorders.

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's syndromes but insufficient human data indicates it is effective for other uses. Although promising for patients with other epilepsy types, stage fright, and schizophrenia, much more research needs to be done before the balance of benefits to harm is known. Health care professionals should discourage its use for indications with less effectiveness evidence.

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 insight from a trained health professional for safe use. CBD's pharmacologic effects when it is baked in confectionery products or added to beverages are unknown and many states are clamping down on this practice. (THC seems stable to heating but heating cannabis converts THC-S into THC and increases the effective amount. It also slows the absorption and gives lower peak but longer duration of effects.)

Myth: All CBD products are the same.
Reality: Non-FDA approved CBD products have CBD doses in the bottle that frequently differ from the dose listed on the label and could be adulterated or contaminated.

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. If your patients use non-FDA approved CBD forms and don't have test results confirming an acceptable THC level, they could be in legal jeopardy.



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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.[20] 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. There were strong trends toward having 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.[20]

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%).[20] 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 one) and more patients in the CBD-Rx group withdrew from the trial (eight versus one).[20]

SIDEBAR: What are Lennox-Gestaut and Dravet syndromes?[19]

Lennox-Gestaut syndrome (LGS) has many different causes such as inflammation of the brain or brain covering, brain malformations, decreased blood and oxygen to the brain, injuries to the frontal lobes of the brain, and tuberous sclerosis complex (genetic disorder with growth of noncancerous tumors in the brain). It creates a constellation of childhood epilepsy disorders. In 25% of cases, clinicians are unable to find a cause. Patients with LGS have similar presentations on electroencephalogram characterized by slow spike and wave epileptiform activity when the person is awake. Multiple seizures types can occur (tonic, atonic or drop attacks, atypical absence, myoclonic, and generalized tonic-clonic) and LGS is associated with cognitive impairment. Only 0.026% of the population has LGS but this translates to 10% of children with epilepsy appearing before 5 years of age.

Dravet syndrome is caused by a rare genetic defect (1 in 20,000 to 40,000 children) arising from *de novo* genetic polymorphisms rather than inheritance. It usually begins in the first year of life in an otherwise healthy infant, and causes seizures throughout life. As seizures continue, most children develop some level of developmental disability.

Both Lennox-Gestaut and Dravet syndromes precipitate frequent and often refractory seizures. Traditional antiepileptic medication, deep brain stimulation, brain surgery, and ketogenic diets can be employed alone or in combination but there are still refractory patients.

TECH TALK: What do these statistical terms mean?

Strength of Evidence – The strength of evidence is how certain you are that the intervention you are assessing will actually deliver the desired or feared results when used in patients. The best way to improve the strength of evidence is to design studies with strong methods; they minimize the chance that study weaknesses will cause the results of the studies. In other words, researchers need to show that the intervention and adequate numbers of participants prove that the study results of the studies are induced by the intervention, not being caused by chance. 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 place. 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. You 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 you extrapolate the blood pressure reductions and assume that this means that the drug also reduces heart attack and stroke risk.

Underpowered – Sometimes an intervention might 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 one person in group B died (25% mortality). It may be that intervention in group A prevented the death but it also might be that someone unfortunately died and it 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.

Intention to Treat Analysis – Intention to treat analyses account for the impact of patient withdrawals on study results. In some studies, many people withdraw before the study's end, but the researchers only analyze the results in people who finish the study. This introduces risk of bias and weakens the strength of evidence. People will leave a study if they feel they aren't seeing benefits in line with the inconvenience or the adverse events they experience during participation. So if more people withdraw from the intervention group than the control group, it might suggest that there are adverse events that caused them to leave (that are now not being counted) or that the intervention was not as effective for some people as was seen the control group. For example, a study starts out with 10 people per group and only four people in the intervention group stay to the end of the study but nine people in the control group stay. The intervention group looks to have worked better with the same risk of adverse events among those completing the study. You would not be very confident in the results of this study because you may only be assessing the effects among the subset of people in the intervention group who perceived benefits or who tolerated that intervention better.

Meta-Analysis – Data from numerous trials can be combined using statistical techniques called meta-analysis. This can provide additional power to be able to assess outcomes that might be underpowered in a single study. Remember that meta-analyzing a number of very poorly constricted studies does not fix the problems in the studies or in the pooled result. It does reduce the chances that the differences seen are, or are not, due to chance.

