Cannabinoid Overview

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Chelsey McIntyre, PharmD, is a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Clinical Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017. Since that time, she has worked with the Natural Medicines database at TRC Healthcare. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care, particularly in patients with chronic conditions.

Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John M. Leonard, MD
Alice Yick Flanagan, PhD, MSW
Sharon Cannon, RN, EdD, ANEF

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare professionals whose patients are taking or are interested in taking cannabinoid products.

Accreditations & Approvals

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A complete Works Cited list begins on page 16.

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NetCE designates this continuing education activity for 1 NBCC clock hour.

NetCE designates this continuing education activity for 3 ANCC contact hours.

IPCE CREDIT™

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The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the various cannabinoids.

Learning Objectives

Upon completion of this course, you should be able to:

1. Explain the difference between hemp and cannabis.
2. Outline the action and effects of delta-9-tetrahydrocannabinol (THC).
3. Review the evidence for the use of cannabidiol for various conditions.
4. Discuss the potential safety concerns of various cannabinoids.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cannabis refers to *Cannabis sativa*, *Cannabis indica*, and hybrids of these two plant species. *Cannabis* is a flowering annual plant that is grown worldwide and is commonly referred to as either cannabis or hemp. *Cannabis* contains more than 100 cannabinoids, which are concentrated in the flowers and leaves [1].

Marijuana, the colloquial term for cannabis, has generally referred to *Cannabis* containing high quantities of the main psychoactive cannabinoid delta-9-tetrahydrocannabinol (THC).

Hemp, on the other hand, has historically referred to *Cannabis* harvested for its fibrous stalks for use in industrial applications, which include fiber, cosmetics, and clothing. Hemp is also harvested for its seeds, which are used to make hemp seed oil. Hemp seed oil contains no to only low levels of cannabinoids, including THC and cannabidiol (CBD). Hemp oil, on the other hand, is obtained from the flower and/or leaves of the plant and contains THC and higher amounts of CBD [2].

GLOSSARY

Cannabis: An informal term used to refer to products classified as marijuana.

Cannabis: A term referring to all forms of the plant, which includes the species *Cannabis sativa* and *Cannabis indica*, as well as hybrids of these two species. This term can refer to both marijuana and hemp.

Cannabinoids: The pharmacologically active chemicals unique to *Cannabis*. These chemicals are primarily found in the flowers and leaves; the stalk and seed of the plant contain only negligible quantities.

THE AGRICULTURE IMPROVEMENT ACT OF 2018

In 2018, the Agriculture Improvement Act, also known as the Farm Bill, completely changed the landscape for the sale of cannabinoid products in the United States. This new bill defines hemp as *Cannabis sativa* and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a THC concentration of not more than 0.3% on a dry weight basis. According to the Farm Bill, cannabis (or what we commonly refer to as marijuana) is considered *Cannabis sativa* containing more than 0.3% THC. The Farm Bill made hemp and its constituents, including CBD, exempt from the Controlled Substances Act and legal for sale [1; 2].

The U.S. Domestic Hemp Production Program was a direct result of the Farm Bill. This program makes it legal to grow hemp in all 50 states and provides details about licensing hemp producers, testing THC levels, disposing plants exceeding maximum THC levels, and ensuring compliance. The Farm Bill paved the way for the legal sale of various cannabinoids and hemp-based products without Drug Enforcement Agency (DEA) oversight, which led to a surge in consumer interest and product availability that has only continued to increase [1; 2].

CANNABINOIDS

Cannabis contains various constituents, including hydrocarbons, amino acids, sugars, fatty acids, and terpenes. Terpenes are the aromatic compounds responsible for its distinctive smell, but they are not unique to *Cannabis*; terpenes are found in many other plants, including citrus [1].

The pharmacologically active constituents unique to *Cannabis* are the cannabinoids. Although THC and CBD often steal the spotlight, *Cannabis* actually contains more than 100 different cannabinoids. The relative abundance of these naturally occurring cannabinoids varies [1].

Some cannabinoids have psychoactive properties. THC is considered to be the primary psychoactive cannabinoid. A number of other cannabinoids are not considered psychoactive but have piqued the interest of researchers as well as the public for a variety of other pharmacologic effects.

The following cannabinoids are the most well-studied to date and will be discussed in more detail during the course [1]:

- THC
- CBD
- Cannabidivarin (CBDV)
- Tetrahydrocannabivarin (THCV)
- Cannabinol (CBN)
- Cannabigerol (CBG)
- Cannabichromene (CBC)

While the focus of this course will be on these plant cannabinoids, or phytocannabinoids, synthetic THC that is chemically identical to naturally occurring THC is also available. Some products approved by the U.S. Food and Drug Administration (FDA), such as dronabinol and nabilone, contain synthetic forms of THC and are regulated as prescription medications. These are not subject to the regulations for products derived from *Cannabis*. Similarly, K2/Spice, the general name for the class of compounds known as synthetic cannabinoids, will not be discussed in this course.

