NOTE: This is a very rough draft of proposed Guidelines for Use of Medical Cannabis. As of 12/20/2019, this draft is not complete and has not been vetted or approved by the Cannabinoid Product Board. Based on recent on-line discussions between members of the Cannabinoid Product Board regarding content in this draft, there are significant concerns that will need to be resolved prior to board approval. There are also several sections that have not yet been completed and are awaiting additional input from members of the Cannabinoid Product Board. This draft is being provided for review purposes only and is not intended at this time to be distributed to the general public or used in any manner as a reference to guide healthcare providers in their recommendation of medical cannabis in the treatment of any condition or illness.

BOXED LARGE, BOLD FONT LEGAL DISCLAIMER (worded by Legislative/DPH Counsel) and CLINICAL CAUTIONARY STATEMENT [to include lack of controlled clinical trials yielding high level evidence of predictable therapeutic benefit for any given condition other than those for FDA approved formulations and warnings/risks of developing cannabis use disorder, potentially irreversible brain damage/mental illness, and legal liability for DUI and potential for adverse work-related consequences]

1) Definitions[1]:

1. **Medical cannabis, or medical marijuana:** cannabis plants and plant material such as flowers, buds, hashish, leaves or full-plant extracts intended for treatment of a defined medical condition.
2. **Cannabis-based medicines or cannabis-derived medicines:** medicinal cannabis extracts with defined or standardized cannabinoid content, e.g. nabiximols/Sativex (CBD+THC), cannabidiol/Epidiolex
3. **Herbal Cannabis:** The whole plant or parts, or material from the whole plant, e.g. buds/flowers, resin, leaves.
4. **Cannabinoids:** Biologically active constituents of cannabis, or synthetic compounds that have affinity for, and activity at cannabinoid receptors, e.g. THC, CBD, Dronabinol, Nabilone,
5. **Endocannabinoids:** endogenous ligands found in the body (e.g. anandamide and 2AG) that have affinity for and activity at cannabinoid receptors (CB1, CB2) that also interact at other peripheral and central nervous system receptors (e.g., TRPV1, PPAR alpha and gamma, orphan GPCR receptors).

1. Medicinal cannabis dosage forms – potential advantages and disadvantages – (adapted from Caroline MacCallam and Ethan Russo)[2]

	Vaporization of flower/bud in a vaporizing device, or a regulated cannabis vape pen (cartridges)	Oral – pill, capsule, oil extract/tincture, or gelatinous cube	Oral-mucosal sublingual oil extract or tincture	Topical – oil or cream/ointment
Onset (min)	5-10 minutes	60-180 minutes	15-45 minutes	Variable
Duration (hr)	2-4 hours	6-8 hours	6-8 hours	Variable
Pros	- Rapid onset of action - Advantage for acute or episodic symptoms - Rapid titration is easier to do	- Convenient and discrete - Possible higher potency and protracted duration of action due to first-past hepatic metabolism → active metabolites (11-OH THC) - May be more useful for continuous symptoms	- Convenient and longer duration of action than vaporization dose forms - Sublingual results in more rapid onset than swallowed oral doses	- Less systemic effect, non-controlled reports suggest potential benefit for for localized symptoms

[1] Häuser W, Finn D, Kalso E, Krcevski-Skvarc N, Kress NG, Morlion B, Perrot S, Schäfer M, Wells C, Brill S. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. *Eur J Pain*. 2018;22:1547–1564.

[2] Caroline A. MacCallum, Ethan B. Russo; Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 40 (2018) 12-19.

Cons	- Dexterity required to load vaporizer. - Vaporizer costs. - Some vaporizers are not very portable - More frequent dosing required -Variable blood levels depending upon the depth and duration of inhalation	- Delayed onset of action. - Rapid titration for acute symptoms is more difficult. - Higher potential for first-time excessive dosing -Highly variable and poor bioavailability of CBD	May cause irritation of the mucosa of the mouth and throat	- Effect may be limited to local area of application, - Absorption and systemic effects may be variable

2. **Chemotypes: Chemically distinct plant phenotypes bred to produce characteristic biochemical intermediates.** The acid forms of the cannabinoids THC and CBD are THCA and CBDA and are synthesized by the cannabis plant from a common precursor, cannabigerolic acid (CBGA). The ratio of cannabinoids (THCA+CBDA) produced from this precursor (CBGA) is determined by 2 co-dominant gene alleles at a single locus. A plant that is homozygous for THCA synthase results in production of mostly THCA and very little CBDA. A plant that is homozygous for CBDA synthase will produce mostly CBDA and very little THCA. A plant that is heterozygous with one allele for CBDA synthase and other allele for THCA synthase will produce both THCA and CBDA in significant amounts often approximating a ratio of 1:1.[3] THCA and CBDA have limited clinical activity in the treatment of most conditions and must undergo decarboxylation (removal of their carboxylic acid group to form THC and CBD) to have their expected clinical effects. Decarboxylation is accomplished by heating the plant or plant extract (see additional details below).

Based on these genetic factors in the source plant/cultivar, medical cannabis and cannabis-based products can be conveniently divided into 3 broad chemotype categories based on relative content of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)[4]

a. Chemotype I - Δ^9-tetrahydrocannabinol (THC)-predominant
b. Chemotype II - significant quantities of both THC and CBD
c. Chemotype III- cannabidiol (CBD)-predominant

In addition to THC and CBD, there may be variable quantities of minor cannabinoids such as Δ^8-THC, Cannabigerol(CBG), Cannabichromene (CBC), Cannabinol (CBN), and terpenoids, flavonoids and other compounds depending on the specific cultivar, growing conditions and manufacturing processes.[5] Some producers may provide lab testing results for minor cannabinoid and terpene content in addition to THC and CBD content but current Utah law only requires testing and and labeling of THC and CBD content.

[3] Roy Upton et al; Cannabis Inflorescence, Cannabis spp. Standards of Identity, Analysis, and Quality Control; American Herbal Pharmacopoeia, Revision 2014, page 28

[4] Hillig KW, Mahlberg PG. A Chemotaxonomic Analysis of Cannabinoid Variation in *Cannabis* (Cannabacea) *American Journal of Botany* (2004) 91(6): 966–975.

[5] Roy Upton et al; Cannabis Inflorescence, Cannabis spp. Standards of Identity, Analysis, and Quality Control; American Herbal Pharmacopoeia, Revision 2014, page 28

Unprocessed herbal cannabis (whole flower) from a specific cultivar is likely to have significant differences in relative and absolute cannabinoid content and THC:CBD ratios, as well as terpene content when compared with processed plant extracts from the same cultivar. These differences are due in part to the physical and chemical characteristics (i.e. vapor pressures, boiling points, solubility in a given extraction solvent, etc.) of individual cannabinoids and terpenes that result in variable extraction efficiency. In-vitro studies show that processing herbal cannabis into extracts or other medical dosage forms results in variable decarboxylation depending on the specifics of the process. Processing may also result in some loss of cannabinoid content as well as substantial loss of many of the terpenes[6] and other plant components believed by some to be essential parts of the "entourage effect" (therapeutic synergy). In addition, some processors may add specific terpenes and/or cannabinoids from other sources to a batch of medical cannabis extract product to achieve batch-to-batch balance and consistency in cannabinoid and terpene content or for other purposes, such as creating a product that would not be possible using only herbal cannabis in the extraction process.[7]

Bioavailability of cannabinoids and terpenes from the whole flower of a specific cultivar, when inhaled via a heated air vaporization device, may also be quite variable depending on inhalation technique, the temperature of the heated air used to heat the whole flower, and physical characteristics of the vaporizing device.[8] This again is due in part to a wide range of individual cannabinoid and terpene boiling points and vapor pressures at any given temperature as well as cannabinoid-specific decarboxylation rates at a given temperature[9].

Although blinded, controlled clinical trials addressing therapeutic synergy (aka the "*entourage effect*")[10] are lacking, there are some observational, pre-clinical and anecdotal published reports[11] which suggest that the chemotype, minor cannabinoid content, and terpene content of various cultivars and processed extracts may result in altered pharmacodynamic effects and side-effects. Because of this, certain chemotypes or cultivars may be perceived as more effective or preferred by individual patients in the treatment of certain disease states.[12]

In the past, separating cannabis cultivars into species categories of *cannabis sativa* or *cannabis indica* has been a strategy used to make cultivar recommendations for anticipated therapeutic

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[6] Romano LL, Hazekamp A. Cannabis Oil: chemical evaluation of an upcoming cannabis-based medicine. Cannabinoids 2013;1(1):1-11

[7] Verbal report from Author, MD, Cannabinoid Product Board Meeting October 2019

[8] Swortwood MJ, Newmeyer MN, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. *Drug Test Anal* (2017) 9(6):905–915. doi:10.1002/dta.2092.

[9] Wang M, Wang YH, Avula B, Radwan MM, Wanas AS, Antwerp JV, Parcher JF, ElSohly MA, Khan IA. Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry. *Cannabis and Cannabinoid Research* Volume 1.1, 2016.

[10] Fine PG, Rosenfeld MJ. Cannabinoids for Neuropathic Pain. *Curr Pain Headache Rep* (2014) 18:451 DOI 10.1007/s11916-014-0451-2

[11] Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology* (2011) 163 1344–1364

[12] Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *The Journal of Headache and Pain* (2018) 19:37

effects and side-effects. Due to cross breeding, hybridization and substantial changes in phytocannabinoid content over the last several decades, experts in the medical cannabis field have concluded that labeling a given cultivar as *"indica" or "sativa"* is no longer very helpful in predicting therapeutic effects. Ethan Russo during a recent interview stated, *"There are biochemically distinct strains of Cannabis, but the sativa/indica distinction as commonly applied in the lay literature is total nonsense and an exercise in futility. One cannot in any way currently guess the biochemical content of a given Cannabis plant based on its height, branching, or leaf morphology. The degree of interbreeding/hybridization is such that only a biochemical assay tells a potential consumer or scientist what is really in the plant. It is essential that future commerce allows complete and accurate cannabinoid and terpenoid profiles to be available."*[13]

3. Medical cannabis dosing strategies and suggestions

NOTE: The medical literature is generally devoid of specific dose recommendations for the use of medical cannabis in the treatment of various disease states. This is due to lack of rigorous dose-finding clinical trials for various disease states and the highly diverse chemical composition of the various cannabis strains and their processed extracts. The starting and titrating dose suggestions outlined in this section are adapted from several sources including:

1. Caroline A. MacCallum, and Ethan B. Russo. Practical Considerations in Medical Cannabis Administration and Dosing. *European Journal of Internal Medicine* 40 (2018) 12-19;
2. Dosing guidance provided by Caroline A. MacCallum during a presentation at the 2019 North American Cannabis Summit;[14] and
3. Dosing recommendations from the United Kingdom package insert for nabiximols/Sativex (whole-plant extract oral mucosal spray with **2.5mg of CBD and 2.7mg THC per spray**, indicated outside of the USA for treatment of spasticity in patients with MS).[15]

Starting dose titration recommendations from the United Kingdom package insert for nabiximols (SATIVEX) are presented below to be used as a point of reference in considering starting doses for medical cannabis:

Nabiximols Titration:

A titration period is required to reach optimal dose. The number and timing of nabiximol sprays will vary between patients.

The number of sprays should be increased each day following the pattern given in the table below. The afternoon/evening dose should be taken at any time between 4 pm and bedtime. When the morning dose is introduced, it should be taken at any time between waking and midday. The patient may continue to gradually increase the dose by 1 spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays.

Day	**Number of sprays in the morning**	**Number of sprays in the evening**	(Total number of sprays per day)
1	**0**	**1**	1
2	**0**	**1**	1

[13] Piomelli, D. & Russo, E.B. (2016). The Cannabis sativa Versus Cannabis indica Debate: An interview with Ethan Russo, MD. Cannabis and Cannabinoid Research, 1(1), 44-46. doi: 10.1089/can.2015.29003.ebr.

[14] MacCallum, C. Presentation given at the 2019 North American Cannabis Summit Jan 28-30, 2019

[15] https://www.medicines.org.uk/emc/product/602/smpc

3	**0**	**2**	2
4	**0**	**2**	2
5	**1**	**2**	3
6	**1**	**3**	4
7	**1**	**4**	5
8	**2**	**4**	6
9	**2**	**5**	7
10	**3**	**5**	8
11	**3**	**6**	9
12	**4**	**6**	10
13	**4**	**7**	11
14	**5**	**7**	12

The nabiximols starting dose is one spray per day (2.7 mg THC per 24 hours) for the first several days and is likely not excessive when co-administered with 2.5mg CBD. The nabiximols dose is subsequently gradually titrated upwards until the desired clinical effect has been achieved, but the maximal recommended nabiximols dose should not exceed 12 sprays per day. Twelve sprays of nabiximols would be the equivalent of approximately 32 mg THC per day.