In another multicenter, a double-blind, placebo-controlled trial, patients (n = 225) with Lennox-Gastaut syndrome (age range two to 55 years) who were resistant to other therapy and experienced two or more seizures per week enrolled. 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.[21] The median percent reduction from baseline in drop-seizure frequency with CBD-Rx was 41.9% in the high dose CBD group (p = 0.005) and 37.2% in the low dose CBD group (p = 0.002) compared with 17.2% in the placebo group.[21]

The most common adverse events among the patients in the CBD-Rx groups were somnolence, decreased appetite, and diarrhea with the events occurring more frequently in the higher-dose group.[21] 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.[21] CBD's global role in patients with epilepsy has been investigated in a meta-analysis of randomized trials totaling 555 subjects, driven by the two trials described in **Table 2**.[22] For two outcomes, greater than 50% reduction in seizures and health-related quality of life, only patients with Lennox-Gastaut and Dravet's syndromes were included. For complete seizure freedom, only 15 of the 306 included patients had a different seizure disorder (secondary generalized epilepsy).[22]

In a data compilation from all CBD-Rx epilepsy trials, the risk of raising the patient's liver function tests correlated to the CBD dose administered (e.g. it increased as the dose increased) and to other drugs the patient received.[23]

Table 2. Meta-analysis Results of CBD in Seizure Control and Quality of Life

Endpoint	Trial Number and Total Sample Size	Relative Risk (RR) with 95% Confidence Interval (CI)
≥50% reduction in seizures	2 trials; 291 participants	RR 1.74 (95%CI 1.24 to 2.3)
Complete seizure freedom	3 trials; 306 participants	RR 6.17 (95%CI 1.50 to 25.32)
Health related quality of life	2 trials; 274 participants	RR 1.73 (95%CI 1.33 to 2.26)

Since CBD-Rx is an effective anti-convulsant therapy, the FDA is concerned that it might cause suicidal ideation.[17] Currently, long-term data is insufficient or study populations have been too small to fully assess for suicidal ideation or suicides.[17] No suicide or suicidal ideation have been reported in the literature or by the FDA. It is important to counsel patients and/or their parents/caregivers on the risk of suicidal ideation so they can seek early intervention if problems arise.

PAUSE AND PONDER: If a 20 month old has uncontrollable frequent seizures, would CBD-Rx be a reasonable option to try even though it is not FDA-approved for that indication?

Promising Future Indications

Aside from Dravet and Lennox-Gastaut syndromes, CBD has been studied for many other diseases and disorders. While Internet sources hype CBD's curative effects in many diseases and disorders, the available evidence is much weaker as summarized in **Table 3**.

Table 3. Relative Strength of Evidence for CBD

Dravet's or Lennox-Gastaut Syndrome Seizures	
First Line Therapy	0
Refractory Disease	++++
Other Seizures	
First Line Therapy	0
Refractory Disease	+++
Anxiety	
THC Induced	++
Public Speaking	++
Stressor Prophylaxis	+
Chronic Anxiety	0
Psychosis/Schizophrenia	
THC Induced	++
Other	+
Pain and/or Spasticity	0
Parkinson's Disease	
Movement disorders	0
Sleep	+
Acne	
Sebum production	+
Fewer Breakouts	0
Rosacea or Eczema	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

Other Epilepsy Syndromes

Two open label studies assess CDB-Rx's role in seizure control in patients with different seizure disorders (not just Dravet and Lennox-Gastaut syndromes).[23] The first is in patients (n = 18) with tuberous sclerosis complex (which may or may not meet the definition of Lennox-Gestaut syndrome) induced refractory epilepsy. After an initial one-month baseline period, all patients began treatment with CBD-Rx. The researchers increased the initial dose of 5 mg/kg/day of CBD by 5 mg/kg/day every week up to a maximum dose of 50 mg/kg/day, if tolerated. Three months after using CDB-Rx, the median percent change in total weekly seizure frequency was 48.8% (Interquartile ratio (IQR) 69.1% to 11.1%). In patients taking clobazam concurrently with CBD-Rx (n = 12), the response rate after three months of treatment was 58.3%, compared to 33.3% in patients not taking clobazam (n = 6).[23]

