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A Guide to Medical Cannabis and Hemp for Healthcare Providers

Dear Healthcare Provider,

This document provides a succinct overview of the clinical information you'll need to safely care for patients who elect to use medical cannabis and hemp CBD products. If you're interested in learning more about the emerging field of cannabinoid medicine, please visit Healer.com.

Sincerely,

Dustin Sulak, D.O.
Co-Founder, Healer

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MEDICAL CANNABIS SAFETY PROFILE: NON-LETHAL, NON-TOXIC

- Effective oral dosing range of plant-based cannabinoids in humans: 0.05 - 25 mg/kg/day[1]
- No deaths occurred in monkeys treated acutely with THC 9,000 mg/kg PO[2] or for 28 days at 250 mg/kg/day PO
- Acute fatal cases in humans have not been substantiated.[3] Six case reports on 13 patients have been published linking recent use of cannabis with sudden death.[4]
- Myocardial infarction may be triggered by inhaled THC due to effects on circulation in individuals who are unable to tolerate orthostatic hypotension or tachycardia.[5]

DRUG INTERACTIONS

- CYP450 inhibition[6]
  - THC: & CBN: 2C9, 3A4
  - CBD: 2C19, 3A4
  - Note – Cannabis is included in most online drug interaction checkers. Additionally, THC can be checked using "Dronabinol" and CBD can be checked using "Epidiolex".
- Cannabis smoking may induce CYP1A2, similar to tobacco smoking, which can increase clearance of theophylline.[7]
- Case reports involving Warfarin suggest a risk for interaction with cannabis via inhibition of hepatic CYP2C9.[8]
- Cannabinoid-opioid interactions: [9, 10, 11]
  - Synergistic analgesia with greater-than-additive effects
  - No enhancement of cardiorespiratory suppression with combination treatment due to very low density of CB receptors in brainstem cardiorespiratory centers
  - Minimal pharmacokinetic interactions in humans with morphine, none with oxycodone
  - Chronic combination-treated animals demonstrate avoidance of opioid tolerance, retention of antinociceptive effect, and upregulation of spinal cord opioid receptor proteins. Clinical evidence suggests these findings translate to humans.
  - Adding low dose cannabinoids to opioids widens the therapeutic window and reduces the need for opioid dose-escalation.
- Alcohol and benzodiazepines: potentiation of sedation[12]
- Cholinergic drugs can modulate the effects of cannabis. Anticholinergic drugs may increase adverse psychoactive effects.[13]
- Most statins, including Simvastatin, Lovastatin, and Atorvastatin, are metabolized by CYP3A4, and the risks of adverse effects, such as myopathy, increase when they are taken with drugs that inhibit CYP3A4.[14] Fluvastatin is primarily metabolized by CYP2C9 and may similarly interact with cannabis. Pravastatin is unlikely to have pharmacokinetic interactions with cannabis.[15]

- Indomethacin has been shown to attenuate some of the effects of THC.[15]
- Due to the anti-inflammatory and immunomodulating effects of cannabis, caution should be used in combination with immunotherapies designed to increase immune activity. For example, clinical data has demonstrated a possible reduction in response rate to nivolumab in cannabis users compared to non-users.[16, 17]

ADVERSE EFFECTS

The adverse effects of medical cannabis are within the range tolerated for other medications.[18] A 2008 review found that in 23 RCTs there was no higher incidence of serious adverse events following medical cannabis use compared with control, while non-serious adverse events were significantly higher in the cannabinoid groups (RR 1.86).[19] Other common adverse effects include:

- A 2015 systematic review of randomized clinical trials found the most common adverse effects, in order of incidence, were disorientation, dizziness, euphoria, confusion, drowsiness, dry mouth, and somnolence.[20]
- Cannabis-naïve patients demonstrate more frequent adverse effects,[21] while regular users experience less psychotomimetic, perceptual altering, and amnestic effects.[22] THC can broaden its own therapeutic window over time due to heterogeneous tolerance-building to various effects,[23] with therapeutic effects more resistant to tolerance development than side effects.[24] Adverse effects can typically be prevented or mitigated with individualized dosing and titration. The guidance of a cannabis clinician and access to diverse formulations and delivery methods allow for personalized treatments that offer an improved adverse effect profile compared to those seen in most controlled clinical trials. Our experience with 18,000 cannabis-using patients in New England has demonstrated that appropriate dosage, delivery method and constituent profile of the product can alleviate many or all the adverse effects.
- The adverse effects of medical cannabis cannot be equated with the effects of illicit cannabis use or abuse. For example, a standardized oromucosal extract spray combining THC, CBD, and other cannabis components has not been abused or diverted to any degree in more than 30,000 patient-years of recorded usage.1 Long term cognitive impairment associated with adult illicit cannabis use has been shown to be completely reversible after a period of abstinence.[25] Conversely, medical cannabis users demonstrate improvement in cognitive tasks after 3 months of treatment.[26]
- While smoking is usually not the preferred delivery method for medical use, even long-term heavy cannabis smokers have no increased incidence of lung cancer,[27] although they can suffer from reversible pulmonary symptoms.[28]
- Adverse effects of hemp-based products containing CBD and/or CBDA are rarely reported in common dosing ranges (<200 mg daily). Based on the clinical experience of my colleagues and myself, the most common adverse effects of CBD are appetite loss, nausea, diarrhea, sleep disturbance, and restlessness. Higher doses of CBD (1500 mg daily) have been shown to increase liver enzymes in some healthy subjects.[29]

THERAPEUTIC POTENTIAL

Cannabinoids have demonstrated therapeutic effects in a broad range of conditions due to the widespread distribution of cannabinoid receptors throughout the body. The endocannabinoid system (ECS) is a regulator of physiologic homeostasis and is an exciting target of pharmacotherapy.

Modulating the activity of the ECS has proven effective in human and/or preclinical studies on mood and anxiety disorders, movement disorders, neuropathic pain, epilepsy, multiple sclerosis, spinal cord injury, cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, insomnia, drug addiction, Alzheimer's disease, and osteoporosis, to name just a few.[30] The vast majority of human research has focused on spasticity, nausea and vomiting, anorexia, and chronic pain.[31]

Some conditions, such as migraine, fibromyalgia, and IBS have pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency, which may be suitably treated with cannabinoid medicines.[32]

CLINICAL EVIDENCE

A 2017 report from the National Academies of Sciences, Engineering, and Medicine found conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting
- For improving patient-reported multiple sclerosis spasticity symptoms

The report also found moderate evidence that cannabis or cannabinoids are effective for: Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.[33]

Increasing but limited clinical data demonstrates that cannabinoids are safe and effective in the treatment of seizure disorders,[34] Tourette syndrome,[35] and several geriatric conditions.[36]

Distinct from non-medical use, studies involving the therapeutic use of cannabis demonstrate improvements in anxiety, depression, and neurocognition.[37, 38]

ENTOURAGE EFFECTS

Cannabis is known to contain hundreds of physiologically active compounds, primarily phytocannabinoids, terpenoids and flavonoids. Whole plant cannabis medicines tend to exhibit superior therapeutic effects and less adverse effects than isolated or synthetic cannabinoids.[39] Currently, the most clinically useful strategy lies in the combination of THC and cannabidiol (CBD), which can be achieved by selecting specific cannabis chemovars (chemical varieties of the plant) or combinations thereof. CBD has been shown to antagonize the undesirable effects of THC, such as intoxication, sedation and tachycardia, while enhancing the analgesic and antiemetic effects. Many patients who experience adverse effects with THC-dominant cannabis are able to better tolerate combination treatment with THC and CBD.

HEMP-BASED PRODUCTS

Until recently, "hemp" varieties of cannabis were grown for non-medical crops, including fiber, hurd (the center of the stalk), and seed; these varieties do not produce high quality medicine. Most countries have regulations that limit the THC content (e.g., 0.3% by weight) of dietary hemp products, such as seed and seed oil.

