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Therapeutic Uses for Cannabinoids

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Cannabis (e.g., hemp, marijuana) and synthetic cannabinoids have a long history of therapeutic, as well as recreational, uses. While over 100 different cannabinoids have been isolated from cannabis, Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most well-known.[1] Many patients request information from providers on the benefits and risks of cannabinoid products. This newsletter will present the evidence for potential uses of THC and CBD products as well as legal restrictions, drug interactions and safety precautions.

Cannabinoid Legal Implications

There are several factors that determine the regulations that apply to cannabinoid products. Hemp-derived products are not considered federally controlled substances if they contain 0.3% or less of THC (by dry weight).[1] CBD products from hemp can be used in cosmetics and some states allow consumable CBD products. Laws governing the use of cannabinoids depends on the state in which you live and the plant that was the basis of the product (hemp vs. marijuana). The product may require a prescription or be available online or at a dispensary or smoke shop. In Oregon, individuals 21 years or older can purchase up to one ounce of cannabis. The Oregon Medical Marijuana Act also allows for the use of marijuana for conditions listed in **Table 1**.[2] Patients that qualify for a medical marijuana may pay lower costs, be able to purchase more potent products and grow additional plants compared to those individuals using marijuana for recreational purposes only. At this time medical cannabis may only be authorized by an Oregon licensed Doctor of Medicine (MD) or Doctor of Osteopathic Medicine (DO).

Table 1. Qualifying Medical Marijuana Uses in Oregon.[2]

• Cancer	• Glaucoma
• Degenerative or pervasive neurological condition	• HIV/AIDs
• Medical condition or treatment for a medical condition that produces one or more of the following: Cachexia, severe pain, severe nausea, seizures and persistent muscle spams	• Post-traumatic stress disorder (PTSD)

Cannabinoid Pharmacology

CBD and THC have unique targets and therapeutic effects due to a non-enzymatic decarboxylation process that results in differing chemical structures.[3] Decarboxylation activates raw cannabis into active forms and can be done through heat or vaporization. THC activates CB 1 receptors in the brain which results in psychoactive effects, which are not associated with CBD. CBD has numerous putative biological targets and has been proposed to act as a negative allosteric modulator of cannabinoid receptors.[4] Lack of quality control and unknown bioavailability of cannabinoid products complicate the predictability of pharmacological effects of non-Food and Drug Administration (FDA) approved products (e.g., edibles, vapors, purified liquids).

Therapeutic Effects of Cannabinoids

Cannabinoids are anecdotally used for a multitude of ailments (e.g., muscle relaxant, analgesia, appetite stimulation). There are only three FDA-approved products. The THC-based synthetic product, dronabinol (Marinol®, Syndros®), is approved for use in adults for anorexia associated with weight loss in patients with Acquired Immunodeficiency Syndrome (AIDS) and nausea and vomiting associated with cancer chemotherapy for patients who have failed standard antiemetic regimens.[5] The third approved product is a CBD derivative, cannabidiol (Epidiolex®), approved for patients aged 1 year or older for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex.[6]

The therapeutic effects of cannabinoids, vary between products and routes of administration. Food may cause erratic absorption of CBD and edible CBD products (e.g., gummy bears, brownies) are associated with the least predictable absorption profiles.[7] Liquid formulations are more predictable with maximum concentrations reported at 3-5 hours after ingestion. Products that are oil based have the best absorption as cannabis is lipophilic. Vaping has the quickest onset of action with maximum concentrations seen at 15-30 minutes.[7] The time it takes to metabolize cannabis is also variable. Most urine drug screens test for THC or its metabolites. Tests may remain positive after a week to 10 days after use and up to 6 weeks if the patient is a heavy user.[1] CBD and hemp oil do not usually cause a positive test due to low levels of THC. Rarely CBD may cause a positive test with use of impure forms or very high doses.[1]

Evidence Supporting the Use of Cannabinoids

There is a lack of evidence to draw strong conclusions on efficacy for the medicinal use of most cannabinoid products, especially those which are not FDA approved. There is limited evidence, beyond anecdotal, to support the use of CBD and THC for some indications (**Table 2**). The majority

of evidence is low-quality and there is a need for randomized clinical trials to determine true effects of treatment. Federal restrictions present a barrier to conducting research in a formalized manner. The National Institute on Drug Abuse (NIDA) has adopted a policy to guide researchers to measure and report findings on cannabis using a standard THC unit of 5 mg. This recommendation does not limit use to 5 mg but rather standardizes the comparable effects of THC.[8] Additional challenges to the use of cannabinoids are the lack of consistency between different dosage forms and potency.

Table 2. Cannabinoid Uses with Limited Evidence.