There are no clinical trials directly comparing the pharmacology of nabiximols/Sativex to medical cannabis products and therefore one cannot directly extrapolate the above dosing recommendations for nabiximols to dosing of medical cannabis products. They are however provided as a general point of reference.

The suggested adult medical cannabis starting doses outlined below are not backed up by clinical trials and may not be appropriate recommendations for all patients or for all conditions being treated. They are however, included in these guidelines to provide qualified medical providers with some basic suggestions to consider when initiating treatment with medical cannabis, especially in cannabis-naïve patients.

Suggested starting dose strategies for oral or sublingual (i.e. ingested) medical cannabis products – Chemotypes I and II (significant amounts of THC)

Bioavailability of orally administered THC and CBD is increased if administered in conjunction with a fatty meal. To avoid unwanted psychoactive side-effects, **"start low and go slow"** especially when using chemotype I products.

Consider starting oral dosing at bedtime to limit adverse events and encourage the development of tolerance as follows:

Days 1–2: 1 mg to 2.5 mg THC-equivalent at bedtime (start at 1 mg if young, elderly, or other concerns).
Days 3–4: If previous dose tolerated, increase by 1 mg to 2.5 mg of THC at bedtime.
Days 5–6: Continue to increase by 1 mg to 2.5 mg THC at bedtime every 2 days until desired effect is obtained or side effects limit additional dose increases.

Most patients dose orally two to three times per day. Consider the following regimen for daytime dosing:

Days 1–2: 1 mg to 2.5 mg THC-equivalent once a day at bedtime to establish individual tolerance
Days 3–4: 1 mg to 2.5 mg THC-equivalent twice a day
Days 5-6+: Increase if needed and as tolerated by 1 mg to 2.5 mg increments administered 2-3 times per day up to 15 mg THC-equivalent/24 hours.

In the event of side effects, reduce to previous, best-tolerated dose.

Doses exceeding 20-30 mg THC/day may increase adverse events or induce tolerance without improving efficacy

Suggested starting dose strategies for oral or sublingual administration of medical cannabis products – Chemotype III – CBD predominant.

Chemotype III medical cannabis extracts with a 1:20 THC:CBD ratio have been used in several clinical trials in Israel.[16] These trials used an extract from a high CBD strain dissolved in olive oil with a THC:CBD ratio of 1:20, (1.5% THC and 30% CBD) administered sublingually. Extrapolating from these studies and general **"start low and go slow"** dose titration recommendations, consider the following for oral or sublingual dosing of Chemotype III – CBD predominant medical cannabis products:

Days 1-2: 0.75mg to 1mg THC-equivalent once at bedtime
Days 3-4 0.75mg to 1mg THC-equivalent twice per day
Days 5-6+ Increase dose **if needed** every 2-3 days to 15 mg THC-equivalent/24 hours divided BID-TID

In event of side effects, reduce to previous, best-tolerated dose.

Doses exceeding 20–30 mg THC/day may increase adverse events or induce tolerance without improving efficacy.

Suggested starting dose strategies for oral or sublingual administration of artisanal cannabidiol (CBD).

Artisanal CBD extracted from the hemp plant (chemotype III) may be produced and sold as full-spectrum CBD extract or purified CBD, and is available over-the-counter or on-line without a prescription or recommendation by a qualified medical provider. These products are not currently highly regulated and may or may not have undergone batch testing for CBD content or purity/contaminants by independent third-party laboratories.

[16] Caroline A. MacCallum. Presentation at the North American Cannabis Summit January 28-30, 2019

Oral CBD has been administered in clinical trials to both healthy volunteers and patients with various medical conditions, as single or multiple doses ranging from 10 mg to 6000 mg [17] [18] [19] [20]. In most of these studies CBD was well tolerated and no severe or serious AEs were reported. Hence, CBD is generally considered to have a favorable safety profile[21]. The most common adverse effects reported in these clinical trials were diarrhea, nausea, headache and somnolence.

Suggested starting dose for oral or sublingual administration of full-spectrum artisanal-grade cannabidiol (CBD) with minimal or no THC is 25 mg daily (usually in divided doses taken with a fatty meal) with gradual upward titration based on clinical effects and/or side effects.

Topical: Research into dermal application and absorption of cannabinoids is limited to animal models. Results suggest that THC and CBD are absorbed from intact mammalian skin with or without permeation enhancers at levels comparable to oral absorption. Blood levels can be maintained for days using dermal patches. Topical preparations (NEED MORE INFO)

Suggestions for initiation of vaporization of herbal cannabis for first-time use or when using a new cultivar or chemotype:

NOTE: Bioavailability of cannabinoids and terpenes from a specific cultivar of herbal cannabis when inhaled via a heated-air vaporization device, may vary significantly depending on inhalation technique, the physical characteristics of the vaporizing device, and the temperature of the heated air used to heat the whole flower.[22] The air temperature in the chamber where the plant material is present is particularly important due to at least two separate mechanisms:

1. Higher set point temperatures in the herbal vaporizer chamber result in progressively complete decarboxylation of cannabinoid acids (THCA and CBDA) in the flower into their more pharmacodynamically active states (THC and CBD).[23] [24] If the air temperature is lower, complete decarboxylation is less likely to occur and an individual may experience a clinical response that is

[17] Blessing EM, Steenkamp MM, Manzanares J Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics, 2015; 12:825–836.

[18] Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A phase I randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in health subjects. CNS Drugs, 2018;32:1053-1067.

[19] Chagas MH, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. J Psychopharmacol, 2014; 28(11):1088–98.

[20] Consroe P, et al. Controlled clinical trial of cannabidiol in Huntington's disease. Pharmacol Biochem Behav, 1991;40:701-8.

[21] Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. Cannabis Cannabinoid Res, 2017;2(1):139-54.

[22] Swortwood MJ, Newmeyer MN, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. *Drug Test Anal* (2017) 9(6):905–915. doi:10.1002/dta.2092.

[23] Wang M, Wang YH, Avula B, Radwan MM, Wanas AS, Antwerp JV, Parcher JF, ElSohly MA, Khan IA. Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry. *Cannabis and Cannabinoid Research* Volume 1.1, 2016.

[24] Christian Lanz, Johan Mattsson, Umut Soydaner, Rudolf Brenneisen. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS ONE* (2016) 11(1): e0147286. doi:10.1371/journal.pone.0147286

significantly different (and in some situations preferable) when compared to what would happen with a higher temperature set point.

2. The vaporizer set point temperature also influences what portion of individual cannabinoids and terpenoids get vaporized and inhaled due to the wide range of individual cannabinoid and terpenoid vapor pressures at any given temperature.[25] At lower vaporizer chamber temperature setpoints, cannabinoids and terpenoids with higher vapor pressures and lower boiling points will generally be more completely vaporized than the cannabinoids and terpenoids that have higher boiling points and lower vapor pressures.

Understanding these two effects of temperature setpoints and adjusting the setpoint upwards or downwards can be used as a tool to improve desired clinical outcomes and/or minimize unwanted side-effects of inhaled herbal cannabis.

When making adjustments in vaporizer temperature setpoints, it is important to understand that current commercially-available vaporizer devices are not third-party calibrated, standardized, or regulated and therefore, labeled or electronic temperature setpoints, if they exist, may not accurately represent what is actually happening inside the vaporizing machine at the level of the flower. An in-vitro study comparing 5 different commercially available herbal cannabis vaporizing devices set at 210°C showed significant differences in delivery efficiency of THC and CBD from inhaled herbal cannabis.[26] There are also anecdotal reports of significant variability in patient-to-patient and disease-specific dose responses to various cultivars and chemotypes.

NOTE: Because of these patient and disease-specific variables, lack of vaporizer device regulation and calibration, and lack of any dose-finding clinical trial data, it is currently impossible to give precise vaporizing dose and titration recommendations that will be appropriate for all patients in all treatment circumstances.

The following treatment suggestions may or may not be appropriate for a specific patient with a specific disease process using a specific cultivar/chemotype in a specific vaporizer device, but are provided to give qualified medical providers and cannabis-naïve adult patients a general idea of how to start and titrate the dosing of vaporized whole flower cannabis.

a. Load the herbal cannabis vaporizer device with an appropriate quantity of prepared herbal cannabis. Turn on the vaporizer device with the temperature set at 180-195°C (356 - 383°F). Wait an appropriate amount of time for the temperature in the heating chamber to reach the set point temperature. This process and quantity of herbal cannabis used may vary depending on vaporizer device being used.
b. Start with 1 full inhalation drawn in over 5 seconds, hold for 10 seconds, then exhale. Wait 15 minutes and, if needed, add 1 additional inhalation every 15–30 minutes until desired symptom control has been achieved or side-effects limit use. [27]

25

26 Christian Lanz, Johan Mattsson, Umut Soydaner, Rudolf Brenneisen. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS ONE* (2016) 11(1): e0147286. doi:10.1371/journal.pone.0147286

27 Caroline A. MacCallum, Ethan B. Russo; Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 40 (2018) 12-19.

c. Vaporizer temperature setpoint is typically between 180 - 195°C. This temperature setpoint is high enough to result in significant decarboxylation of THCA, CBDA , and other cannabinoid acids into their clinically active decarboxylated states (THC, CBD). Higher set-point temperatures (e.g. 210-230°C) result in rapid and near complete decarboxylation of THCA and CBDA,[28] (see figure 1) and are more likely to promote decarboxylation and release of other less-studied cannabinoids, terpenes and other plant constituents into the vapor phase, especially cannabinoids and terpenes with higher boiling points (and anecdotally higher likelihood of sedation and intoxication).[29] However higher set point temperatures may also increase the amounts of pre-combustion products of pyrolysis, and promote degradation of THC into CBN.[30] Due to these effects, higher temperature set points are more likely to result in possibly unwanted side-effects including excessive intoxication, sedation, and euphoria. Because of these uncertain but important factors, adjusting the temperature set-point on the vaporizer device may be helpful in achieving a better clinical response depending on what is being treated and which side-effects one is trying to avoid.
d. Unwanted side effects such as fatigue, anxiety, euphoria, impairment of mental status, tachycardia, drop in blood pressure, and dizziness may be less likely to be severe or clinically significant when the vaporizer set point temperature is between 180 - 195°C (or lower), **and the starting dose is low and titration is slow.**
e. Slow upward dose titration and use of chemotypes II or III (containing significant quantities of CBD) has been observed anecdotally to promote some tolerance to the psychoactive sequelae and other side-effects of THC, which may be especially important for naïve users and those who may be more sensitive to the psychogenic effects of THC.[31]
f. **Most patients using a vaporizer device for medicinal purposes will use 1–3 grams of herbal cannabis per day.** Dose escalation over time is not generally observed. Additional needs over time require reassessment. **Less than 5% of patients require > 5 g of herbal cannabis per day[32].**
g. Use of THC-predominant herbal cannabis via a vaporizing device in **high doses above 5 grams per day is probably not justified** and may suggest possible tolerance, misuse, or need for additional evaluation or a different treatment approach.

In event of side effects, reduce to previous, best-tolerated dose and consider adjusting the temperature set point to a lower temperature.