Due to the exploding popularity of cannabidiol (CBD) following CNN's 2013 documentary, *Weed*, which followed the story of a 4-year-old girl whose treatment-resistant seizures were relieved by a non-impairing, CBD-dominant variety of cannabis, cannabis breeders have developed type III, CBD-rich flowers with ultra-low THC content, in an effort to qualify as a hemp product. In 2018, the FDA approved Epidiolex, a highly purified liquid CBD extract, for the treatment of two rare seizure disorders, Lennox-Gastaut syndrome and Dravet syndrome, and in 2020 for tuberous sclerosis. In recent years, demand for CBD products has grown immensely, with a 2019 analysis reporting 6.9% of Americans were using CBD products at that time.[40]

Over 65 distinct pharmacologic targets for CBD have been identified on the basis of in vitro studies, including receptors, ion channels, enzymes, and transporters.[41]

While the activity at many of these targets requires concentrations that are unlikely to occur in vivo, CBD is strongly pleiotropic, yet it is remarkably safe and well-tolerated. CBD has broad therapeutic applications including the following effects:[42]

- anticonvulsive
- anti-inflammatory
- analgesic
- antioxidant
- antifibrotic
- anxiolytic
- antipsychotic
- procognitive
- neuroprotective

Cannabidiolic acid (CBDA), the precursor to CBD synthesized by the cannabis plant, is a promising therapeutic agent due to its overlapping pharmacological properties with CBD but superior bioavailability and efficacy at lower doses. For example, both CBD and CBDA are antiemetics via activation of the 5-HT1A serotonin receptor in rodent models of nausea, but while CBD demonstrated antiemetic effects at 5 mg/kg ip, CBDA was effective at 0.0005 mg/kg ip.[43] Similarly, in a rodent model of carrageenan-induced hyperalgesia, orally administered CBD was effective at preventing hyperalgesia at 10 mg/kg, while oral CBDA was effective at 0.1 mg/kg.[44] In a rodent model of the seizure disorder Dravet syndrome, CBD reduced seizures at 100 mg/kg, while CBDA was effective at 10 mg/kg.[45] In humans, the oral bioavailability of CBDA is higher than that of CBD in decoction and oil by 5- and 11-fold, respectively.[46] Overall, early results with CBDA indicate promising therapeutic attributes that warrant more investigation.

Patients are increasingly turning to hemp products CBD and CBDA for relief of, most often, anxiety and pain. Though some early clinical evidence supports safety and efficacy for these conditions[47, 48, 49, 50, 51] more research is needed and underway.

FOR MORE INFORMATION

The Society of Cannabis Clinicians (cannabisclinicians.org)
Handbook of Cannabis for Clinicians by Dustin Sulak, D.O. Norton Professional, 2021