Condition	Evidence	Strength of Evidence
CBD (oral)		
• Psychotic episodes in patients with Parkinson's disease	Small, non-controlled study (n=6) lasting 4 weeks demonstrated reductions in BPRS and PPQ with CBD 150 mg/day, compared to baseline levels[9]	Low
• Anxiety associated with public speaking	Small study (n=24) randomized patients to CBD 600 mg/day or placebo demonstrated reductions in anxiety, cognitive impairment, discomfort and alert levels with CBD[10]	Low
• Anxiety	Small study (n=72) demonstrated anxiety score reduction in 79% of patients in the first month[11]	Low
• Refractory seizures in patients with Dravet syndrome	- FDA-approved (Epidiolex®; Schedule V) - PC trial of 120 children and young adults with Dravet syndrome (baseline seizure rate of 14/month) received oral CBD 20 mg/kg which decreased conclusive seizures by 22.8% (95% CI, -41.1 to -5.4; P=0.01) more than placebo[12]	Low
• Refractory seizures in patients with Lennox-Gastaut syndrome	- FDA-approved (Epidiolex®) - PC trial of 171 patients (age 2-55 years, baseline seizure frequency of 74/month) with Lennox-Gastaut syndrome received oral CBD 20 mg/kg as add on therapy which decreased monthly drop seizure frequency by 17.21% (95% CI, -30.32 to -4.09; P=0.0135) more than placebo compared to baseline[13]	Low
THC (oral)		
• Refractory chemotherapy -induced nausea and vomiting	- FDA-approved (Marinol® capsules; Schedule III) - FDA-approved (Syndros® solution; Schedule II) - Meta-analysis of 6462 patients demonstrated a complete response with cannabinoids in 47% of patients compared to 20% with placebo (OR 3.82; 95% CI, 1.55 to 9.42: P < 0.05)	Low
THC (oral or inhaled)		
• Appetite stimulant in patients with HIV or AIDs	- FDA-approved (Marinol®; Schedule III)[5] - FDA-approved (Syndros® solution; Schedule II) Study in 139 patients showed an improvement of 9 points on a visual analog scale compared to placebo (p<0.05) for the outcome of improvement in appetite	Low
• Refractory chronic pain	Plant derived cannabinoids were found to reduce pain 40% more than control	Low

	(OR 1.41, 95% CI, 0.99 to 2.00); results not SS (pooled analysis of 7 trials, n=178)[14]	
• Symptom Improvement in: - Tourette syndrome - PTSD	Limited to case reports and anecdotal evidence[1,7]	Low

Abbreviations: AIDS – Acquired Immunodeficiency Syndrome; BPRS – Brief Psychiatric Rating Scale; CBD – cannabidiol; CI – confidence interval; HIV – Human Immunodeficiency Syndrome; FDA – Food and Drug Administration; OR – odds ratio; PC – placebo-controlled; PPQ – Personal Problems Questionnaire; PTSD – post-traumatic stress disorder; RCT – randomized controlled trial; SS – statistically significant; THC - Δ-9-tetrahydrocannabinol

Adverse Events Associated with Cannabinoids

The use of cannabinoids commonly results in adverse events, with an incidence rate of approximately 50%.[7] Adverse events are more commonly seen with higher doses and prolonged use.[7] CBD may cause decreased appetite and weight loss, diarrhea, dizziness, drowsiness, sleep disturbance, abnormal liver enzymes and fatigue.[7;1] Liver injury at higher doses (e.g., 20 mg/kg/day) or when used in combination with clobazam or valproate has also been reported with CBD use.[1] THC has been associated with euphoria, hyperemesis syndrome and psychoactive effects (e.g., dizziness, sedation, disorientation, dissociation, paranoia, euphoric mood, feeling drunk and disturbances in attention).[7] A systematic review and meta-analysis found that cannabis use in adolescents, 18 years of age and under, resulted in increased risk of depression and suicidality; however, additional high-quality studies are needed to substantiate findings.[15] Findings from the use of rimonabant, an inverse agonist of the cannabinoid receptor used for weight-loss, resulted in withdrawal from the European market due to serious psychiatric adverse effects (this product was never approved in the United States).[16]

Cannabinoid Drug Interactions

Cannabinoids are metabolized by numerous metabolic systems which have the potential to cause multiple drug interactions (**Table 3**). The Cytochrome P-450 enzymes systems, 3A4, 2C9, 2C19, 2D6 and 1A2 are responsible for the metabolism of both THC and CBD.[7] CBD is also metabolized by secondary metabolic pathways and transport proteins (e.g., UGT1A9, UGT2B7, BCRP, BSEP), with the potential to increase adverse effects of the substrate medication.[7] THC has demonstrated the potential to displace highly protein bound drugs which can increase drug levels and increase the risk of toxicity.[1] THC may also produce an additive effect when used in combination with hypnotics, sedatives, psychotropics and alcohol.

Table 3. CBD and THC Drug Interactions[1]

Enzyme	Drug Characteristic	Recommendation	Example Drugs*
Cannabidiol (CBD)			
CYP3A4	Moderate to Strong Inhibitors	Reduce CBD dose	ritonavir, verapamil, voriconazole
CYP2C19	Moderate to Strong Inhibitors	Reduce CBD dose	fluconazole, omeprazole
CYP3A4	Inducers	Consider increasing CBD dose	carbamazepine, St. John's wort
CYP2C19	Inducers	Consider increasing CBD dose	primidone, rifampin
CYP2C8	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	amiodarone, carbamazepine, warfarin
CYP2C9	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	amitriptyline, phenytoin
CYP2C19	Substrates of enzyme	May increase drug levels – consider lowering dose of drug	clobazam (active metabolite), citalopram, clopidogrel, phenytoin, valproic acid
Delta-9-tetrahydrocannabinol (THC)			
CYP2C9	Inhibitors	Consider reducing THC dose	ginkgo, sulfamethoxazole
CYP3A4	Inhibitors	Consider reducing THC dose	ritonavir, verapamil, voriconazole
CYP2C9	Inducers	Consider increasing THC dose	carbamazepine, phenytoin
CYP3A4	Inducers	Consider increasing THC dose	carbamazepine, St. John's wort

Abbreviations: CBD – cannabidiol; THC - Δ-9-tetrahydrocannabinol
Key: * Interaction potential for all drugs that utilize that enzyme system

- Marinol, Syndros and Epidiolex require prior authorization for OHA Fee-For-Service patients
- OHP patients qualify for a reduced medical marijuana card fee

Cannabis products may have a role in the management of medical ailments. Multiple dosage routes, unknown composition and varying costs complicate the use of non-

approved products. Additionally, there are few high quality studies to guide expected outcomes and adverse events. Patients should be made aware of potential drug interactions and adverse reactions associated with both CBD and THC products.

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