Figure 1.
Decarboxylation Rate Constants for THCA and CBDA as a function of temperature

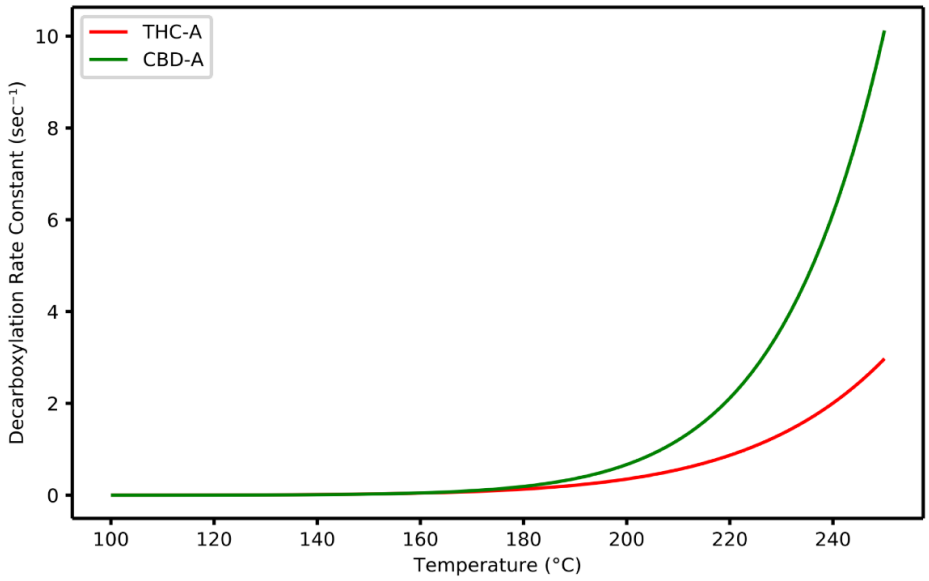
[28] Christian Lanz, Johan Mattsson, Umut Soydaner, Rudolf Brenneisen. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS ONE* (2016) 11(1): e0147286. doi:10.1371/journal.pone.0147286

[29]

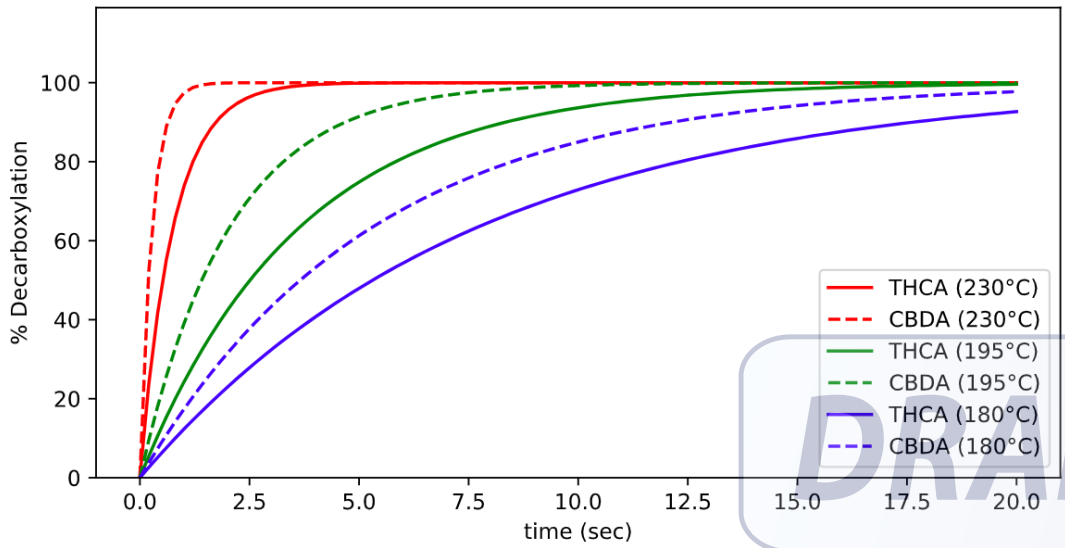
[30] Christian Lanz, Johan Mattsson, Umut Soydaner, Rudolf Brenneisen. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS ONE* (2016) 11(1): e0147286. doi:10.1371/journal.pone.0147286

[31] Caroline A. MacCallum, Ethan B. Russo; Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 40 (2018) 12-19.

[32] Ware MA et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *The Journal of Pain*, Vol 16, No 12 (December), 2015: pp 1233-1242



Modeled % decarboxylation of THCA and CBDA at different temperatures as a function of time



These graphs were prepared by Mark Redd, (PhD Candidate, chemical engineering) using energy of activation data and rate constants for decarboxylation from Wang M, et.al. Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry. Cannabis and Cannabinoid Research Volume 1.1, 2016[33]
The first graph shows that at any relevant specific temperature, THCA has a lower rate constant for decarboxylation than does CBDA and therefore is more slowly decarboxylated than CBDA.

[33] Wang M, Wang YH, Avula B, Radwan MM, Wanas AS, Antwerp JV, Parcher JF, ElSohly MA, Khan IA. Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry. *Cannabis and Cannabinoid Research* Volume 1.1, 2016

The second graph models decarboxylation of THCA and CBDA as a function of time at 180℃, 195℃ and 230℃. Decarboxylation rate constants increase exponentially as a function of temperature and are higher for CBDA than for THCA. As a result, at any given temperature, decarboxylation of CBDA will likely happen at a faster rate than decarboxylation of THCA. . Depending on the design of a vaporizer device, rapidity of inhalation, and the set point temperature, moisture content of the flower, grit size of the preparation, etc, it is plausible that a significant portion of THCA could be vaporized without being decarboxylated to its active form (THC), especially at lower temperature set points, and this may partially explain anecdotal reports of fewer problems with THC side effects and intoxication when the temperature set point is lower. It is important to note that In a separate in-vitro study comparing 5 commercially-available herbal cannabis vaporizer devices, analysis of the vapor at a set point of 210℃ showed nearly complete decarboxylation of THC in 4/5 of the devices.[34]

Suggestions for initiation of inhalation of medical cannabis using concentrated cannabis extract loaded in a vaping cartridge attached to a battery-powered vaping pen device. (NEED MORE INFO)

Potential for biphasic "bell-shaped" or inverted "U" dose-response curve

Cannabis and cannabinoid-containing products including THC and CBD have been shown in some studies to demonstrate a non-linear dose-response curve.[35] Placebo-controlled trials using nabiximols/Sativex® in the treatment of chronic pain and anecdotal clinical observations suggest an inverted U-shaped dose-response curve, meaning that as the dose of THC and/or CBD **is** increased, the clinical effects can sometimes be less than what was observed on a lower dose. These observations can be patient specific and may not be uniform in all patients. A good example of this is use of cannabis to manage anxiety associated with PTSD and other mental health disorders. Low-dose cannabis or cannabis with lower THC content or reduced THC potency due to the presence of CBD, may result in symptom reduction but higher daily doses of THC, or THC administered without significant amount of CBD (Chemotype I cannabis) may result in paradoxical worsening of anxiety to levels that are higher than those experienced prior to starting treatment with cannabis. Nausea, anorexia, cyclical vomiting, and weight loss in people using higher doses of cannabis are other examples of this phenomenon, as cannabis has classically been observed to stimulate appetite and prevent nausea in some clinical situations. (need references for this section)

Cannabis dose-response variables to consider

The therapeutic effects and side-effects of a specific cultivar or chemotype in the treatment of a patient's condition can be variable and dependent on multiple possible factors including:

a) Individual patient-specific responses to a given cultivar or chemotype
b) Absolute dose size of THC (mg), CBD (mg), and other cannabinoids.
c) Relative content ratios of THC:CBD (chemotypes I, II, III), other cannabinoid content and terpenes although reliable information regarding predictable clinical effects of various chemotypes and cultivars is extremely limited and variable depending on individual patient factors that are not well understood.[36]

[34] Christian Lanz, Johan Mattsson, Umut Soydaner, Rudolf Brenneisen. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS ONE* (2016) 11(1): e0147286. doi:10.1371/journal.pone.0147286

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[36] Health Canada; Information for Healthcare Professionals - Cannabis (marihuana, marijuana) and the cannabinoids. Feb 2013, page 13

d) Route and technique of administration of the chemovar – oral vs. oral/mucosal vs. topical creams vs. vaporization of whole flower, use of concentrated extracts in an electric vape pen, etc. *(see section 1 above)*
e) Bioavailability of cannabinoids due to variables in absorption related to dose form, route of administration, product variation additives (long-chain triglycerides etc), and concurrent food intake in the case of orally-ingested dose forms. Pre-clinical studies in rodents showed 2.5 to 3 times higher bioavailability of orally administered THC and CBD when taken in conjunction with dietary fats (a fatty meal).[37] Similarly, co-administration of Sativex with food increased exposure to both THC and CBD (2.8 fold increase in AUC of THC, and 5-fold increase in AUC of CBD) compared to fasting conditions.[13]
f) In the case of vaporized cannabis, the technique used for inhalation (speed of inhalation) and temperature set points[38] may affect extent of decarboxylation, vaporization, and resultant bioavailability.
g) Variable "first-pass" hepatic metabolism (mostly with oral ingestion). THC is metabolized by the liver to 11-hydroxy THC which is several times more potent than THC and, depending on the degree of first-pass metabolism, will likely have variable effects.
h) Drug interactions with other medications affecting pharmacokinetics and pharmacodynamics of the cannabis and cannabinoids
i) Development of tolerance to some effects and side-effects with longer duration of use
j) Pre-treatment handling of flower/bud
    (1) Excessive handling of buds/flowers may result in damage to trichromes[39] with possible reduced potency and shortened shelf life due to accelerated oxidation and degradation
    (2) THC and CBD undergo decarboxylation when heated. Decarboxylation happens rapidly at higher temperatures over 160 C. Without decarboxylation during processing or administration (cooking or heating in a vaporizer device), THC-A and CBD-A have substantially diminished clinical effects.
k) Shelf life and storage conditions of the chemovar
    (1) Degradation of THC occurs by exposure to oxygen and light.
    (2) Shelf-life studies of dried buds/flowers show 90% of original THC content at 1 year when stored at room temperature in the dark
    (3) THC degradation products include Cannabinol (CBN) which has minimal psychoactive effects.

Contraindications

1. **Pregnancy** - ***Potential adverse effects of maternal cannabis use on fetal development and child/adolescent development*** (See the Canadian cannabis monograph entitled *"Information for Healthcare Professionals – 2018"* for additional details)
   The endocannabinoid system, – first detected around day 16 of human gestation - is thought to play an important role in neural circuitry and brain development by regulating neurogenesis and migration and outgrowth of axons and dendrites, and axonal path finding. Because THC crosses the placenta and interacts with the endocannabinoid system of the developing embryo and fetus, use of cannabis during pregnancy, may have significant adverse effects on fetal somatic and neural development and may have long-term neuropsychiatric effects. [40]

[37] Zgair A, Wong JC, Lee JB, Mistry J, Sivak O, Wasan KM, Hennig IM, Barrett DA, Constantinescu CS, Fischer PM, et al. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicine. Am J Transl Res 2016;8(8):3448-59.

[38] Hazekamp A, Ruhaak R, Zuurman L, Van Gerven J, Verpoorte R. Evaluation of a Vaporizing Device (Volcano1) for the Pulmonary Administration of Tetrahydrocannabinol. *Journal of Pharmaceutical Sciences*, Vol. 95, 1308–1317 (2006)

[39] Roy Upton et al; Cannabis Inflorescence, Cannabis spp. Standards of Identity, Analysis, and Quality Control; American Herbal Pharmacopoeia, Revision 2014, page 31

[40] Alpar A, Di Marzo V, Harkany T. At the tip of an iceberg: Prenatal marijuana and its possible relation to neuropsychiatric outcome in the offspring. *Biol Psychiatry* 2016 Apr 1;79(7):e33-45.

Preclinical studies in rodents have shown that *in-utero* exposure to THC or cannabinoids is associated with axonal bundle malformation prenatally; decreased birth weight neonatally; hyperactivity, learning impairment, vocalization, and impaired synapse formation postnatally; impaired consolidation of long-term memory and inhibited social interaction and play behavior during adolescence; and memory impairment, reduced synaptic plasticity, cognitive impairment, altered social behavior, and an anxiogenic-like profile in adulthood. [41] The endocannabinoid system also regulates skeletal development and these effects probably account for the observation that small for gestational age babies are associated with the maternal use of cannabis during pregnancy.

A recent systematic review of human studies concluded that cannabis use during pregnancy is associated with reduced birth weight, increased likelihood of requiring neonatal intensive care unit treatment, and maternal anemia,[42] but there also appears to be some possible long-term effects on the development of children born to mothers who used cannabis heavily during pregnancy. Prenatal cannabis use has been associated with lower scores on language, memory and abstract/visual reasoning domains in children of preschool age [43] [44] [45]. In school-aged children, prenatal cannabis exposure was also associated with deficits in attention and presence of impulsivity and hyperactivity.[46] Later, in children between 9 and 12 years of age, prenatal cannabis exposure was associated with decreased performance in executive functions (e.g. impaired working memory, inattention, impulsivity and inability to plan)[47] [48], with these deficits also appearing in 13 to 16-year olds[49] and 18- to 22-year olds[50] . The exact mechanisms behind these effects are not yet completely understood, but are theorized to result from cannabis' interference with the endocannabinoid system and resulting nervous system development.[51]

Based on current available data, the risk of adverse pregnancy and post-partum outcomes in women using cannabis during pregnancy appears to be substantial. **Women who are pregnant and women who are sexually active and not on a reliable form of contraception should not use cannabis or cannabis-based medical treatments.**

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[41] Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. Eur Child Adolesc Psychiatry 2014 Oct;23(10):931-41.