REVIEWING THE EVIDENCE: EFFICACY AND SAFETY

TETRAHYDROCANNABINOL (THC)

THC, or the delta-9 THC isomer more specifically, is the most prominently occurring THC isomer and the most familiar psychoactive cannabinoid found in *Cannabis*. Recreational use of cannabis can be attributed to THC. While pure THC does exist, it is typically studied in the form of a cannabis extract standardized to THC content, or it is used in conjunction with other cannabinoids (often CBD).

Selective breeding and the use of genetic modification has altered the *Cannabis* plant in important ways over the past few decades. For example, cannabis preparations confiscated in the United States have contained increasingly higher concentrations of THC over time. From 1995 to 2014, the average THC content increased from 4% to approximately 12%. And in one decade, from 2008 to 2017, the average THC concentration increased from 9% to 17%. This can significantly increase the "dose" of THC, leading to more substantial impairment and a higher likelihood of associated adverse effects [1].

THC is known to exert most of its pharmacologic activity through the endocannabinoid system. This system is comprised of endocannabinoids, endogenous neurotransmitters that bind to cannabinoid (CB) receptors. CB1 receptors are found in the central nervous system; CB2 receptors are found on immune cells, including leukocytes, and to a lesser extent in the brain [1].

Laboratory and animal research shows that THC exhibits psychoactive, analgesic, and antispasticity effects that are modulated through CB1 agonism. THC seems to be a partial CB1 receptor agonist with limited CB2 agonist activity, but it has also demonstrated anti-inflammatory and immunosuppressive effects via CB2 agonism. The well-known antiemetic effects of THC seem to be achieved through agonism

of both CB1 and CB2. Unfortunately, because most human research on the use of THC involves the use of whole cannabis, it is not always easy to determine which clinical effects are attributable to THC alone [1].

Efficacy

While cannabis is often used recreationally, either inhaled or ingested, it is frequently touted for a variety of conditions, such as amyotrophic lateral sclerosis, dementia, HIV/AIDS-related wasting, Crohn disease, epilepsy, glaucoma, chronic pain, and chemotherapy-induced nausea and vomiting. However, there is not good evidence indicating that cannabis is beneficial for use in these conditions. There is some evidence for the use of THC-containing products in patients with multiple sclerosis and in those with neuropathic pain.

Multiple Sclerosis

While it is unclear if smoking cannabis improves multiple sclerosis-related symptoms, a prescription product available in Canada and most of Europe, as well as other products containing the combination of THC and CBD, seem to reduce spasticity in patients with multiple sclerosis. Nabiximols, a prescription oromucosal spray containing whole-plant cannabis extract (Sativex), is available in most of Europe and Canada but is not yet approved in the United States. Each actuation of this cannabis extract spray is standardized to deliver THC 2.7 mg and CBD 2.5 mg [1].

A meta-analysis of the available research shows that using a prescription oromucosal spray containing cannabis extract for at least two weeks modestly reduces subjective spasticity, but not bladder dysfunction, when compared with placebo. Effects might last more than 11 months, but discontinuation of use may cause rebound symptoms. Much of the research on the prescription product was funded by the manufacturer.

The American Academy of Neurology states that a prescription cannabis extract does not improve objective measures of spasticity, reduce the number of urinary incontinence episodes, or reduce multiple sclerosis-related tremors [1].

A meta-analysis of the available research in patients with multiple sclerosis shows that taking oral cannabis extracts containing THC 25–30 mg and CBD 8–18 mg (e.g., Cannador, Society of Clinical Research) daily for up to 15 weeks modestly reduces subjective spasticity, neuropathic pain, and bladder dysfunction, but not objective spasticity measures, when compared with placebo [1].

Despite generally positive research on multiple sclerosis-related symptoms with prescription or other standardized products, research on the use of any other cannabis products is limited. Keep in mind that nonprescription cannabis products can contain a wide range of THC or CBD, in very different ratios, which would be expected to significantly alter any effects, clinical or adverse.

The American Academy of Neurology asserts that clinicians might offer oral cannabis extract to patients with multiple sclerosis to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain).

(https://www.aan.com/Guidelines/home/GuidelineDetail/641. Last accessed October 25, 2022.)

Level of Evidence: A (Established as effective for the given condition in the specified population.)