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ENDNOTES

[1]Russo, Ethan B., Alice P. Mead, and Dustin Sulak. "Current Status and Future of Cannabis Research." The Clinical Researcher 29:2 (2015): 58-64.
[2]Thompson, George R., et al. "Oral and intravenous toxicity of Δ 9-tetrahydrocannabinol in rhesus monkeys." *Toxicology and applied pharmacology* 27.3 (1974): 648-665.
[3]Grotenhermen, Franjo. "Pharmacology of cannabinoids." *Neuroendocrinology Letters* 25.1/2 (2004): 14-23.
[4]Drummer, Olaf H., Dimitri Gerostamoulos, and Noel W. Woodford. Cannabis as a cause of death: a review." *Forensic science international* 298 (2019): 298-306.
[5]Mittleman, Murray A., et al. "Triggering myocardial infarction by marijuana." *Circulation* 103.23 (2001): 2805-2809.
[6]Stout, Stephen M., and Nina M. Cimino. "Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review." *Drug metabolism reviews* 46.1 (2013): 86-95.
[7]Jusko, W. J., Schentag, J. J., Clark, J. H., Gardner, M., & Yurchak, A. M. (1978). Enhanced biotransformation of theophylline in marihuana and tobacco smokers. *Clinical Pharmacology & Therapeutics,* 24(4), 406-410.
[8]Damkier, P., Lassen, D., Christensen, M. M. H., Madsen, K. G., Hellfritzsch, M., & Pottegård, A. (2019). Interaction between warfarin and cannabis. *Basic & clinical pharmacology & toxicology*, 124(1), 28-31.
[9]Cichewicz, Diana L. "Synergistic interactions between cannabinoid and opioid analgesics." *Life sciences* 74.11 (2004): 1317-1324.
[10]Abrams, D. I., et al. "Cannabinoid–opioid interaction in chronic pain." *Clinical Pharmacology & Therapeutics* 90.6 (2011): 844-851.
[11]Cooper, Ziva D., et al. "Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability." *Neuropsychopharmacology* (2018): 1.
[12]Grotenhermen, Franjo. "Pharmacokinetics and pharmacodynamics of cannabinoids." *Clinical pharmacokinetics* 42.4 (2003): 327-360.
[13]McPartland, John M., Dan J. Blanchon, and Richard E. Musty. "CLINICAL STUDY: Cannabimimetic effects modulated by cholinergic compounds." *Addiction biology* 13.3-4 (2008): 411-415.
[14]Paoletti, R., Corsini, A., & Bellosta, S. (2002). Pharmacological interactions of statins. *Atherosclerosis. Supplements,* 3(1), 35–40.
[15]Perez-Reyes, M., Burstein, S. H., White, W. R., McDonald, S. A., & Hicks, R. E. (1991). Antagonism of marihuana effects by indomethacin in humans. *Life sciences,* 48(6), 507-515.
[16]Taha, T., et al. "The effect of cannabis use on tumor response to nivolumab in patients with advanced malignancies." *Annals of Oncology* 28 (2017): v544.
[17]Taha, T., et al. "Cannabis impacts tumor response rate to nivolumab in patients with advanced malignancies." *The Oncologist* 24.4 (2019): 549.
[18]Joy JE, Watson SJ, Benson JA, editors. Marijuana and medicine: Assessing the science base. Washington DC: Institute of Medicine, National Academy Press; 1999.
[19]Wang, Tongtong, et al. "Adverse effects of medical cannabinoids: a systematic review." *Canadian Medical Association Journal* 178.13 (2008): 1669-1678.
[20]Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., ... & Schmidlkofer, S. (2015). Can- nabinoids for medical use: a systematic review and meta-analysis. Jama, 313(24), 2456–2473.
[21]Hall W, Pacula R. Cannabis Use and dependence: Public Health and Public Policy. Cambridge University Press, 2003.
[22]D'Souza D, et al. Blunted psychotomimetic and amnestic effects of Δ-9- tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacol 2008;33(10):2505-16.
[23]Pertwee, Roger G. "Pharmacological and therapeutic targets for Δ9 tetrahydrocannabinol and cannabidiol." Euphytica 140.1-2 (2004): 73-82.
[24]De Vry, J., et al. "Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development." Behavioural pharmacology 15.1 (2004): 1-12.
[25]Tait, Robert J., Andrew Mackinnon, and Helen Christensen. "Cannabis use and cognitive function: 8-year trajectory in a young adult cohort." Addiction 106.12 (2011) 2195-2203.
[26]Gruber, Staci A., et al. "The grass might be greener: medical marijuana patients exhibit altered brain activity and improved executive function after 3 months of treatment." Frontiers in pharmacology 8 (2018): 983.
[27]Hashibe, Mia, et al. "Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study." Cancer Epidemiology Biomarkers & Prevention 15.10 (2006): 1829-1834.
[28]Tetrault, Jeanette M., et al. "Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review." Archives of Internal Medicine 167.3 (2007): 221-228.
[29]Watkins, Paul B., et al. "Cannabidiol and Abnormal Liver Chemistries in Healthy Adults: Results of a Phase I Clinical Trial." Clinical Pharmacology & Therapeutics (2020).
[30]Pacher, Pál, Sándor Bátkai, and George Kunos. "The endocannabinoid system as an emerging target of pharmacotherapy." Pharmacological reviews 58.3 (2006): 389-462.

ENDNOTES

[31]Grotenhermen, Franjo, and Kirsten Müller-Vahl. "The therapeutic potential of cannabis and cannabinoids." Deutsches Ärzteblatt International 109.29-30 (2012): 495.