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[48] Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: Effects on neuropsychological outcomes at 10 years. Neurotoxicol Teratol 2002 05;24(0892-0362; 3):309-20.

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[51] Volkow ND, Compton WM, Wargo EM. The risks of marijuana use during pregnancy. *JAMA* 2017;317(2):129-30.

2. **Lactation** - Clinical evidence shows that cannabinoids and their metabolites accumulate in the breast milk of mothers who smoke cannabis and are transferred to newborns through breastfeeding[52] [53]. THC concentrations in breast milk in humans may be up to eight-fold higher than that found in maternal blood[54]. In a case-control study[55] exposure to cannabis/cannabinoids from breast milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age but separating out the effects of breastfeeding from prenatal exposure was problematic. Although robust clinical data are lacking, it is clear that cannabinoids and their metabolites are present in breast milk in concentrations that could result in a significant exposure for a nursing infant. Weighing the uncertain but potential risks of this exposure against the risks of alternatives to breast-feeding is problematic, but the available data regarding exposure to cannabis through breast milk, and the evidence suggesting potential for harm to infants and children due to cannabis are concerning. **Women who are breast-feeding their infants should not use cannabis or cannabis-based medicines.**

3. **Unstable Cardiovascular conditions including ischemic heart disease, arrhythmia, congestive heart failure, poorly controlled hypertension**. (NEED MORE INFO). THC increases myocardial oxygen consumption due to decreased peripheral vascular resistance, increased heart rate, and increased cardiac output.

4. **History of allergic reaction to cannabinoids, cannabis, or components of medical cannabis preparations**

5. **Schizophrenia spectrum and other psychotic disorders.** Clinical studies suggest that acute exposure to THC or THC-predominant cannabis is associated with dose-dependent, acute and usually transient behavioral and cognitive effects mimicking acute psychosis[56]. While this does not happen in the majority of individuals using cannabis, if it does happen, it warrants stopping the use of cannabis-based medicines, lowering the dose of cannabis-based medications, or switching to a chemotype that has a lower quantity of THC (chemotypes II or III).

   Epidemiological studies suggest a significant association between THC-predominant (chemotype I) cannabis use, and subsequent development of psychosis and schizophrenia, especially in individuals who begin use at an early age and use larger quantities on a daily basis (heavy use)[57] [58]. The risk of schizophrenia associated with cannabis use is especially high in individuals who have a personal or family

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[57] Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull* 2016 Feb 15.

[58] Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. Brit J Psychiatry. 2009;195:488–491.

history of schizophrenia[59]. A number of studies also show certain gene polymorphisms that, when combined with early cannabis use, are associated with a much higher incidence of the development of psychosis and schizophrenia than individuals with the same gene polymorphisms who do not use cannabis.[60]

Cannabis use is associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms[61]. Continued cannabis use after onset of psychosis predicts adverse outcomes, including higher relapse rates, longer hospital admissions, and more severe positive symptoms when compared with individuals who discontinue cannabis use or are non-users[62]. The overall weight of evidence suggests that the association between cannabis exposure and schizophrenia is modest but consistent.

Individuals with current psychosis or history of schizophrenia and other psychotic disorders should not use cannabis or cannabis-based medicines with significant THC content (chemotypes I and II).

Individuals with a family history of schizophrenia or history of significant adverse childhood experiences may be at increased risk for psychotic outcomes related to cannabis use[63] and, if contemplating treatment with cannabis or cannabis-based medicines, they should start treatment with lower doses of chemotypes III, and only if necessary, chemotype II cannabis-based medicines. They should avoid treatment using chemotype I cannabis or cannabis-based medicines that contain high amounts of THC or are THC predominant.

Warnings/Precautions

1. **Use in children, adolescents, and young adults** may result in altered brain development and function with possible long-term negative consequences including negative mental health outcomes and long-term cognitive impairments.[64] [65] [66] Use of cannabis or cannabinoids for treatment of various conditions in this population should be considered only after failure of robust treatment attempts using conventional interventions and then only after a careful risk/benefit assessment and discussion with the patient or

[59] Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot - A review of the association between cannabis and psychosis. Front Psychiatry 2014 May 22;5:54.

[60] Wilkinson ST, Radhakrishnan R, D'Souza DC. Impact of cannabis use on the development of psychotic disorders. *Curr Addict Rep* 2014 Jun 1;1(2):115-28.

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[62] Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, Camuri G, Altamura AC, Murray R, Bhattacharyya S. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; 3: 215–25

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[64] Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A 2012 Oct 2;109(40):E2657-64.

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patient's guardian(s). ***Under current Utah code all individuals using cannabis under age 21 will need approval from the Compassionate Use Board.***

h. **Cannabis Use Disorder** may develop in up to 10% of adults using cannabis and up to 16% of children and adolescents using cannabis. (data from World Health Organization - WHO)[67] The age of onset of cannabis use is inversely proportional to the incidence of cannabis use disorder, i.e. the younger a person is when they start to use cannabis, the more likely they are to have a problem with cannabis dependence and abuse.

i. **Cannabis Hyperemesis Syndrome** – use of cannabis on a regular basis or at high doses may result in cannabis hyperemesis syndrome. The symptoms include episodic severe intractable vomiting, abdominal pain, and compulsive use of hot showers to treat the symptoms. Treatment with antiemetics is usually not effective. Treatment consists of stopping cannabis use or substantially lowering the dose and/or frequency of use[68]

j. **Altered mental status:** Use of cannabis, especially in cannabis-naive patients or in patients who use higher doses of type I chemovars may experience acute problems with altered mental status, psychotic reactions, suicidal ideation, confusion and disorientation. Patients should be warned to not engage in safety-sensitive activities such as driving, machine or equipment operation, or other potentially dangerous activities that require unimpaired judgement or coordination while using cannabis or cannabis-based medications (Sativex).

k. **Driving a vehicle or operating hazardous equipment:** Substantial measurable impairment of psychomotor function, reaction time, and simulated driving skills occurs during the first 2-3 hours after inhaled doses of cannabis but significant impairment has been detected up to 6-8 hours after inhaled doses of cannabis. ***Based on available data and making conservative recommendations, patients should abstain from driving for a minimum of 8 hours after an inhaled dose of cannabis.***[69] Patients using sublingual or orally-ingested cannabis-based medicines need to understand that the effects of oral ingestion on psychomotor function and driving skills may be more intense and typically persist longer than inhaled doses of cannabis. Patients may need to abstain from driving substantially longer than 8 hours after an orally-ingested dose of cannabis-based medicine.

l. **Use of cannabis in combination with alcohol** has been observed to result in substantial additive intoxication and impairment of cognition and motor skills including driving ability. Concurrent use of alcohol and cannabis should be strongly discouraged.

m. **CNS-sedating medications:** Cannabis should be avoided or used with significant caution in patients using sedative-hypnotics, or other medications that may cause mental sedation.

n. **Cardiovascular side-effects:** Use of cannabinoids may cause tachycardia, substantial changes in blood pressure, and episodes of postural hypotension and should not be used in patients with unstable vital signs, congestive heart failure, myocardial infarction, known/suspected structural or vascular heart disease, or known cerebrovascular disease.

o. **Use in the elderly** may result in lightheadedness, mental confusion, balance problems, and unstable gait, and may increase risk of falls, injuries and other adverse outcomes.

p. **Hypersensitivity:** Cannabis should be avoided in persons with hypersensitivity to cannabinoids including plant, extract, oil, pharmaceutical, and other forms of cannabinoids.

q. **Pre-existing pulmonary diseases:** Chronic inhalation of smoked cannabis has been associated with symptoms of morning cough, sputum production and wheezing that improved with cessation of use of cannabis.[70] There is substantial evidence of a statistical association between cannabis smoking and worse respiratory symptoms and more frequent episodes of chronic

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69 Neavyn MJ, Blohm E, Babu KM, Bird SB. Medical marijuana and driving: A review. J Med Toxicol 2014 Sep;10(3):269-79.

70 Hancox RJ, Shin HH, Gray AR, Poulton R, Sears MR. Effects of quitting cannabis on respiratory symptoms. European Respiratory Journal (2015) 46:80-87.

bronchitis.[71] Although there are some data suggesting improved airway dynamics with acute use of smoked cannabis, chronic use is not associated with improvements in pulmonary function. Smoked cannabis should be avoided in persons with respiratory diseases such as COPD. Data regarding pulmonary effects of inhalation of herbal cannabis using a vaporizer device, or cannabis extracts using a vape pen are lacking. Inhalation of vaporized herbal cannabis or cannabis extract administered via a vape pen device should be done with caution in individuals with pre-existing pulmonary diseases.

r. **Schizophrenia and other psychotic disorders:** THC-predominant cannabis (chemotype I) and high doses of THC should be avoided in individuals with a history of schizophrenia and other psychotic disorders. As noted in the "Contraindications" section above, use of cannabis is associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms.[72] Continued cannabis use after onset of psychosis predicts adverse outcomes, including higher relapse rates, longer hospital admissions, and more severe positive symptoms when compared with individuals who discontinue cannabis use or are non-users.[73]

s. **Bipolar and other mood disorders:** A 2015 systematic review and meta-analysis of 6 studies of bipolar disorder and cannabis use[74] sampled a total of 2391 individuals who had experienced mania symptoms. The studies reviewed support a significant association between cannabis use and the exacerbation of manic symptoms in those with previously diagnosed bipolar disorder. The available evidence suggests that cannabis may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases. Furthermore, a meta-analysis of two studies suggests that cannabis use is associated with an approximately 3-fold (Odds Ratio: 2.97; 95% CI: 1.80–4.90) increased risk for new onset of manic symptoms.

t. **Depression and suicidality:** A 2019 systematic review and meta-analysis of 11 studies comprising 23,317 adolescents[75] showed an odds ratio (OR) of developing depression for cannabis users in young adulthood compared with nonusers was 1.37 (95% CI, 1.16-1.62). The pooled OR for suicidal ideation in cannabis using adolescents was 1.50 (95% CI, 1.11-2.03), and the OR for suicidal attempt was 3.46 (95% CI, 1.53-7.84) in cannabis uses vs non-users.

u. **Pre-existing Substance Use Disorders:** Cannabis should be avoided in persons with a history of Substance Use Disorders including Alcohol Use Disorder due to increased risk of developing cannabis use disorder (CUD).

v. **Possible pregnancy:** Cannabis should be avoided in women of childbearing age not on a reliable contraceptive and should be stopped immediately if pregnancy occurs.

w. **Diabetic Ketoacidosis risk in patients with insulin dependent diabetes mellitus -** A retrospective study from Colorado showed that self-reported cannabis users had a 2-fold increase in the incidence of diabetic keto-acidosis compared to self-reported non-users. (need references)

x. **Osteoporosis and metabolic bone disease -** Animal and in vitro human studies implicate cannabinoids in age-related bone remodeling, and possible osteopenia and osteoporosis. (need

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[71] National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press (section 7-1)

[72] Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull* 2016;42(5):2162-1269

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[74] Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: A systematic review and meta-analysis. Journal of Affective Disorders (2015) 171:39-47. https://doi.org/10.1016/j.jad.2014.09.016

[75] Gobbi G, Atkin T, Zytynski T et al. Associations of cannabis use in adolescence and risk ro depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. (2019) JAMA Psychiatry 76:426-434.

references) Patients with metabolic bone disease or risk for osteoporosis who are using cannabis on a regular or frequent basis should consider bone densitometry monitoring to assess possible adverse effects of cannabinoids on bone metabolism.

y. **Transaminase elevation** - Based on the Epidiolex package insert, chronic daily use of higher doses of CBD should probably include monitoring serum hepatic transaminase levels, especially in patients with active hepatic inflammation, history of hepatic insufficiency, or concurrent use of valproate, clobazam, or other medications that have been associated with transaminase elevations.

REFERENCES:
Health Canada: Information for Healthcare Professionals: cannabis and the cannabinoids
National Institute on Drug Abuse: Marijuana Research Report

1) Adverse Reactions and Effects

1. Cognition:[76]

(1) Acute effects of cannabis use are established with strong evidence and include impairment of short-term memory, attention, concentration, executive functioning and visuoperception.