Neuropathic Pain

Inhaled cannabis seems to temporarily improve neuropathic pain, but it is unclear what the optimal dose might be. A meta-analysis of small studies in patients with chronic neuropathic pain secondary to a variety of causes shows that inhaling cannabis containing THC 1.6–96 mg daily for up to two weeks reduces pain intensity. To achieve a pain reduction of at least 30%, six patients would need to be treated [1].

A small individual clinical study in patients with spinal cord injury shows that inhaling cannabis containing THC 2.9% or 6.7% reduces neuropathic pain, with a number needed to treat of three to achieve a pain reduction of at least 30% during an eight-hour period [1].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Care Excellence recommends against starting *Cannabis sativa* extract to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so.

(https://www.nice.org.uk/guidance/cg173. Last accessed October 25, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Safety

Most commonly, dizziness, dry mouth, fatigue, headache, increased appetite, nausea, paranoid and dissociative thinking, and sedation are associated with cannabis when consumed via any usual route. When inhaled, cannabis use has commonly been associated with upper respiratory tract symptoms, such as cough and wheeze. Intoxicating doses of cannabis can impair memory, motor coordination, reaction time, and visual perceptions for as long as eight hours [1].

Serious adverse effects have also been reported with ingestion or inhalation of cannabis, usually with large doses or with extended use. Respiratory effects specifically are associated with smoking or vaping cannabis and can include coughing, wheezing, inflammation of the upper respiratory tract, and e-cigarette, or vaping, product-use associated lung injury (EVALI). Potential neurologic effects include anxiety, psychosis, cognitive impairment, mood disturbances, cannabinoid hyperemesis syndrome (CHS), withdrawal syndrome, and seizures. Atrial fibrillation, ventricular arrhythmia, and myocardial infarction are possible cardiovascular effects [1].

Abuse Potential

Cannabis can be habit-forming. Meta-analyses show that as many as 47% of regular cannabis users develop some form of dependence and up to 9% of all users develop cannabis use disorder. For context, substance use disorders occur in approximately 20% to 30% of all tobacco users, 15% of those who try cocaine, and 25% of those who try heroin. However, it is not always clear if those presenting with cannabis use disorder are truly addicted or simply demonstrating high levels of dependence with heavy use. Additionally, it is unclear how the increasing concentration of THC in cannabis affects this dependence rate [1].

Drug Interactions

In vitro research and some case reports show that using cannabis can increase the risk of bleeding when administered with drugs, herbs, and supplements that increase the risk of bleeding. Patients receiving warfarin, other anticoagulants, or antiplatelet agents should be monitored more closely for bleeding, especially when cannabis use is not on a regular or consistent basis.

Cannabis can also affect certain cytochrome P450 (CYP450) enzymes. Based on pharmacology and some in vitro research, cannabis might inhibit or induce CYP450 enzymes, including CYP 2C9, 2E1, and 3A4, potentially increasing or decreasing the levels and corresponding effects of substrates of these enzymes. Based on pharmacology, certain CYP450 inhibitors and inducers might increase or decrease the levels and corresponding effects of cannabis, but these concerns are theoretical at this time [1]. Theoretically, using cannabis with drugs, herbs, and supplements that have sedative properties may cause additive therapeutic and adverse effects.

Even though many of these interactions have not been substantiated in humans, they could be useful to keep in mind, especially for patients taking narrow therapeutic index drugs or patients who are regular users of cannabis. Gather information from patients about cannabis use and add this to their medical history or patient profile. Consider the impact of cannabis use when patients start or stop a medication or complain of any new side effects.

Special Populations

Pregnancy and Lactation

Cannabis crosses the placenta, and use during pregnancy has been associated with numerous negative maternal and fetal outcomes in observational studies. THC is excreted into the breast milk for at least six weeks following cessation of use and can cause delayed motor development in the infant [1]. Patients should be informed of these risks and discouraged from using cannabis while pregnant or breastfeeding.

Patients with Diabetes

In patients with type 1 diabetes, cannabis use has been associated with worsened glycemic control, increased glycated hemoglobin (HbA1c), and an increased risk for diabetic ketoacidosis. In patients with type 2 diabetes, cannabis use has been associated with an increased risk for diabetic nephropathy, myocardial infarction, and peripheral arterial occlusion. Until more is known, tell patients with diabetes to be cautious using cannabis [1].

CANNABIDIOL (CBD)

CBD is a nonpsychoactive constituent of *Cannabis* and may constitute up to 40% of cannabis extracts. Since hemp is not subject to regulation by the DEA, hemp is the main source of most of the available CBD products on the market [3].