The second study was for patients (n = 137, aged one to 30 years) with refractory seizures regardless of genetic etiology, although approximately 40% had either Dravet or Lennox-Gastaut syndromes.[24] Patients were given CBD-Rx 2 to 5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day. The median reduction in monthly motor seizures was 36.5% (IQR 64.7% to 0%).[24]

Anxiety

Multiple studies have assessed CBD's impact on anxiety.[25-37] All studies use single dose CBD so the efficacy or safety of chronic therapy is unknown. In most studies, normal volunteers were

used so their response might be different than those with social anxiety or generalized anxiety disorders.[25-37] The studies used a range of CBD doses from multiple manufacturers.

In several of the trials, single dose CBD was given to counteract anxiety induced by single dose THC.[25-28] While two validated anxiety scales were beneficially impacted by concurrent CBD use, this result cannot be used as evidence of anti-anxiety effects arising from things other than THC agonism of the CB1 receptor.[25-28] Other trials assessed CBD use a couple of hours before public speaking.[29-31] 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.[29-31] 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.[29-31] Researchers also assessed the acute use of CBD before stressful or anxiety-provoking situations other than public speaking.[32-37] Unfortunately, the results are inconsistent and it is unclear whether patients taking CBD before non-public speaking anxiety-provoking events is an effective strategy.[32-37]

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.[33,38] The first trial found CBD had no impact on the Positive and Negative Syndrome Scale (PANNS) score without THC use of versus placebo. It did find suppression of THC-induced changes at 30 minutes.[33] The second trial compared CBD to placebo 210 minutes before intravenous THC 1.5 mg was given.[38] 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.[38]

Two randomized, placebo controlled trials assessed the impact of moderate length CBD therapy on patients with schizophrenia.[39-41] 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).[39] The second trial found no significant benefits of CBD therapy 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.[40]

In a double-blind, randomized, actively controlled trial, CBD was directly compared to the atypical antipsychotic amisulpride in patients (n = 39) with acute schizophrenia.[41] After three antipsychotic-free days (or greater than three months after a depot injection), patients were randomized 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 as well as the Brief Psychiatric Rating Scales (BPRS) scores improved significantly in both groups versus baseline 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 and approximately three kilograms (6.6 pounds) less weight gain at 28 days of therapy and less prolactin release at both 14 and 28 days.[41] This improved safety profile could be an important advantage for CBD either as monotherapy or as an adjunctive therapy if it provides reasonable efficacy.[41]

Pain and Spasticity

The studies assessing CBD alone for pain relief are scant and two of three use methodologies with very weak strength of evidence.[42,43] The first two trials are 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 the benefits seen in these trials were due to CBD, natural alleviation of symptoms over time, or the placebo effect. The first trial could be confounded by a lack of intention-to-treat methodology with a high withdrawal rate.[42,43] Similarly, the first trial used CBD-enriched hemp oil; hemp oil constituents (other than CBD) might have provided some of the benefits.[42]

One randomized, double-blind, multi-group crossover trial assessed pain and spasticity. In this trial, patients (n = 24) with multiple pain and spasticity disorders were enrolled.[44] Only 12 patients, 16 patients, and eight patients completing 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±22.6 versus 44.5±22.7, P less than 0.05) but no significant improvements in spasm (54.6±19.1 versus 47.3±22.6), spasticity (47.8±18.5 versus 42.3±18.1), bladder function (60.5±28.4 versus 54.9±28.8), or coordination (38.3±22.9 versus 40.6±21.1) compared with placebo.[44]