(2) Cognitive effects persist after last use to a degree and duration dependent on multiple factors including length and frequency of exposure, age of onset of use, duration of abstinence, and residual confounding factors.

(3) Some brain imaging studies associate regular (weekly or more frequent) cannabis use with structural changes in gray and white matter in different brain regions.

(4) Early-onset use and use of high-potency, THC-predominant cannabis is associated with a higher degree of impairment.

(5) Methodological limitations and differences in duration of abstinence and measures of cognition contribute to discrepancies in available study results. Drawing definitive conclusions on the long-term brain effects of cannabis use is further confounded by factors such as polysubstance use and mental health functioning of study participants.

1. Psychomotor performance and driving[14]:

(1) Cannabis significantly impairs judgment, motor coordination, and reaction time, and studies have found a direct relationship between blood THC concentration and impaired driving ability. Higher blood levels are associated with more significant impairment.

(2) Period of driving impairment may persist for several days after last use in individuals who use cannabis on a regular basis (weekly or more frequently). This effect is due to the gradual release back into the blood stream of fat-soluble cannabinoids that were deposited and built up in fatty tissues during regular or heavy use of cannabis.

(3) Regular (weekly or more frequent) cannabis users develop only partial tolerance to impairing effects.

(4) Combining alcohol with cannabis is associated with increased impairment and risk of harm.

2. Mental Health Adverse Effects

Katherine L. Carlson, MD, FASAM

(1) Anxiety, PTSD, and Mood Disorders:

[76] Katherine L. Carlson, MD, FASAM. Monograph on Central Nervous System Adverse Effects of Cannabis. Submitted to the Utah Cannabinoid Product Board 7/10/2019

(a) Clinical studies indicate that while occasional (less than weekly) cannabis use can reduce anxiety symptoms, regular (weekly or more frequent) cannabis use, or use of high-dose THC can produce anxiety symptoms.

(b) Epidemiologic studies indicate that regular cannabis use is associated with worsening of mental health-related functions including impaired social activities, impaired performance, and impaired productivity.

(c) Regular (weekly or more frequent) cannabis use or use of THC-predominant cannabis is associated with the onset of anxiety, depressive and bipolar disorders, and the persistence of symptoms related to PTSD, panic disorder, depressive disorder, and bipolar disorder.

(d) Individuals with genetic predisposition and other vulnerabilities are more susceptible to developing mental health side effects and experiencing poorer mental health outcomes.

(2) Schizophrenia and Psychosis:

(a) Cannabis use is associated with an increased risk of acute, transient psychotic reactions including paranoia, disorganized behavior, illusions, depersonalization, derealization, and distorted sensory and bodily perceptions.

(b) Cannabis use is associated with development of schizophrenia, especially among regular (weekly or more frequent) users..

(c) The risk of schizophrenia is especially high in users with particular genetic polymorphisms and/or personal or family history of psychotic disorder.

(d) Cannabis use is associated with earlier onset/younger age of onset of schizophrenia.

(e) Cannabis users with schizophrenia or with a personal history of psychosis are strongly discouraged from using cannabis due to worsening clinical outcomes and exacerbation of psychotic symptoms.

(3) Suicidal Ideation, Attempts, and Mortality

(a) Epidemiologic evidence suggests a link between regular (weekly or more frequent) or high dose cannabis use and suicidality

(4) Cannabis Use Disorder and Other Substance Use Disorders

(a) Epidemiologic and clinical evidence associates regular (weekly or more frequent) cannabis use and use before the age of 18 with development of Cannabis Use Disorder, a form of addiction.

(b) Epidemiologic and clinical evidence associate use of cannabis with other substance use disorders including alcohol, nicotine, and opioid use disorder.

(c) Multiple factors in addition to exposure to cannabis contribute to the risk of developing a substance use disorder.

REFERENCES:
Health Canada: Information for Healthcare Professionals: cannabis and the cannabinoids
National Institute on Drug Abuse: Marijuana Research Report

1.
2.
3.
4. Dizziness
5. Euphoria
6. Nausea
7. Paranoia
8. Abnormal thinking
9. Decreased Appetite
10. Diarrhea
11. Fatigue
12. Insomnia

2) Cannabis Drug Interactions

Author, PharmD, MS

The clinical relevance of possible drug interactions with cannabis and cannabinoids is expected to vary considerably depending on the specific product used, route of administration, individual characteristics, ratio of THC (delta-9-tetrahydrocannbinol) and CBD (cannabidiol) and dose of the product.[1] Significant pharmacokinetic drug interactions are possible either through the effects on drug metabolizing enzymes (e.g., cytochrome [CYP] P450 enzymes) or drug transporters (e.g., UDP-glucuronosyltransferases [UGTs]). Pharmacodynamic effects leading to additive toxicity are also possible. It has been suggested that clinically significant drug interactions are unlikely to occur; however, few drug interaction studies have been conducted.[2] The lack of documented interaction should not be interpreted as the absence of an interaction, but rather a lack of published evidence. Given the possibility of drug-drug interactions and limited understanding of these effects, cannabis should be used cautiously with other medications. Monitor closely for adverse effects and consider dose adjustments as clinically appropriate.

Based on available information, clinicians should be aware of possible interactions, monitor for clinical effects and adjust as needed. The U.S. Food and Drug Administration (FDA) list of common CYP inhibitors and inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers) and/or the Drug Interactions Flockhart Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx) may be referenced to estimate possible CYP450 mediated drug interactions with cannabis products.

Effect of Other Drugs on Cannabis

In vitro studies demonstrate:

1. THC is a substrate of CYP3A4, CYP2C9, and 2C19.[1] Secondary metabolism of THC may occur via UGT isoforms.[3]
2. CBD is a substrate of CYP2C19 and CYP3A4, and may also be a potential substrate of CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A5.[1]
3. Cannabinol (CBN) is a substrate of CYP2C9 and CYP3A4.[3]
4. Drugs which inhibit CYP3A4 or CYP2C9 may increase THC levels.
5. Drugs that inhibit CYP2C19 or CYP3A4 may increase CBD levels.
6. Inducers of CYP3A4, CYP2C9, or CYP2C19 may decrease THC and CBD plasma levels.
7. As CBD is potentially metabolized by a wider variety of CYP isoenzymes, CBD plasma levels may be additionally increased by inhibitors of the isoenzymes other than those that affect both THC and CBD.[1]

Information from clinical studies

Administration of ketoconazole (a CYP3A4 inhibitor) with the oromucosal cannabis extract (Sativex®) resulted in increases in the area under the curve (AUC) of THC and its metabolite by up to 1.8-fold and 3.6-fold respectively. The AUC of CBD was also increased by ketoconazole (2-fold).[3] Administration of Sativex® with fluconazole 200 mg (a CYP2C9 inhibitor) increased the C_{max} and mean AUC of THC (by 22% and 32%, respectively) and increased C_{max} of CBD (by approximately 40%) without appreciable changes in AUC. The CYP3A4 and CYP2C19 inducer, rifampicin, reduced the Cmax and AUC of both THC (by 40% and 20%, respectively) and CBD (by 50% and 60%, respectively) when administered with Sativex®. Product labeling for Sativex® recommends avoiding use of Sativex® with strong enzyme inducers (such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort) and to follow careful titration, particularly within 2 weeks after stopping the inducer if the medications must be used together. No significant changes in THC/CBD were observed when omeprazole (a CYP2C19 inhibitor) was administered is the THC:CBD oromucosal spray.[4] The product labeling for Epidiolex®, a CBD oral solution, warns that moderate or strong inhibitors of CYP3A4 or CYP2C19 increase the concentration of CBD and a reduction in the dose of CBD may be needed. Similarly, inducers of CYP3A4 and CYP2C19 may decrease the concentrations of CBD and an increase in CBD dose may be needed during co-administration of these agents.[5]

Effects of Cannabis on Other Drugs

In vitro studies show that:

1. THC induces CYP1A2 and may decrease the levels of CYP1A2 substrates.
2. CBD inhibits CYP3A4 and CYP2D6, and may increase the levels of CYP3A4 substrates and CYP2D6 substrates.[3]
3. THC may also inhibit CYP3A4, CYP3A5, CYP2C9, and CYP2C19.
4. CBD may also additionally inhibit CYP2C19, CYP3A4, and CYP3A5.[1]
5. Further, smoking cannabis is known to induce CYP1A2, which may lead to reductions in plasma levels of CYP1A2 substrates.[1,3,6]
6. Additional effects on other medication levels are possible through possible stimulation or inhibition of the P-glycoprotein drug transporter.[1]
7. In vitro studies for the FDA-approved CBD product, Epidiolex® indicate potential interactions between CBD and CYP1A2 substrates and CYP2B6 substrates (through CBD induction or inhibition of CYP1A2). Therefore, dose adjustments of medication metabolized by these enzymes may need to be considered as clinically indicated.

8. CBD may also interact with UGT2B7 and UGT1A9 substrates, and CYP2C8 and CYP2C9 substrates. Dose reductions of substrates of these enzymes can be considered as clinically indicated.

NEED A USER-FRIENDLY CHART HERE with lists of actual substrates of CYP1A2, CYP3A4, CYP2D6, CYP3A5, CYP2C8, CYP2C9, CYP2C19, UGT2B7 and UGT1A9 and potential effects of THC and CBD on the substrates

Information from clinical studies or case reports

Warfarin: Case reports suggest frequent use of cannabis may increase the international normalized ratio (INR) in people using warfarin. Cannabis use should be avoided in warfarin users.[7]

Fluoxetine: There have been case reports of mania following co-administration of fluoxetine and cannabis, which may have been mediated by CYP2D6.[6]

Clobazam: The FDA-approved CBD product, Epidiolex®, increased the levels of the active metabolite of clobazam 3-fold and dose-reductions of clobazam may be needed if adverse reactions occur during administration with Epidiolex®. Per package insert labeling, Epidiolex® may also increase the levels of CYP2C19 substrates (e.g., diazepam) and dose reductions of the CYP2C19 substrate may be considered when administered with CBD.[5] These observations may also apply to medical cannabis products that have significant amounts of THC.

Morphine/Oxycodone: A small clinical study (n = 21) in patients with chronic pain found inhaled vaporized cannabis did not significantly affect serum levels of morphine or oxycodone (though non-statistically significant decreases in the morphine C_{max} were observed) without additional side effects (other than a "high") over a short-term period of 5 days.[10]

Indinavir/Nelfinavir: In a study of patients with human immunodeficiency virus on a stable regimen of the protease inhibitor indinavir (800 mg TID) or nelfinavir (750 mg TID), smoked cannabis (3.95% THC) decreased C_{max} of indinavir by a statistically significant amount (14.1%) after 14 days of treatment. Slight changes in the 8-hour AUC (decrease of 10.2% for nelfinavir, and 14.5% for indinavir) and C_{max} of nelfinavir (decrease by 17.4%) were also observed. Over the course of 21 days, there were no significant changes in CD4 counts compared to patients receiving placebo.[12] The authors suggested that these changes were unlikely to have clinically significant effects in the short-term.[11,12]

Docetaxel/Irinotecan: Administration of a cannabis tea (200 mL at 1 g/L) for 15 days with irinotecan (600 mg) or doxetaxel (180 mg) did not significantly affect docetaxel or irinotecan clearance, C_{max} or AUC.[13]

GIven the limitations of these studies and the possibility of variability based on dosage form, dose, and route of administration, caution is warranted. This should not be interpreted as definitive proof of a lack of drug-drug interaction.

Additive Effects and Adverse Reactions

Cannabis can cause CNS depression and may have additive effects with other CNS depressants such as alcohol, sedatives, and hypnotics.[1,8] Cannabis may also theoretically have additive effects with psychotropic agents (e.g., mania, tachycardia, delirium), medications with anticholingeric properties (e.g., sedation), and cocaine (e.g., tachycardia, euphoria).[9] Concomitant use of Epidiolex® and valproate increased the incidence of elevated liver enzymes in clinical trials.[5] Further, concomitant use of cannabis with other cannabinoid products (e.g., dronabinol, nabilone) can cause an overdose.[1]

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15) State Approved Qualifying Medical Conditions

1. Pain lasting longer than 2 weeks – "Chronic Pain" Author MD

Summary: There is moderate evidence to support the conclusion that medical cannabis and cannabinoids can have clinically significant beneficial effects in the management of chronic pain, particularly pain that is due to nerve damage or neuropathy. This is based on supportive findings from good to fair quality studies with very few opposing findings.