Unlike THC, extensive laboratory research has confirmed that CBD does not act on CB receptors. Instead, CBD seems to interact or interfere with a number of endocannabinoid and non-endocannabinoid signaling systems. For instance, CBD can inhibit the cellular uptake and degradation of anandamide, an endocannabinoid. Anandamide is a highly potent, endogenous agonist of CB1 and CB2. By altering the function of this molecule, CBD can indirectly affect the function of the endocannabinoid system.

CBD also seems to act on other receptors. CBD has demonstrated activity on transient receptor vanilloid type 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1). TRPV1 and TRPA1 are ion channels expressed almost exclusively by sensory neurons that play an important role in various sensations, including pain, cold, itch, and other protective responses. CBD can also enhance the activity of 5-HT1A (serotonin) receptors and has demonstrated affinity for various other pharmacologically important receptors throughout the body, such as peroxisome proliferator-activated receptors (PPAR) [3].

Legal Implications

In May 2019, FDA approved of a specific, oil-based prescription formulation of CBD (Epidiolex). While the passage of the 2018 Farm Bill exempted hemp and its constituents, including CBD, from the Controlled Substances Act and made them legal for sale, FDA approval of a prescription CBD product further complicated things [3].

Because CBD is the active ingredient in a prescription product, it has been said that legally it cannot be included in foods and dietary supplements. However, this sentiment has been disputed and enforcement has been lacking. Dietary supplements and foods containing CBD are abundant in the marketplace [3].

Efficacy

CBD is frequently touted for mental health, pain management, sleep, substance use disorder, and gastrointestinal disorders, but the majority of the evidence for CBD use is for treatment-resistant epilepsy. Research for other purported indications is inconclusive [3].

Because of how readily available CBD products have become, you may be getting a lot of questions from patients about the touted uses of these products. We will first discuss the use of CBD with the most evidence, and then we will briefly review the evidence available for some other conditions of interest.

Treatment-Resistant Epilepsy

A prescription CBD solution approved by the FDA is labeled for the adjunctive treatment of Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. Prescription CBD is an oil-based oral solution standardized to contain CBD extract 100 mg/mL in sesame oil. The extract is highly purified from a plant source. Originally classified by the DEA as a Schedule V controlled substance, it was descheduled in April 2020 [3].

In children with Dravet syndrome and children and adults with Lennox-Gastaut syndrome or tuberous sclerosis complex, adjunctive treatment with this prescription formulation reduces seizure frequency from baseline by 39% to 49%, compared with only 13% to 27% in those receiving placebo. Nearly half of patients experience at least a 50% reduction in seizure frequency from baseline. Results of open-label extension studies demonstrate similar efficacy for sustained periods of up to three years [3].

While this prescription formulation has also been evaluated for use in other forms of epilepsy (e.g., Sturge-Weber syndrome, febrile infection-related epilepsy syndrome [FIRES], epileptic encephalopathy of genetic origin), the available research is limited, and it is not labeled for these uses. It is unclear if other CBD products are beneficial for use in seizure disorders [3].

Mental Health

Research on the use of CBD for mental health benefits is inconclusive. In healthy patients, several small, low-quality studies show that oral CBD 15 mg or 150 mg modestly improves emotional exhaustion, depression or anxiety symptoms, and the ability to cope with stress, when compared with standard care or placebo, but it is not clear if CBD is beneficial in patients diagnosed with anxiety or depression [3].

In patients with social anxiety disorder, oral CBD 300 – 600 mg daily or as a single dose reduces overall anxiety and anxiety associated with public speaking. However, for some patients, anxiety was only reduced before or after and not necessarily during the speaking event. CBD does not seem to reduce speaking anxiety in patients at higher risk for psychiatric complications. Differences due to study size, baseline anxiety, and the use of nonstandardized products may explain some of the variability in outcomes observed [3].

In patients with post-traumatic stress disorder, a small study shows that taking high-purity oral CBD 300 mg attenuates cognitive impairment associated with the recall of traumatic events when compared with placebo. However, it does not improve anxiety, alertness, or discomfort. Patients in the CBD group had more psychiatric comorbidities at baseline [3].

Pain

Although CBD products, both oral and topical, are regularly touted for pain relief, they do not seem to reduce acute pain and effects on chronic pain are even less clear. Even though CBD salves and balms are really popular for muscle and joint pain relief, there does not seem to be evidence supporting topical absorption of CBD.

In healthy volunteers with experimentally induced pain, several small clinical studies show that single oral doses of CBD 200 – 800 mg do not seem to reduce acute pain when compared with placebo. In patients with acute low back pain presenting to the emergency department, oral CBD 400 mg, in addi-

tion to the standard treatment of acetaminophen 1,000 mg with ibuprofen 400 mg, does not reduce pain or the need for rescue analgesia with oxycodone over two hours when compared with placebo [3].