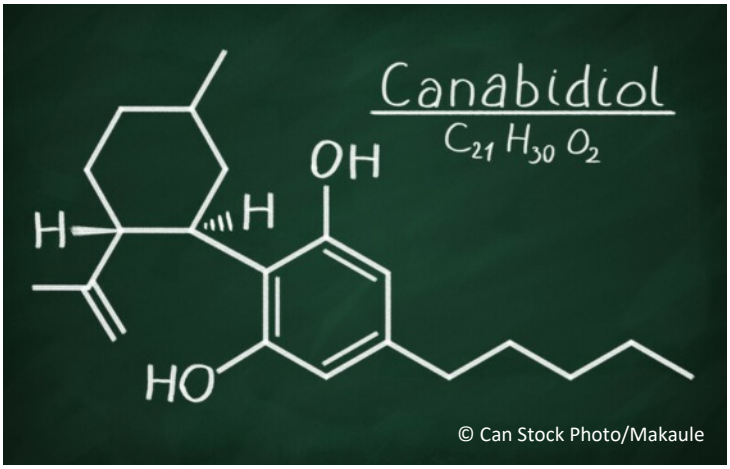
Parkinson's Disease

Only one available trial examined CBD administered to people with Parkinson's disease.[45,46] 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.[45] 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 300mg/day had significant improvements as compared with placebo in the Parkinson's Disease Questionnaire-39 (p = 0.05).[45] Four 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.[46] All REM sleep behavior disorder-affected patients received CBD (75mg/day in one patient and 300mg/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 300mg/day CBD) had a reduction to one episode per week.[46]

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,

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?



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researchers administered 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.[47-49]

In a second study, male volunteers applied a cannabis seed extract (3%) in a vehicle to one cheek or a 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 less than 0.05). CBD's contribution apart from other cannabis constituents' contributions 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 also unknown.[47-49]

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. No data suggests that CBD-enhanced moisturizers improve outcomes as compared with unenhanced moisturizers.

Crohn's Disease

CBD is an anti-inflammatory cannabinoid that has been shown to be beneficial in an animal model of inflammatory bowel disease (IBD). It has only been studied in one human trial. Twenty patients with refractory Crohn's disease were randomized to receive oral CBD 10 mg twice daily or placebo. After eight weeks of treatment, no differences in IBD 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.[50]

Cancer

Some *in vitro* and animal models suggest CBD has cancer preventive or treatment effect.[51] A few case reports suggest efficacy.[52,53] 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.

CBD'S PROFILE

Pharmacokinetics

The CDB-Rx CBD product demonstrates a less than dose-proportional increase in concentration over the range of 5 to 20 mg/kg/day 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 five- and four-–fold, respectively, but the package insert has no specific recommendations about administering CBD with or without food.[17] Following a single CBD 1500 mg dose (1.1 times the maximum recommended daily dosage), plasma clearance is 1111 L/h.[17]

Drug Interactions

CBD has many potential drug interactions both as a substrate and as an inhibitor and inducer of metabolic enzymes. CBD is primarily metabolized in the liver by cytochrome P450 (CYP2C19 and CYP3A4) and uridine 5'-diphospho-glucuronosyltransferase (UGT1A7, UGT1A9, and UGT2B7).[17] The impact of CYP3A4 and CYP2C19 inducers and inhibitors on CBD was explored for a combined CBD/THC product.[54] 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).[54]

CBD's main metabolite is the 7-OH-CBD metabolite that is subsequently converted into the 7-COOH-CBD metabolite, both of which may have anticonvulsant properties. After repeat dosing, 7-OH-CBD and 7-COOH-CBD metabolites' AUCs are 38% lower and 40-fold higher respectively than CBD's AUC.[17,55] Protein binding of CBD and its metabolites was found to be 94% *in vitro*. CBD can be excreted in feces with some minor renal clearance.[17]

CBD inactivates some CYP enzymes in the short term but then, like other anticonvulsants, induces them with chronic dosing.[55] Upregulation of CYP3A4 and CYP2B10 mRNA have occurred in mice and induction of CYP1A1 occurred *in vivo*.[55] In contrast, CBD seems to be an inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 metabolism.[17]

To test CBD's enzyme inhibition and induction effects, researchers assessed the impact of CDB-Rx on clobazam and its N-desmethylclobazam metabolite in 13 subjects (age range four to 19 years) with refractory epilepsy.[56] The mean increase in clozabam and N-desmethylclozabam levels was 60% and 500% after four weeks of concomitant therapy. CBD was determined to be a CYP2C19 inhibitor.[56] The package insert therefore suggests clinicians consider reducing the dose of sensitive CYP2C19 substrates such as diazepam and clobazam, as clinically appropriate, when coadministered with CBD.[17]

PAUSE AND PONDER: How can pharmacists proactively ensure that CBD products are not interacting with patients' prescribed therapy if they buy their CBD products from a smoke shop or over the Internet?