Chronic pain is the most common condition (87-94%) cited by individuals who are seeking to use cannabis for medical purposes.[77] A meta-analysis (JAMA 2015) [78] of 8 placebo-controlled trials involving 254 patients with chronic pain showed >30% reduction in pain in 37% of patients using cannabis or cannabinoids compared to 31% of patients getting placebo (OR, 1.41 [95% CI, 0.99-2.00]; 8 trials). Seven of these 8 trials used nabiximols, an oral mucosal spray with a 1:1 ratio of THC:CBD, and 1 trial using smoked inhaled cannabis. The single placebo-controlled trial in this review that used smoked cannabis (3.6% THC) looked at patients with pain due to HIV-associated peripheral neuropathy and showed an odds ratio for significant pain reduction of 3.43 (CI = 1.03-11.48) when compared with placebo.[79]

A systematic review (2015) looked at **chronic peripheral neuropathic pain** treated with inhaled forms of cannabis (smoked or vaporized flower).[80] Underlying conditions included neuropathy due to HIV, trauma, spinal cord injury, diabetes mellitus, and complex regional pain syndrome. In this review meta-analysis of 5 randomized placebo-controlled trials performed in the USA involving a total of 178 middle-aged patients showed an odds ratio for significant pain relief (>30% reduction) of 3.22 (CI = 1.59 – 7.42) when compared with placebo and that inhaled cannabis appeared to provide significant short term relief from chronic neuropathic pain for one in 5-6 patients being treated.

A double-blind, placebo-controlled, crossover trial (2012) of 39 patients suffering from **neuropathic pain of various etiologies** studied the effects of inhalation of vaporized cannabis. The active treatment consisted of 800 mg of flower (bud) containing either a low dose of Δ9-THC (1.29% Δ9-THC; total available amount of Δ9-THC 10.3 mg) or a medium dose of Δ9-THC (3.53% Δ9-THC; total available amount of Δ9-THC 28.2 mg) during three separate 6-hour sessions. Treatment using vaporized cannabis flower was associated with a statistically significant reduction in pain intensity.[81] Both the 1.29% and 3.53% Δ9-THC doses were equianalgesic and significantly better in achieving analgesia than placebo. The number-needed-to-treat (NNT) to achieve a 30% pain reduction was 3.2 for the low-dose vs. placebo, and 2.9 for the medium-dose vs. placebo. The authors suggested that the NNT for active vs placebo is in the range of two anticonvulsants commonly used to treat neuropathic pain (pregabalin, 3.9; gabapentin, 3.8). Cannabis treatment in this study was associated with a small impairment of certain cognitive functions, with the greatest effects seen in domains of learning and memory.

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[79] Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68(7):515-521.

[80] Andreae MH et al. Inhaled cannabis for chronic neuropathic pain: an individual patient data meta-analysis. *J Pain* 2015 December ; 16(12): 1221–1232.

[81] Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J.Pain* 2012 12/10;14(1528-8447; 1526-5900; 2):136-48.

Results from a randomized, double-blind, placebo-controlled, crossover trial (2016) involved 42 patients being treated for neuropathic pain related to injury or disease of the spinal cord.[82] There were three blinded 8-hour treatment sessions held on separate days using a cannabis preparation with no THC (the placebo), cannabis with 2.9% THC, and cannabis with 6.7% THC. The cannabis samples were administered through a Volcano vaporizer device with the temperature set at 185°C. Initial treatment consisted of 4 protocol-driven inhalations from the Volcano holding bag, followed by a second dosing 3 hours later of 4-8 inhalations based on patient preference. Compared with placebo, active treatments were effective in reducing pain scale scores ($P<0.05$) and the 6.7% THC cannabis was numerically superior but did not achieve statistical significance when compared directly with results of the 2.9% THC cannabis. Number needed to treat to get 30% reduction in pain compared with placebo was 3 for the 6.7% cannabis and 4 for the 2.9% cannabis. Psychoactive side-effects showed a dose-dependent association.

A review on the use of smoked cannabis for the treatment of **neuropathic pain** suggested that the efficacy of smoked cannabis (NNT = 3.6, for a 30% reduction in pain) was comparable to that of traditional therapeutic agents (e.g. gabapentin, NNT = 3.8), slightly less than that observed with tricyclic antidepressants (NNT = 2.2), but better than lamotrigine (NNT = 5.4) and selective serotonin reuptake inhibitors (NNT = 6.7)[83]. In this review the concentrations of THC in smoked cannabis ranged between 2% and 9% with an average concentration of 4% yielding good efficacy. Furthermore, the authors suggest that cannabis may present a reasonable alternative or adjunctive treatment for patients with severe, refractory painful peripheral neuropathy who have tried other therapeutic avenues without satisfactory results.

A 12-week blinded randomized placebo-controlled study from England (2012) involved 279 patients with **stable multiple sclerosis**.[84] Active treatment (N= 144) was an oral extract from Cannabis sativa in soft gelatin capsules containing cannabidiol (range 0.8 -1.8 mg) and Δ9 THC (2.5mg). Treatment consisted of a starting dose of one capsule (2.5mg Δ9 THC) twice per day with 2-week dose titration phase and a 10-week maintenance phase. Total treatment duration was 12 weeks. Participants were assessed at 2, 4, 8 and 12 weeks after the start of treatment. The maximum allowable total daily dose was 25mg Δ9 THC. By the end of the 12-week study, 46% of those receiving the active oral cannabis extract treatment had self-titrated to maximum dose of 25mg/day of Δ9 THC vs. 70% of the placebo group. The rate of relief from muscle stiffness and body pain after 12 weeks was almost twice as high with oral cannabis extract group than with placebo (29.4% vs 15.7%; OR 2.26; 95% CI 1.24 to 4.13; p=0.004). Adverse reactions were mild to moderate in intensity and were 2 times more frequent in the treatment group than the placebo group

The 2017 report from the National Academies of Sciences Medicine and Engineering on the health effects of cannabis concludes that *"There is substantial evidence that cannabis is an effective treatment for **chronic pain** in adults"* [85]. However, the authors of this report also cautiously note that only a handful of studies have evaluated the use of cannabis in the United States and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse. They also note that many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States and that very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States.

In summary, most systematic reviews of controlled clinical trials using cannabis and cannabis-based medicines, support the conclusion that cannabis and cannabis-based medicines demonstrate a modest analgesic effect and provide an option for treatment of chronic non-cancer pain - particularly chronic neuropathic pain that has not responded to treatment attempts using FDA-approved conventional treatments and interventions.

General considerations for recommending medicinal cannabis in the treatment of chronic pain:[86]

1. In some patients, oral preparations may be more helpful than vaporized cannabis flower due to longer duration of action of oral preparations and first-pass hepatic metabolism of orally ingested THC to 11-hydroxy THC (more potent that THC).

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[82] Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A. An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. *J Pain* 2016 Sep;17(9):982-1000.

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

[86] Adapted from: MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 49 (2018) 12–19.

2. In patients using orally ingested cannabis-based medicines for treatment of pain, sublingual administration of medical cannabis extracts, vaporization of cannabis flower, or use of a medical cannabis vape pen, can be utilized as add-on treatments for episodic exacerbations of symptoms.
3. CBD may attenuate THC side-effects, which may be useful for daytime dosing, or when driving is required.
4. Medical cannabis patients, in contrast to recreational users, frequently use chemotypes with significant amounts of CBD and generally use the smallest amount of THC needed to get the greatest improvement in symptom control, function, and quality of life, with the fewest adverse events.
5. Data from blinded controlled clinical trials comparing various ratios of CBD:THC and therapeutic synergy (entourage effect) of various cannabis chemotypes and cultivars are lacking, but anecdotal reports and preclinical and observational data suggest that terpenoids and phytocannabinoids other than THC and CBD may have some antinociceptive and/or anti-inflammatory effects, and relative amounts of CBD may alter the effects and side-effects of THC.[87] Because of this, changing ratios of CBD:THC or using a different chemotype or cultivar may result in improved outcomes in pain management with fewer side-effects in the individual patient where N=1.
6. Management of pain using medical cannabis may follow a bell-shaped dose-response curve and escalation of doses of medical cannabis products past a certain amount may not always result in improved control of pain and in some cases may actually result in loss of therapeutic effect along with increased risk of adverse reactions.[88]
7. THC tolerance may be abrogated via a drug vacation of at least 48 hours, preferably longer. Patients may then find that much lower doses provide symptomatic benefit equal to or better than previously experienced (see suggested regimen devised by Dustin Sulak, DO: www.healer.com).
8. Cannabis should be stored in a safe place such as a lock box in the home.
9. Physicians must clearly communicate the potential risks of cannabis, no differently than with any other psychoactive medication.
10. Documentation should include a standard 'treatment agreement' form for medical-legal purposes. (See https://www.drcarolinemaccallum.com/cannabis-resources/).
11. Patients should keep a 'symptom inventory' chart indicating response or efficacy for each cannabis product for each symptom as an aid for physicians in determining treatment response to cannabis in follow up visits. (See https://www.drcarolinemaccallum.com/cannabis-resources/).

Treatment suggestions for use of orally ingested extracts of Cannabis for Cannabis-naïve individuals with chronic pain[89]:

1. Review currently-used prescription medications and check for drug-drug interactions between THC/CBC and any prescribed medications the individual is taking.
2. When treating chronic pain, consider beginning treatment with a chemotype containing both THC and CBD. Anecdotal reports from some experienced cannabis treatment providers suggest that a product with a 1:1 ratio of CBD:THC (chemotype II) or higher levels of CBD is a reasonable starting place with lower risk of adverse reactions.[90] However, based on other anecdotal reports, some individuals may do subjectively better with other CBD:THC ratios (CBD predominant chemotype III, or THC predominant chemotype I) or cultivars containing higher levels of other specific cannabinoids and/or terpenes.
3. Start with a low oral dose of 2.5mg THC-equivalent at bedtime **and go slow**:
    a. Days 1–2: 1 mg to 2.5 mg THC-equivalent at bedtime (start at 1 mg if young, elderly, or other concerns).
    b. Days 3–4: if previous dose tolerated, increase by 1 mg to 2.5 mg THC at bedtime.
    c. Days 5–6: continue to increase by 1 mg to 2.5 mg THC at bedtime every 2 days until desired effect is obtained.
    d. In event of side effects, reduce to previous, best tolerated dose.
4. Some individuals may require cannabis-based medications for daytime use depending on their symptoms. Many patients treating pain dose orally two to three times per day. Consider the following regimen:
    a. Days 1–2: 1 mg to 2.5 mg THC-equivalent once a day.
    b. Days 3–4: 1 mg to 2.5 mg THC twice a day.

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87 Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology* (2011) 163 1344–1364.

88 Portenoy RK, Ganae-Motan ED et al, Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial *Journal of Pain* 13;5 (2012) 438-449

89 Adapted from: MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 49 (2018) 12–19.

90 https://healer.com/programs/strategies-for-non-psychoactive-cannabis-use/ Also similar information was provided during a presentation by Ethan Carruthers PharmD, October 20, 2018.

c. Days 5 +: Increase as needed and as tolerated to 15 mg THC-equivalent/24 hours divided BID-TID.
d. Doses exceeding 20–30 mg/day of THC may increase adverse events or induce tolerance without improving efficacy.

5. Do not expect rapid onset of analgesia using orally-administered cannabis extracts. Orally-ingested THC is metabolized to 11-hydroxy THC during first-pass hepatic metabolism. 11-hydroxy THC is up to 5x more potent than THC and can cause significant intoxication and bothersome adverse reactions, especially in cannabis-naive individuals.[91] Absorption of orally-administered medical cannabis products and the 11-hydroxylation process may take several hours and can be variable depending on bioavailability factors such as concurrent dietary intake. Absorption and bioavailability of orally-administered cannabis-based medicines are usually increased when taken with a fatty meal.
6. If treatment of acute exacerbations of chronic pain is desired, the use of sublingually administered cannabis extract, or inhalation of vaporized flower or vaporized cannabis oil extract (vape pen) may be preferable to orally ingested (swallowed) cannabis extract due to relatively rapid onset of effects with these alternative treatment modalities.