A small observational cohort study shows that taking oral CBD for eight weeks is associated with reductions in pain and opioid use and improvements in sleep quality. However, due to the observational nature of the study, it is unclear if this is a direct result of CBD use [3].

Sleep

Although CBD has demonstrated sedative effects in animal research, it has not been evaluated for insomnia or other sleep disorders in clinical studies [3].

Substance Use Disorders

In patients with various substance use disorders, CBD may play a role in reducing cravings and substance use, but it is unclear if these marginal benefits actually translate into relapse prevention. Unfortunately, most studies in this area are generally small and low quality. Interestingly, CBD has been evaluated for use in patients with cannabis use disorder.

In patients with cannabis use disorder of moderate severity, a small clinical study shows that taking synthetic CBD oil 400 mg or 800 mg in two divided doses daily for four weeks seems to reduce overall cannabis consumption, based on urine metabolite levels, when compared with placebo. The 400-mg dose, but not the 800-mg dose, seems to increase self-reported abstinence from cannabis by about 0.5 days per week when compared with placebo [3].

Safety

Oral CBD has been used with apparent safety at doses of 200–1,200 mg daily in the short term, for up to four to 13 weeks. CBD seems to be well tolerated when taken by mouth. Prescription CBD is reported to cause somnolence in up to 30% of patients and diarrhea in up to 24% of patients, but keep in mind that doses for treatment-resistant epilepsy exceed those used in most nonprescription CBD products. Doses of prescription CBD exceeding 15–20 mg/kg daily and/or taken in combination with other anticonvulsants (e.g., clobazam, valproic acid) are more likely to cause certain adverse effects like somnolence, diarrhea, elevation of liver transaminases, and weight loss/gain. Decreased appetite, drowsiness, dry mouth, fatigue, and vomiting have also been commonly reported. Pharmacogenetic variation has been shown to affect susceptibility to CBD-associated adverse effects including diarrhea, sedation, and elevation of liver transaminases [3].

Abuse Potential

There has been some concern that CBD can be used as a substance of abuse, but overall, these concerns seem unfounded. Single 750-mg doses of CBD were rated no differently than placebo for "drug-liking", likelihood of repeat use, or occurrence of positive effects (e.g., feeling "high" or "stoned") among healthy recreational polydrug abusers in a clinical study. Higher single doses of 1,500 mg or 4,500 mg were rated with a higher likelihood for repeat use and the presence of "positive effects", but these ratings were still lower than those for dronabinol, a synthetic version of THC, and alprazolam [3].

Unlike THC, limited research suggests that CBD does not cause driving impairment. A small study has found that inhaling vaporized cannabis containing CBD 13.75 mg does not increase lane weaving when compared with placebo. Lane weaving observed in those inhaling this product was equivalent to having a blood alcohol concentration (BAC) of 0.02%, which is below the lower limit of clinically relevant impairment that is considered to occur with a BAC of 0.05%. Keep in mind that the study only tested a single dose of CBD, which may not be indicative of real-world use [3].

Abrupt discontinuation following short-term CBD use does not seem to be associated with withdrawal symptoms in healthy volunteers [3].

Drug Interactions

CBD can affect certain CYP450 enzymes. Some clinical research has suggested that CBD might inhibit CYP2C9, 2C19, and 3A4, potentially increasing the levels and corresponding effects of substrates of these enzymes. This represents the potential for a large number of drug interactions. Based on in vitro and animal research, CBD also might inhibit CYP 1A1, 1A2, 1B1, 2A6, 2B6, and 2C8 enzymes, but these concerns are theoretical at this time. Patients receiving substrates of these enzymes, especially narrow therapeutic index drugs metabolized by CYP2C9, 2C19, or 3A4, should be monitored for potential interactions. Based on theoretical pharmacology, certain CYP450 enzyme inhibitors and inducers might increase or decrease the levels and corresponding effects of CBD [3].

Clinical studies have demonstrated modest to substantial increases in the concentrations of some drugs when CBD, including prescription CBD, is used concomitantly. These drugs include brivaracetam, caffeine, citalopram, clobazam, eslicarbazepine, everolimus, rufinamide, sirolimus, stiripentol, tacrolimus, topiramate, and zonisamide. Theoretically, using CBD with drugs, herbs, and supplements that have sedative properties may cause additive therapeutic and adverse effects [3].

Gather information from patients about CBD use and add this to their medical history or patient profile. Consider the impact of CBD use when patients start or stop a medication or complain of any new side effects.

Special Populations

Children

While a specific prescription CBD oral solution product has been used safely in children as young as 1 year of age, the safety of other forms of CBD have not been evaluated in children [3].