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.[17,55,56] 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.

NONPRESCRIPTION PRODUCTS

Quality Concerns

The FDA-approved CBD product provides the CBD concentration specified on the label with little variation over time. That is, patients 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 and tested them in triplicate using HPLC in a commercial laboratory.[57] Triplicate test results were averaged and reported 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, only 31% were labeled 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 0-6.4) in 21% of samples which would place people selling, possessing, or using these products at risk of arrest and prosecution.[57] People have failed THC drug tests despite reported use of CBD products only.[58,59]

The FDA has issued warning letters to numerous manufacturers for false claims and has also tested those products for CBD content. It found many of these products contain little to no CBD in marked contrast to their labeled amounts.[60] The U.S. is not the only country with concerns. In the Netherlands, for example, eight CBD products were assessed and 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.[61]

It is impossible to know the exact CBD dose patients take if they buy products that are not FDA-approved or that are independently tested by outside laboratories. ConsumerLabs assessed multiple CBD products for CBD content and found the labeled CBD dosages had little correlation with the products' CBD concentrations.[62] No CBD products have been verified by the United States Pharmacopeia.[63]

Inaccurately labeled CBD concentration or variability in CBD concentrations in products create potentially dangerous implications.[64] For example, in a systematic review of non-CBD antiepileptic drugs, our University of Connecticut Evidence-Based Practice Center found that seizure control was impacted by small changes in drug concentration. While brand and generic antiepileptic drugs were equally efficacious when started *de novo*, switching from a brand to a generic or vice versa increased the risk of emergency medical services or hospitalization. This suggests that for seizure control, using CBD products with differing CBD content or products in which CBD concentrations vary from batch to batch could harm patients.[64] This is especially risky since the FDA-approved indications for CBD-Rx include use in children two years of age or older.

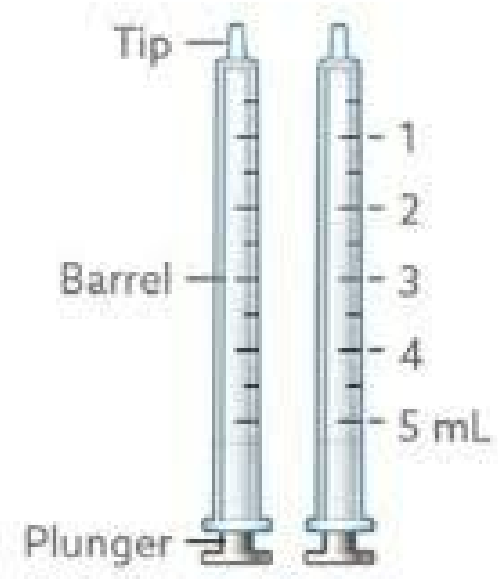
Adulteration and Contamination

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 symptoms (e.g., seizures, confusion, unconsciousness, and hallucinations). An in-depth investigation found that a CBD product included a synthetic cannabinoid.[65] From that time to May of 2018, 52 people in that region were harmed by synthetic cannabinoid contamination.[65]

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. Polycyclic aromatic hydrocarbons are classified as class IIa carcinogens and genotoxic mutagens according to the International Agency for Research on Cancer.[61,66] Additionally, pesticide or heavy metals contamination in unregulated CBD products is possible.[61]

USING CDB-RX PROPERLY IN SEIZURE DISORDERS

CBD-Rx's recommended starting dosage is 2.5 mg/kg twice daily for one week and then doubling the dose the second week (5 mg/kg twice daily). Many patients can continue the 5 mg/kg twice daily dosage for prolonged maintenance but some may need to increase to a maintenance dosage of 10 mg/kg twice daily if seizures remain uncontrolled.[17]



To increase the maintenance dosage, increase the CDB-Rx dose in 2.5 mg/kg twice daily increments with a week in between each titration. For example, increasing 7.5 mg/kg twice daily for a week to 10 mg/kg twice daily thereafter. Using the highest recommended maintenance dose of 10 mg/kg twice daily can provide better siezure protection but the higher dosage increases the adverse effects, including the risk of liver damage. To prevent breakthrough seziures, patients should step down the dosage in weekly intervals. When patients experience moderate hepatic impairment, prescribers should reduce the starting, normal maintenance, and maximum maintenance doses by one-half. If severe hepatic impairment occurs, the prescriber should then reduce doses to 0.5 mg/kg twice daily, 1 mg/kg twice daily, and 2 mg/kg twice daily (starting, normal maintenance, maximum maintenance), respectively.[17]