[32]Russo, Ethan. "Clinical Endocannabinoid Deficiency (CECD): Can this Concept Explain Therapeutic Benefits of Cannabis in Migraine, Fibromyalgia, Irritable Bowel Syndrome and other Treatment-Resistant Conditions?" *Neuroendocrinology Letters* 25.1/2 (2004): 31-39.

[33]National Academies of Sciences, Engineering, and Medicine. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* National Academies Press, 2017.

[34]Sulak, Dustin, Russell Saneto, and Bonni Goldstein. "The current status of artisanal cannabis for the treatment of epilepsy in the United States." *Epilepsy & Behavior* 70 (2017): 328-333.

[35]Abi-Jaoude, Elia, et al. "Preliminary evidence on cannabis effectiveness and tolerability for adults with Tourette syndrome." *The Journal of neuropsychiatry and clinical neurosciences* 29.4 (2017): 391-400.

[36]Abuhasira, Ran, et al. "Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly." *European journal of internal medicine* 49 (2018): 44-50.

[37]Walsh, Zach, et al. "Medical cannabis and mental health: A guided systematic review." *Clinical psychology review* 51 (2017): 15-29.

[38]Gruber, Staci A., et al. "The grass might be greener: medical marijuana patients exhibit altered brain activity and improved executive function after 3 months of treatment." *Frontiers in pharmacology* 8 (2018): 983.

[39]McPartland, John M., and Ethan B. Russo. "Cannabis and cannabis extracts: greater than the sum of their parts?." *Journal of Cannabis Therapeutics* 1.3-4 (2001): 103-132.

[40]Veiga, A. (2019, March 21). *Cannabis-derived CBD oil finding place in ever more products.* ABC News. https://abcnews. go.com/Business/wireStory/cannabis-derived-cbd-oil-finding-place-products-61835976

[41]Bih, C. I., Chen, T., Nunn, A. V., Bazelot, M., Dallas, M., & Whalley, B. J. (2015). Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics*, 12(4), 699-730.

[42]Russo, E. B., & Marcu, J. (2017). Cannabis pharmacology: the usual suspects and a few promising leads. Advances in Pharmacology, 80, 67–134.

[43]Rock, E. M., & Parker, L. A. (2013). Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea-induced behaviour) in rats. British Journal of Pharmacology, 169(3), 685–692.

[44]Rock, E. M., Limebeer, C. L., & Parker, L. A. (2018). Effect of cannabidiolic acid and Δ9-tetrahydrocannabinol on carrageenan-induced hyperalgesia and edema in a rodent model of inflammatory pain. Psychopharmacology, 235(11), 3259–3271.

[45]Anderson, L. L., Low, I. K., Banister, S. D., McGregor, I. S., & Arnold, J. C. (2019). Pharmacokinetics of phytocannabinoid acids and anticonvulsant effect of cannabidiolic acid in a mouse model of Dravet syndrome. Journal of Natural Products, 82(11), 3047–3055. https://doi.org/10.1021/acs.jnatprod.9b00600

[46]Pellesi, L., Licata, M., Verri, P., Vandelli, D., Palazzoli, F., Marchesi, F.,Cainazzo, M., Pini, L. & Guerzoni, S. (2018). Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (MOH)—a pilot study. European Journal of Clinical Pharmacology, 74(11), 1427-1436.

[47]Bergamaschi, Mateus M., et al. "Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients." *Neuropsychopharmacology* 36.6 (2011): 1219-1226.

[48]Shannon, Scott, et al. "Cannabidiol in anxiety and sleep: a large case series." *The Permanente Journal* 23 (2019).

[49]Capano, Alex, Richard Weaver, and Elisa Burkman. "Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study." *Postgraduate medicine* 132.1 (2020): 56-61.

[50]Gulbransen, Graham, William Xu, and Bruce Arroll. "Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand." BJGP open 4.1 (2020).

[51]Kimless D, Caloura MK, Kirakosyan A, Goldner S (2020) The effects of cannabidiol-based sublingual tablets on diabetic neuropathic pain. *Journal of Diabetes & Metabolism* 11:860.

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