Pregnancy and Lactation

Due to concerns related to contamination with THC, heavy metals, pesticides, and more, CBD may not be safe for use while pregnant or breastfeeding. Frequent contamination of CBD can be dangerous to the fetus. Similarly, animal research has demonstrated that high levels of CBD can adversely affect the reproductive system of male offspring. The FDA strongly advises against its use during pregnancy [3].

CANNABIDIVARIN (CBDV)

Cannabidivarin is a nonpsychoactive cannabinoid with structural similarity to CBD. The concentration of cannabidivarin is greater in *Cannabis indica* than in *Cannabis sativa*. While cannabidivarin is structurally similar to CBD, it is the biosynthetic precursor to tetrahydrocannabivarin, which results from the isomerization of cannabidivarin under acidic conditions. Based on the available laboratory and animal research, it seems to act through many of the same receptor pathways as CBD [4].

Efficacy

Although there is interest in using cannabidivarin for various neurologic or neuromuscular and gastrointestinal disorders, research is mostly limited to in vitro and animal studies. While the FDA and the European Medicines Agency have granted cannabidivarin an orphan designation for use in the treatment of Fragile X syndrome and Rett syndrome, there is not enough reliable information about the clinical effects of cannabidivarin for these uses [4].

Epilepsy

A large, high-quality clinical study in patients with inadequately controlled focal seizures failed to show that adjunctive therapy with cannabidivarin reduces seizure frequency when compared with placebo, prompting the industry sponsor to abandon research for this indication [4].

Neuropathic Pain

There is limited evidence on the use of cannabidivarin in patients with HIV-associated neuropathic pain. A small clinical study in patients with HIV-associated neuropathic pain failed to show that cannabidivarin reduces pain or medication use when compared with placebo [4].

Safety

Cannabidivarin seems to be safe for short-term use in adults. Doses of up to 800 mg twice daily for up to eight weeks have been evaluated in clinical research, but there is no data for use of higher doses of longer durations. Diarrhea, dizziness, and nausea are commonly reported with use, and higher doses have been associated with abdominal pain, headache, rash, and somnolence [4].

TETRAHYDROCANNABIVARIN (THCV)

Tetrahydrocannabivarin is a nonpsychoactive analogue of THC that is naturally occurring in *Cannabis sativa*. Tetrahydrocannabivarin may also be derived from cannabidivarin. As with THC, tetrahydrocannabivarin acts on the endocannabinoid system, with a higher affinity for CB2. Laboratory and animal research shows that it exhibits some anti-inflammatory, antiemetic, and antitumor effects via CB1 and CB2 agonism. Additionally, research in healthy adults has shown that tetrahydrocannabivarin might affect overall food intake through CB1 agonism in the brain [5].

Efficacy

This cannabinoid has not been extensively studied in humans, but there is increasing interest in its use as an anti-inflammatory, anticonvulsant, analgesic, antipsychotic, and appetite suppressant. Available research for these conditions is limited to in vitro and animal studies [5].

Safety

While tetrahydrocannabivarin has been used with apparent safety in clinical research for up to 13 weeks, a thorough evaluation of safety outcomes has not been conducted [5].

CANNABINOL (CBN)

Cannabinol, a metabolite of THC, is present in *Cannabis* in trace amounts. Some research suggests that it might be mildly psychoactive, while other research shows no psychoactive activity. Regardless, it appears to bind to CB2 receptors and demonstrates weak affinity for CB1 receptors [6].

Efficacy

Although there is interest in using cannabinol as an analgesic, appetite stimulant, immunomodulator, and sleep aid, it has not been evaluated in clinical studies [6].

Safety

Cannabinol has not been thoroughly evaluated for safety [6].

Drug Interactions

In in vitro studies, certain CYP 450 enzyme inhibitors increased the levels and effects of cannabinol. In other in vitro research, cannabinol inhibited certain CYP450 enzymes, potentially increasing the levels and effects of substrates of these enzymes. Even though these interactions have not been substantiated in humans, they could be useful to keep in mind, especially for those taking narrow therapeutic index drugs or those who are regular users of cannabinol [6].

CANNABIGEROL (CBG)

Cannabigerol, a CBD-like nonpsychoactive cannabinoid, is naturally occurring in *Cannabis sativa* and is abundant in industrial hemp. Cannabigerol also utilizes some of the same receptor pathways as CBD [7].

Efficacy

Although there is interest in using cannabigerol for conditions such as cachexia, dyslipidemia, Huntington disease, and inflammatory bowel disease, available research is limited to in vitro and animal studies. Some research shows that the anti-inflammatory effects of cannabigerol might be greater when used in combination with CBD, but cannabigerol also seems to reverse the antiemetic effects of CBD when used concomitantly [7].