Treatment suggestions for use of vaporized cannabis flower and vaporized cannabis extract oil for treatment of pain[92]:

1. For vaporized cannabis inhalation, patients should start with 1 inhalation and wait 15 minutes. Then, they may increase by 1 inhalation every 15–30 min until desired symptom control has been achieved or side-effects limit use.
2. Higher THC concentrations in herbal cannabis and vape pen concentrates may allow utilization of lower quantities. Patients should titrate accordingly to avoid adverse events.
3. THC-mediated side effects such as fatigue, tachycardia and dizziness are avoidable when starting dose is low and titration is slow.
4. Slow upward-dose titration can promote tolerance to psychoactive sequelae of THC, which is especially important for naïve users. Tolerance is not thought to develop to the medical benefits of cannabis.
5. Attainment of euphoric effects is not required to attain symptom control.
6. **Most patients using an herbal cannabis vaporizer device for medicinal purposes will use 1–3 grams of herbal cannabis per day.** Dose escalation over time is not generally observed. Additional needs over time require reassessment. **Less than 5% of patients require > 5 g of herbal cannabis per day[93].**
7. Use of THC-predominant herbal cannabis via an herbal cannabis vaporizing device in **high doses above 5 grams per day is probably not justified** and may suggest possible tolerance, misuse, or need for additional evaluation or a different treatment approach.

2. Chemotherapy-induced nausea and vomiting

Draft submitted by Author MD 12/9/2019

SUMMARY: There is substantial evidence to support the conclusion that cannabinoids are effective for the treatment of chemotherapy-induced nausea and vomiting (CINV). This is based on supportive findings from good-quality studies with very few or no credible opposing findings.

[91] Presentation by Joseph Bubalo, PharmD, Assistant Professor of Medicine, Oregon Health Sciences University "Clinical Cannabis for the Health Care Provider: Show Me the Evidence. September 29, 2018; Oregon Health Sciences University

[92] Adapted from: MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 49 (2018) 12–19.

[93] Ware MA et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *The Journal of Pain*, Vol 16, No 12 (December), 2015: pp 1233-1242

Smoked cannabis has been used for treatment of chemotherapy-induced nausea and vomiting (CINV) refractory to prescription antiemetics for a number of decades,[94] but there have only been a few controlled clinical trials evaluating the use of smoked cannabis, and/or orally-administered cannabis preparations in the treatment of CINV. Most controlled clinical trials using cannabinoids for treatment and prevention of CINV have looked at the use of dronabinol and other synthetic cannabinoids (nabilone). Many of these trials were conducted prior to the advent of 5-HT_3 serotonin antagonists (e.g. ondansetron), and neurokinin-1 inhibitors, and used classical anti-emetics (e.g. phenothiazines, metoclopramide) or a placebo in the control arms. Pre-clinical data also suggest potential efficacy of other cannabinoids besides THC in the treatment of CINV (see below).

Pre-clinical data regarding various cannabinoids in prevention and treatment of CINV:
A review of preclinical data published in the 2018 Health Canada document "*INFORMATION FOR HEALTH CARE PROFESSIONALS - Cannabis (marihuana, marijuana) and the Cannabinoids,*"[95] includes some important findings regarding possible mechanisms of action as well as relative potency of various cannabinoids (⊗-8 THC, ⊗-9 THC, ⊗-9 THCA, CBDA, CBD, THCV, and CBDV) in treatment and prevention of nausea and vomiting including CINV. In addition to being a CB1 and CB2 agonist, ⊗-9 THC has been demonstrated to act as an 5-HT_3 antagonist similar to ondansetron, suggesting that cannabinoids may affect CINV by more than one mechanism. In several animal models of acute and anticipatory chemically-induced nausea and vomiting, non-psychoactive ⊗-9 THCA (the non-decarboxylated acid form of ⊗-9 THC which does not have significant affinity for CB1 receptors) has been shown to be as much 10 times more potent than the decarboxylated and psychoactive ⊗-9 THC. ⊗-8 THC is reportedly not as psychoactive as ⊗-9 THC but in animal models it has been shown to be more potent and effective in preventing and treating nausea and vomiting than ⊗-9 THC.

CBDA and CBD have both been shown to be attenuate nausea. In one study, CBDA was found to be 1000 times more potent than CBD in attenuating nausea. In an animal model comparing CBDA, THC, and chlordiazepoxide in the treatment of anticipatory nausea and vomiting, CBDA (the non-decarboxylated form) was found to be 5-500 times more potent than THC and 20 times more potent than chlordiazepoxide in the treatment and prevention of anticipatory nausea and vomiting. Some animal models suggest a clear synergistic effect of adding Δ-9 THC in low doses to CBDA in the treatment of chemical-induced nausea and vomiting and anticipatory nausea and vomiting. Other cannabinoids that have shown potential effect in pre-clinical trials in the treatment of nausea and vomiting include THCV and CBDV.

Taken together, the findings from the above pre-clinical studies in animals suggest that Δ9-THC, CBD, CBDA, and THCA may suppress acute nausea and vomiting as well as anticipatory nausea to varying degrees, and with varying potencies and efficacies, whereas THCV and CBDV

[94] Vinciguerra, V.; Moore, T.; Brennan, E. Inhalation marijuana as an antiemetic for cancer chemotherapy. N. Y. State J. Med. 1988, 88, 525–527. Accessed at https://archive.org/details/newyorkstatejour8819medi/page/n839

[95] INFORMATION FOR HEALTH CARE PROFESSIONALS - Cannabis (marihuana, marijuana) and the Cannabinoids. Published by Health Canada, October 2018, Pages 59-62.

suppress acute nausea. Furthermore, certain subthreshold combinations of some of these cannabinoids can produce synergistic anti-nausea and vomiting effects that may be greater than the sum of their individual effects when used alone. Despite these intriguing preclinical data, there have been very few clinical trials evaluating the potential usefulness of phytocannabinoids other than Δ-9 THC in the treatment of CINV in humans.

Systematic reviews of synthetic oral cannabinoids (dronabinol and nabilone):
A quantitative systematic review published in the British Medical Journal (2001)[96] included 30 randomized controlled studies involving 1366 patients with CIVN, comparing oral cannabinoids (dronabinol, nabilone etc.) to placebo or conventional antiemetic therapies (prochlorperazine, metoclopramide, chlorpromazine, haloperidol, domperidone, or alizapride). In all studies reviewed, oral cannabinoids were more effective than placebo and also more effective than active treatment with conventional antiemetics (risk ratio: 1.38; 95% CI: 1.18 to 1.51). Six to eight patients would need to be treated with cannabinoids for one to benefit who would have vomited or had nausea had they all received a conventional antiemetic.

A 2016 Cochran review[97] of 23 randomized controlled trials looking at cannabinoids for treatment of CINV found that fewer people who received cannabis-based medicines experienced nausea and vomiting than people who received placebo. The proportion of people who experienced nausea and vomiting who received cannabis-based medicines was similar to conventional anti-nausea medicines. However, more people experienced side effects on cannabis-based medicines such as 'feeling high', dizziness, sedation and dysphoria compared with either placebo or other anti-nausea medicines. In cross-over trials where people received cannabis-based medicines and conventional medicines in turn, overall, people preferred the cannabis-based medicines.

⊗-8 THC in pediatric patients
In one small open-label trial in Israel (1995), eight children with various hematologic malignancies were administered Δ8-THC (18 mg/m^2) two hours before the initiation of chemotherapy as well as every six hours for the next 24 hours. In this trial, Δ8-THC completely prevented vomiting, and no delayed nausea or vomiting episodes were observed in the next two days following antineoplastic treatment.[98] Δ8-THC could also be administered at doses considerably higher than the doses of Δ9-THC generally administered to adult patients, with a lack of major side effects. Although this was not a blinded-controlled trial and, as a result, subject to substantial bias, the treatment providers noted in that in similar pediatric oncology

[96] Martin R Tramèr, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore, Henry J McQuay Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review, BMJ VOLUME 323 7 JULY 2001; 16-21.

[97] Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD009464. DOI: 10.1002/14651858.CD009464.pub2.

[98] Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sci 1995;56(0024-3205; 0024-3205; 23-24):2097-102.

cases, emesis was observed in about 60% of patients even though metoclopramide (0.3 mg/kg) was being used as antiemetic agent.

Dronabinol vs. ondansetron

In a study of 61 patients comparing ondansetron to dronabinol in the treatment of CINV, treatment response was similar with dronabinol (54%), ondansetron (58%), and combination therapy (47%) when compared with placebo (20%). Nausea absence was significantly greater in active treatment groups (dronabinol, 71%; ondansetron, 64%; combination therapy, 53%) versus placebo (15%; $p < 0.05$ vs. placebo for all) but there was no added benefit of combining dronabinol to ondansetron compared with either agent by itself. Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Active treatments were well-tolerated.[99]

Medical cannabis vs. placebo:

In a 1979 study, fifteen patients with osteogenic sarcoma receiving high-dose methotrexate chemotherapy were studied in a randomized, double-blind, placebo-controlled trial of oral and smoked delta-9-tetrahydrocannabinol (THC) as an antiemetic. Each patient served as his or her own control. Fourteen of the 15 patients had a reduction in nausea and vomiting on THC as compared to placebo and THC was significantly more effective than placebo in reducing the number of vomiting and retching episodes, degree of nausea, duration of nausea, and volume of emesis ($P < 0.001$). There was a 72% incidence of nausea and vomiting on placebo. When plasma THC concentrations measured < 5.0 ng/mL, 5.0 to 10.0 ng/mL, and > 10.0 ng/mL, the incidences of nausea and vomiting were 44%, 21 % , and 6%, respectively.[100] Dosing of THC in this particular trial was 10mg/m^2 body surface area given orally or by inhalation every 3 hours for a total of 5 doses beginning 2 hours prior to the beginning of the 6 hour methotrexate infusion. Getting exact THC doses in cannabis cigarettes as well as empty placebo cannabis cigarettes required multiple pretreatment ethanol extractions of all THC from the herbal cannabis used in this study followed by needle injection of a known quantity of THC into each cigarettes used in active treatment.

In 1981 this same research group reported a second clinical trial involving 8 patients using the exact same placebo-controlled study design as the above trial and the same THC dosing protocol, but a different chemotherapy regimen (Adriamycin and Cytoxan). Compared with placebo, no benefit was noted from use of oral THC or smoked THC in the prevention or

[99] Eyal Meiri, Haresh Jhangiani, James J. Vredenburgh, Luigi M. Barbato, Frederick J. Carter, Hwa-Ming Yang & Vickie Baranowski. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting, *Current Medical Research and Opinion*, (2007) 23:3, 533-543, DOI: 10.1185/030079907X167525

[100] Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky, Simon RM, Rosenberg SA. Delta-9-Tetrahydrocannabinol as an Antiemetic in Cancer Patients Receiving High-Dose Methotrexate: A Prospective, Randomized Evaluation. Annals of Internal Medicine. 1979; 91:819-824.

treatment of CINV.[101] The researchers noted significantly lower serum levels of THC in this second study despite similar dosing of THC and hypothesized that the positive effects of THC in the treatment of CINV may be specific for certain chemotherapeutic agents, or Adriamycin and/or Cytoxan may somehow limit the bioavailability of THC resulting in lower serum levels and diminished clinical effects.

The third study investigating cannabis for the treatment of CINV was a randomized crossover trial in 20 patients who received dronabinol and cannabis.[102] Overall, 5 of the patients reported a positive antiemetic
response. Of the entire cohort, 4 patients preferred smoked cannabis, 7 preferred dronabinol, and 9 had no preference.

A review of multiple U.S. state clinical trials using smoked and/or oral cannabis to treat CINV[103] reported that patients who smoked cannabis showed a 70 to 100% relief from nausea and vomiting, while those who used a Δ9-THC capsule experienced 76 to 88% relief. Plasma levels of > 10 ng/mL Δ9-THC were associated with the greatest suppression of nausea and vomiting, although levels ranging between 5 and 10 ng/mL were also effective. In all cases, patients were admitted only after they failed treatment with standard phenothiazine anti-emetics. In studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration in treatment of CINV.