A calibrated 5 mL or 1 mL oral syringe is provided with CDB-Rx for accurate dosing. Patients with calculated CDB-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 inaccurate; patients should not use them as measuring devices. 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. Prescribers should monitor patients' weight; any weight gain of four kilograms (8.8 pounds) of body weight or more requires administration of an additional 10 mg of CDB-Rx.[17]

Pharmacists should be mindful that children grow quickly and CDB-Rx doses may require adjustment to maintain effectiveness and prevent breakthrough seizures. Patients should not abruptly stop their CBD products because this can result in breakthrough seizures; instead, patients should contact their physicians and work together to plan a downward titration.

COUNSELING FOR CBD AND CDB-RX

CDB-Rx comes with oral syringes. 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. Pharmacists should remind patients with seizure disorders who are prescribed CDB-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 CDB products over the counter; technicians who see patients purchasing these products should invite discussion with the customer, especially if the customer or a family member is using CDB-Rx.

Pharmacists should screen patients who are prescribed CDB-Rx to avoid drug interactions and to monitor patients when it's impossible to avoid the risk of adverse drug interactions. Pharmacists should be vigilant, especially when patients are prescribed diazepam and clozabam. Patients using CDB-Rx should avoid all other CBD products, including vaporization liquids, oral products, or CBD-containing food and drink products.

Counseling for CBD Generally

People interested in oral CBD for non-FDA approved indications should be cautioned that no human studies exist for most diseases and while preliminary trials in anxiety, psychosis or schizophrenia, and Parkinson's disease sleep disorders are promising, oral CBD should not be used to replace FDA-approved therapies. Patients should disclose CBD use to the all of their healthcare clinicians so they can assess the impact and potential adverse events. Patients should be reminded to only buy CBD products with independent laboratory verification of the CBD dosage, THC percentage, and lack of contamination and adulteration. (See the Tech Talk Sidebar.) It is dangerous to use substandard products in which the active ingredient varies from batch to batch for serious diseases or disorders.

For all oral CBD products, patients should be instructed about therapy's main risks including sedation and gastrointestinal distress. Due to possible sedation, patients should not 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 should check with their pharmacists before starting new over the counter drugs or dietary supplements to avoid drug interaction-induced adverse events. Here, again, the pharmacy technician's role is to watch for purchases of these products.

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 from the oral CBD. Finally, pharmacists should tell patients and/or their caregivers about

Tech Talk: Understanding CBD Product Verification Absent FDA Approval[3,67]

As of March 2019, CVS—the large retail pharmacy chain—announced that it will sell CBD products in 800 stores in eight states (Alabama, California, Colorado, Illinois, Indiana, Kentucky, Maryland, and Tennessee). CBD products are flooding the market but are not FDA-approved. Without 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. Cannabis plants absorb heavy metals, pesticides, and other potentially harmful chemicals that may be in the soil or water easily, and analysts find these contaminants in the leaves, flowers, and stems.[3] Therefore, consumers—and the pharmacists and technicians who advise them—need to investigate the CBD products available on the market. Consumers can request CBD products' Certificate of Analysis (CoA), 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 for contaminants and THC and CBD concentrations.

When looking at the CoA, consumers can be more confident of the 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 (i.e. 250 mg in the bottle) and not the CBD concentration (i.e. 2.5 mg/mL). Of course, products should clearly define a "dose," and list the amount of CBD in a dose and not in the entire product.

These products may contain other related compounds besides THC and CBD.

the risk of suicidal ideation and that this warning is not specific to oral CBD products but has been seen 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 doctor immediately.