Safety

Cannabigerol has not been thoroughly evaluated for safety [7].

CANNABICHROMENE (CBC)

Cannabichromene, a nonpsychoactive cannabinoid, is one of the most abundant cannabinoids found in *Cannabis*. Cannabichromene does not strongly affect CB1 receptors, but it does have activity at CB2 receptors [8].

Efficacy

Although there is interest in using cannabichromene for its anti-inflammatory, analgesic, and anticonvulsant effects, available research is limited to in vitro and animal studies. Some research shows that the analgesic effects of cannabichromene might be greater when used in combination with other cannabinoids (e.g., cannabinol) [8].

Safety

A thorough evaluation of safety outcomes with cannabichromene has not been conducted [8].

Drug Interactions

Preliminary clinical research suggests that cannabichromene might have sedative and hypnotic effects. Be aware that using cannabichromene with drugs, herbs, and supplements that have sedative properties may cause additive therapeutic and adverse effects [8].

GENERAL SAFETY CONSIDERATIONS

DELTA-8 TETRAHYDROCANNABINOL (DELTA-8 THC)

Delta-8 THC, an isomer of delta-9 THC (THC), is another psychoactive cannabinoid found in *Cannabis* that has serious safety issues. Delta-8 THC is estimated to be 50% to 75% as psychoactive as delta-9 THC [9].

The concentration of naturally occurring delta-8 THC in cannabis and hemp is low, and therefore most delta-8 THC is synthetically manufactured from CBD. Delta-8 THC may be synthetically derived from delta-9 THC and CBD [9].

Neither the safety nor efficacy of delta-8 THC has been evaluated in clinical studies.

Legal Implications

Because delta-8 THC is not acknowledged in the 2018 Farm Bill, its U.S. federal regulatory status is unclear. It is banned or restricted in some states, while remaining legal in others. The combination of its unclear regulatory status and its psychoactive effects have led to rapid increases in delta-8 THC availability and interest [9].

Safety

A thorough evaluation of safety outcomes with delta-8 THC has not been conducted. In the first seven months of 2021 alone, hospitalization occurred in 18% of 661 reported exposures to delta-8 THC. In the eight-month period ending in July 2021, 14 of 22 cases reported to the FDA presented to the hospital for adverse effects related to delta-8 THC-containing products [9].

According to data compiled from sources including the FDA, the Centers for Disease Control and Prevention (CDC), and the American Association of Poison Control Centers, some of the most common adverse effects associated with delta-8 THC include

difficulty thinking and speaking, a dreamlike state, euphoria, feeling "high," and vision and time distortion. Serious safety signals also have been observed, including Brugada ECG pattern and cannabinoid hyperemesis syndrome, frequently leading to emergency room visits and hospitalization [9].

CLASS-WIDE SERIOUS ADVERSE EFFECTS OF CANNABINOIDS

Cannabinoid Hyperemesis Syndrome (CHS)

Excessive and prolonged cannabis use (e.g., two to three times daily over two years) can lead to a condition called cannabinoid hyperemesis syndrome (CHS). It is characterized by cyclic attacks of nausea and vomiting that are not alleviated by conventional antiemetics. Anecdotally, patients commonly report temporary relief of their symptoms with bathing in extremely hot water, and this is often what clues providers in to this diagnosis. CHS has occurred with smoking and/or oral use and has even been linked to severe complications resulting in death in several cases [10].

There are also case reports of CHS with delta-8 THC and K2/Spice. Non-THC cannabinoids (e.g., CBD, cannabigerol) also may play a role [10].

The cornerstone of long-term treatment for CHS is complete discontinuation of cannabis use, but benzodiazepines and capsaicin also may play a role in short-term symptom management [10].

E-cigarette, or Vaping, Product-Use Associated Lung Injury (EVALI)

E-cigarette, or vaping, product-use associated lung injury (EVALI) has occurred among adults and children using e-cigarette, or vaping, products. The majority of patients experiencing EVALI reported using THC-containing products in the three months prior to the development of symptoms. It is not clear if EVALI is the direct result of THC or another component of the formulation, like vitamin E acetate. The FDA has warned the public to stop using all THC-containing vaping products because of this risk [1].

CONTAMINATION CONCERNS

Contamination concerns are rampant with cannabis products, increasing the risk of serious adverse effects with their use. *Cannabis sativa* is a phytoremediator. Phytoremediators are plants that readily absorb contaminants from the soil. For this reason, cannabis products are at high risk for contamination from pesticides, heavy metals, bacteria, and fungus.

Most commercially available delta-8 THC is synthetically manufactured from CBD. For this reason, delta-8 THC products may contain heavy metals and other contaminants that may have been added or accidentally created during the synthesis of delta-8 THC. The process of synthesis may also increase the risk for variability in delta-8 THC content [1; 9].

Product Quality and Cross Contamination with Other Cannabinoids

Product quality is lacking and cross contamination of cannabis products with other cannabinoids is abundant. Commercially available CBD products, especially those intended for vaping, have been frequently shown to be contaminated with THC or synthetic cannabinoids.

An analysis of seven commercially available CBD e-liquid formulations found that two products were contaminated with an undeclared synthetic cannabimimetic (5F-ADB) and another two contained undeclared THC. Off-the-shelf evaluations of commercially available oral CBD products have consistently demonstrated issues with product standardization and labeling.

In an analysis of 84 commercially available CBD products in the United States, only 31% of products were accurately labeled and 21% of products contained unlabeled THC. Other assessments of 14 products commercially available in Europe and 25 products available in the United States found that up to 90% of the products were inaccurately labeled and that up to 86% of products contained detectable quantities of THC [11; 12].

CBD is also available in an e-liquid formulation for use in e-cigarettes intended for vaping. Interestingly, when CBD is exposed to temperatures typically occurring in e-cigarettes, it can be converted to delta-8 THC, cannabinol, cannabichromene, and other cannabinoids. Commercially available CBD, especially those intended for vaping, may be contaminated with synthetic cannabinoids, increasing the risk of serious associated adverse effects [11; 12].

The increasing prevalence of delta-8 THC is also causing contamination concerns, as both the contaminant and the frequently contaminated. Some products labeled as hemp containing CBD might contain undeclared delta-8 THC. Delta-8 THC products might also contain other cannabinoids given that they are synthesized from other cannabinoids [9].

DRUG TESTING CONCERNS

In general, THC can be detected in blood tests for up to three days, saliva tests for up to four days, urine tests for anywhere from three to 21 days, and hair tests for up to 90 days after cannabis use [13; 14].

Frequent contamination issues may be the root cause for many false positive results. For example, patients who use CBD might return a positive test due to the presence of trace amounts of THC. Use of other cannabinoids might also be responsible for false positive results on certain immunoassays testing for THC in the urine. Clinical research shows that high dose cannabinol use resulting in cannabinol urine concentrations about five times greater than the minimum THC concentration produce a positive THC signal on a specific immunoassay [13; 14].

Make sure patients are adequately informed of the risks and unknowns related to drug testing with cannabinoids and cannabinoid-containing products.

SAFETY IN CHILDREN

Cannabis

There has been a recent uptick in accidental ingestion of cannabis-containing edibles in children ages 12 years and younger. Legalization of recreational cannabis and the availability of these more appealing food forms, like gummies, are likely to blame. Accidental ingestion of cannabis-containing edibles in children has been associated with ataxia, coma, hypotonia, hypothermia, lethargy, nystagmus, respiratory depression, seizures, and tremors [1].

Delta-8 THC

With the rise in popularity of delta-8 THC, delta-8 THC-containing gummies and other products resembling candy or cookies have been mistakenly consumed by children, often resulting in hospital admission. In the first seven months of 2021 alone, the American Association of Poison Control Centers statistics indicate that 39% of the 661 reported exposures to delta-8 THC occurred in children younger than 18 years old, with some requiring ICU admission. In two cases, children presented with deep sedation, hypotension, and a slowed heart rate following accidental ingestion of gummies containing delta-8 THC. In another case, a 2-year-old child presented with sedation and acute encephalopathy following accidental ingestion of gummies containing an estimated delta-8 THC dose of 15 mg/kg [9].

CBD

While prescription CBD (Epidiolex) has been safely used in children, there is not enough reliable information about the safety of other forms of CBD in children. In a poison control center report of 1,581 CBD exposures in children and adults, 5.7% of cases involved tachycardia. Most exposures were oral, single-substance exposures, but it is not clear what doses of CBD precipitated these reports [3].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of medical marijuana and other cannabinoids be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

Use of cannabis and cannabinoid-containing products continues to increase as regulations generally allow for increased access. In addition to recreational use, these products have consistently been touted for their health benefits, but the reality is that there is not a lot of evidence for their use, especially outside of prescription or other standardized products. Further, these products are not without serious safety concerns, including adverse effects, drug interactions, contamination, and product quality concerns. When patients ask questions or offer information about their potential or current usage of these products, it is imperative that clinicians provide evidence-based recommendations and appropriate safety warnings to help patients make informed decisions.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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