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

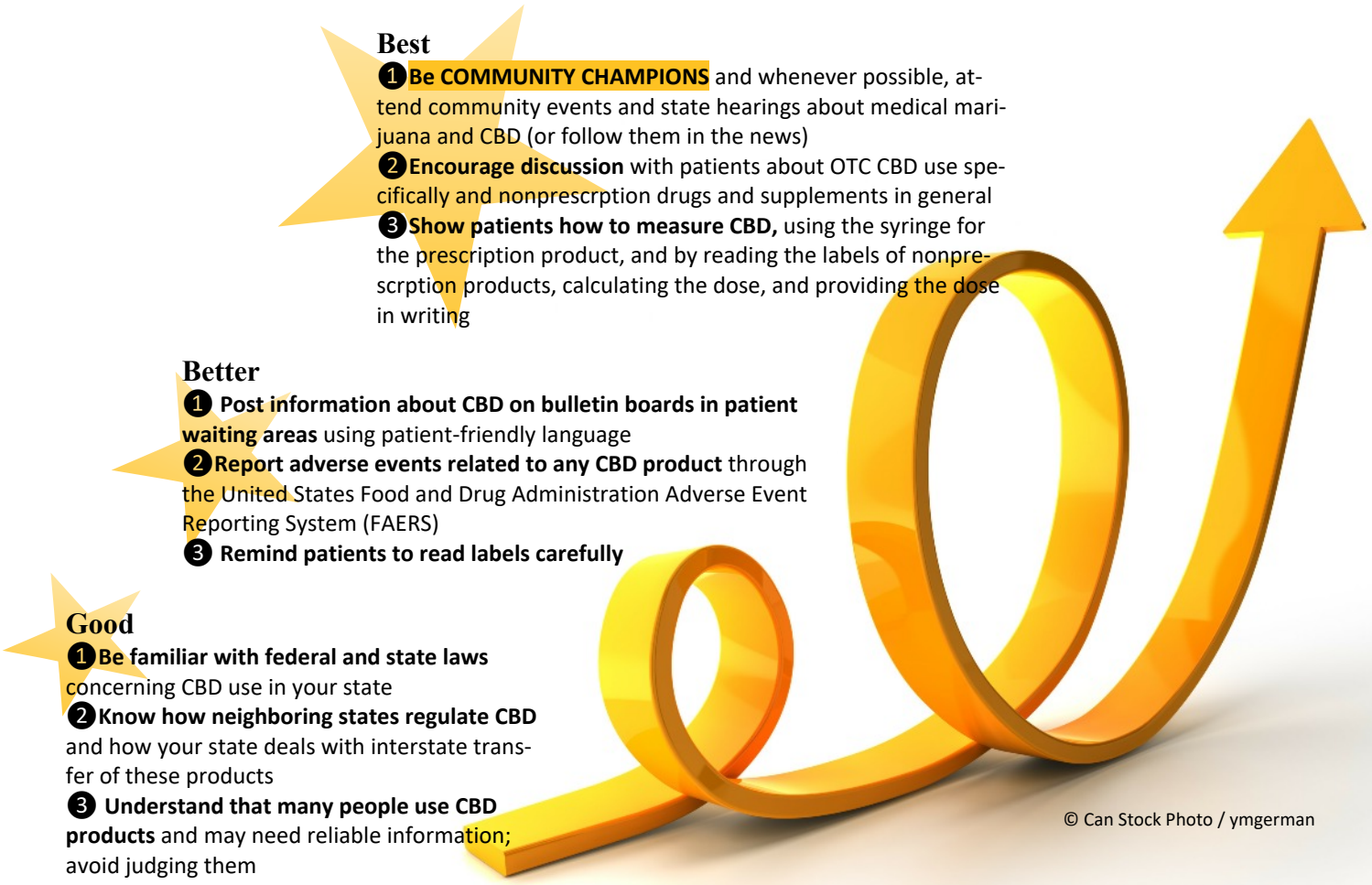
Finally, CBD is a drug, not a trendy food or beverage additive. Pharmacists should recommend against using CBD products without healthcare provider input, especially if the patient is taking other CBD products or other drugs that could interact.

Figure 1 summarizes steps pharmacists and pharmacy technicians can take to ensure patient safety.

Conclusion

If patients use non-FDA approved forms of CBD, they risk variable CBD and THC dosages, adulteration, and contamination. If not FDA-approved, products tested by an independent laboratory are safer. CBD is an effective new 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 the 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. Advancing Pharmacists and Pharmacy Technicians Role in Safe Use of CBD



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