A 2007 small 16-patient placebo-controlled trial using nabiximols or placebo added to standard antiemetic treatment in patients with incomplete control of CINV, showed that this whole-plant cannabis extract oral-mucosal spray containing a 1:1 ratio of THC:CBD (Sativex) was effective as an add-on treatment in CINV.[104] The proportion of patients showing complete response with no CINV was significantly higher in the nabiximol group [5/7 (71.4%) *vs.* 2/9 (22.2%) in the placebo group. Average 24-hour oral mucosal spray dose administered during the 120 hours after chemotherapy was 4.8 sprays per 24 hour time block or 13 mg THC/24 hours and 11 mg of CBD/24 hours. A separate study on the bioavailability and pharmacokinetics of low and high-doses of nabiximols showed them be similar to orally administered synthetic THC (dronabinol)

[101] Chang AE, Shiling DJ, Stillman RC, et al. A prospective evaluation of delta-9-tetracannabinol as an antiemetic in patients receiving Adriamycin and Cytoxan chemotherapy. Cancer 1981;47:1746–51.

[102] Levitt, M., Faiman, C., Hawks, R., Wilson, A., 1984. Randomized double-blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. *Proceedings of the American Society of Clinical Oncology* 3, 91. *Reported in: D.I. Abrams. Integrating cannabis into clinical cancer care. Curr Oncol. 2016 Mar;23(S2):S8-S14*

[103] Musty R, Rossi R. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. *J Cannabis Therapeutics* 2001;1(1):29-42.

[104] Duran M, Pérez E, Abanades S, Vidal X, Saura C, Majem M, Arriola E, Rabanal M, Pastor A, Farré M, Rams N, Laporte JR, Capellà D. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol (2010) 70:5, 656–663

at similar doses of THC.[105] At this time, nabiximols have not been FDA-approved for use in the USA.

Things to consider prior to recommending medical cannabis for the treatment of CINV:

1. From a patient perspective, CINV is one of the more distressing aspects of chemotherapy.
2. Preventing acute, delayed, and anticipatory CINV is preferable to attempts at treatment.
3. Oral cannabinoids (dronabinol and nabilone) have been shown to be more effective than placebo in prevention and treatment of acute and delayed CINV.
4. Established first-line antiemetic treatment regimens (e.g. 5-HT3 antagonists, neurokinin-1 antagonists, and corticosteroids) for a given chemotherapy intervention should be used unless contraindicated or not tolerated.
5. Dronabinol or nabilone (oral FDA-approved cannabinoids for treatment of CINV) can be used as monotherapy or in combination with other antiemetics and have the advantage over medical cannabis of possible insurance coverage.
6. There is no controlled study of artisanal medical cannabis preparations or inhaled herbal cannabis that shows superiority over current first-line CINV therapies, or oral FDA-approved cannabinoids (dronabinol and nabilone), but observational studies, and individual patient experience and anecdote suggest that some patients may have a beneficial response with inhaled cannabis or orally-ingested or sublingually administered preparations of medical cannabis as sole treatment or add-on therapy to standard antiemetic therapy in the treatment of CINV.[106]
7. Some observational data suggest that inhaled cannabis (smoked or vaporized) may be more useful in the treatment of CINV than oral dosage forms of synthetic THC and orally administered medical cannabis extracts.[107]
8. Prior patient experience with first-line therapies and inhaled and/or orally-ingested forms of medical cannabis should be taken into consideration when recommending treatment of CINV using medical cannabis.
9. There are problems with variable absorption and bioavailability with all forms of medical cannabis, especially orally-ingested products taken on an empty stomach with no food, or taken orally during active nausea and vomiting.
10. The antiemetic dose-response curve for use of cannabinoids in the treatment of CINV has not been studied but may not be linear, meaning escalation of dose may or may not result in improved therapeutic response and in some cases, dose escalation could hypothetically result in worsening symptoms of CINV.
11. **Always check for drug-drug interactions** prior using medical cannabis – THC and CBD can affect serum levels of chemotherapeutic agents and other medications metabolized by several of the cytochrome P450 enzymes (see Drug Interaction Section above).

[105] Erin L. Karschner, W. David Darwin, Robert S. Goodwin, Stephen Wright, and Marilyn A. Huestis. Plasma Cannabinoid Pharmacokinetics following Controlled Oral 9 -Tetrahydrocannabinol and Oromucosal Cannabis Extract Administration Clinical Chemistry 57:1 66–75 (2011)

[106] D.I. Abrams. Integrating cannabis into clinical cancer care. *Curr Oncol*. 2016 Mar;23(S2):S8-S14

[107] Musty R, Rossi R. Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials. *J Cannabis Therapeutics* 2001;1(1):29-42.

Dosing suggestions for treatment of CINV using orally and sublingually administered medical cannabis products:

There are no dose-finding studies to guide the use of oral medical cannabis extracts or inhaled forms of cannabis in the prevention and treatment of CINV. The dose suggestions below are based only on FDA-approved oral dosing recommendations for dronabinol (MARINOL) in the treatment of CINV. Bioavailability and pharmacodynamic effects of orally and sublingually-administered medical cannabis extracts may differ substantially from an orally ingested dose of of a single cannabinoid, dronabinol. Because of these variables, the dosing suggestions below may not be appropriate for all patients with CINV:

1. Start with 5 mg/m^2 THC equivalent, administered 1 to 3 hours prior to the administration of chemotherapy and then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses per day.
2. In elderly patients, and those with unstable vital signs or co-occurring cardiovascular problems, consider initiating THC equivalent at 2.5 mg/m^2 once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS symptoms and cardiovascular adverse outcomes.
3. The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial response, as tolerated to achieve a clinical effect, in increments of 2.5 mg/m^2 .
4. The maximum dosage of THC equivalent should not exceed 15 mg/m^2 **per dose** for 4 to 6 doses per day.
5. **Adverse reactions are dose-related and psychiatric symptoms increase significantly at higher and maximal dosages.**
6. Monitor patients for adverse reactions and consider decreasing the dose to 2.5 mg once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS adverse reactions

Note:

The above dosing suggestions for CINV are above and beyond the conservative recommendation of *"start low and go slow"* and are more aggressive than those listed in the general dosing guidelines in this document. They are not based on any clinical trials using actual medical cannabis preparations and are intended only to be used as dosing suggestions for treatment of severe CINV that has not adequately responded to first-line therapies.

These dosing suggestions are based on dronabinol and do not take into consideration variations in bioavailability or any possible additional pharmacodynamic effects or side-effects of medical cannabis extracts due to possible therapeutic synergy related to other cannabinoids and terpenoids that may be present in a given oral or sublingual medical cannabis preparation. Although there are no clinical trial results and very limited observational data in humans, preclinical animal data suggest that it is possible that

cannabinoids in addition to decarboxylated ⊗-9 THC may have significant clinical effects on CINV symptoms in humans.

Caution should be exercised when trying to balance the acute need to control symptoms of CINV in a physically compromised individual against the potential for significant side effects associated with the use of higher doses of THC in chemotypes I and II medical cannabis products. In cannabis naïve patients who are elderly or significantly compromised, use of THC equivalent doses that are lower than the above suggestions should be considered.

Dosing suggestions for treatment of CINV using inhalation of heated vaporized herbal cannabis:

Use of inhaled cannabis preparations may be preferred over oral preparations by some patients suffering from CINV. When inhaling vaporized herbal cannabis from a heated vaporizing device to treat CINV, different chemotypes and cultivars as well as using different temperature set points on a single cultivar, may result in significant differences in treatment outcomes. There is currently no clinical trial data to guide a qualified healthcare provider in choosing any particular cultivar, chemotype, or temperature set point in the treatment of CINV, but titration suggestions outlined below from the general dosing section of this document may be a helpful starting point**:**

1. Load the herbal cannabis vaporizer device with an appropriate quantity of prepared herbal cannabis. Turn on the vaporizer device with the temperature set at 180-195°C (356 - 383°F). Wait an appropriate amount of time for the temperature in the heating chamber to reach the set point temperature. This process and quantity of herbal cannabis may vary depending on vaporizer device being used.
2. About 15 minutes prior to chemotherapy, start with 1 full inhalation drawn in over 5 seconds, hold for 10 seconds, then exhale. Wait 15 minutes and, if needed, add 1 additional inhalation every 15–30 minutes until desired symptom control has been achieved or side-effects limit use. [108]

Dosing suggestions for treatment of CINV using medical cannabis administered via vape pens:

In the case of vape pens that use concentrated medical cannabis extracts/oils, there is no temperature set points but the actual dose of THC and CBD can be estimated based on inhalations per cartridge for a specific vape pen, and laboratory test results for mg of THC and CBD per cartridge. While this may be interesting information and may help avoid excessive dosing and side effects, due to variability of inhalation technique, it may still be prudent to follow the symptom-based titration suggestions below:

[108] Caroline A. MacCallum, Ethan B. Russo; Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 40 (2018) 12-19.

1. About 15 minutes prior to starting chemotherapy, take 1 full inhalation drawn in over 5 seconds, hold for 10 seconds, then exhale. Wait 15 minutes and, if needed, add 1 additional inhalation every 15–30 minutes until desired symptom control has been achieved or side-effects limit use.
2. Extra caution and less-aggressive dosing should be considered in the elderly and in otherwise compromised adults and children

As always, <u>in event of significant side effects, stop use of medical cannabis until side-effects have resolved, and then reduce to previous, best-tolerated dose.</u>

3. MS or persistent debilitating Muscle spasms – Author, MD

Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks myelin present in the central nervous system. A number of biologic-based disease modifying agents, immune antagonists, and symptom-based therapies are approved for the treatment of this chronic and potentially debilitating progressive disorder. The 2017 National Academy of Sciences and Engineering literature review on the medical effects of Cannabis and cannabinoids concluded that sufficient conclusive evidence for patient-reported improvement in multiple sclerosis-related spasticity justified the use of medical marijuana in the treatment of MS (National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: National Academies Press; 2017.). An extensive literature review conducted by the Government of Canada (2018 CANADA information-health-care-professionals-cannabis-cannabinoids-eng.pdf) concluded that:

- *Evidence from pre-clinical studies suggests THC, CBD and nabiximols improve multiple sclerosis(MS)associated symptoms of tremor, spasticity and inflammation.*
- *The available evidence from clinical studies suggests cannabis (limited evidence) and certain cannabinoids (dronabinol, nabiximols, THC/CBD) are associated with some measure of improvement in symptoms encountered in MS and spinal cord injury (SCI) including spasticity, spasms, pain, sleep and symptoms of bladder dysfunction.*

Evidence for disease-modifying and neuroprotective effects of cannabis in preclinical models of multiple sclerosis support the use of medical marijuana in the early treatment of MS. Although a single study of pure THC administered to patients with chronic and progressive MS failed to demonstrate an improvement in disability or neuropathology, the relevance of the use of a single agent purified cannabinoid to the use of medical marijuana is unclear (Pract Neurol 2019;0:1–6. doi:10.1136/pract neurol-2018-002137). In summary, evidence supports the use of medical cannabis as a first-line disease modifying agent in the early treatment of MS, for the treatment of MS-associated spasticity of both striated and smooth muscle, as well as for anxiety and sleep-associated complications of MS. (needs additional references and further discussion)

4. Terminal Illness when life expectancy is less than 6 months or on hospice

5. Epilepsy/debilitating seizures

Summary: With the exception of CBD/Epidiolex, there is insufficient evidence to support the conclusion that medical cannabis or cannabinoids (other than CBD) are effective or ineffective treatments for various types of epilepsy or seizure disorders.

Epilepsy consists of dozens of separate and distinct syndromes. Over 20 prescription medications, including CBD, are approved by the FDA for the treatment of specific types of seizure disorders. Multiple case reports, dating back to the 19th century, describe benefits of cannabis in the management of epilepsy. Many animal studies have shown that experimental seizures alter endocannabinoid physiology, administration of endocannabinoids and phytocannabinoids have anticonvulsant properties, and that CB1 receptor agonists act synergistically with prescription anticonvulsant medications to increase efficacy. Studies also demonstrate the development of tolerance to the anti-seizure effects of cannabis and rebound increases in seizure frequency with cannabis discontinuation.

Individuals seeking medical cannabis for management of epilepsy, typically have problems with breakthrough seizures despite attempts using multiple medications and combinations of medications, or have experienced significant side-effects from FDA-approved AED's and want to try alternative treatments.[109]

The medical literature contains many retrospective, patient-reported seizure-frequency studies on the effects of cannabis in patients with seizure disorders. These reports as a rule, generally show either a decrease in seizure frequency or no effect.

A widely quoted Cochran review published in 2014 of 4 clinical trials involving a total of 48 patients found a partial beneficial effect of CBD in two trials and no effect in 2 trials. Study design limitations—small sample size, lack of blinding and randomization, and incomplete data sets—were noted in all four studies.

A subsequent meta-analysis by the American Academy of Neurology concluded that, because of a lack of high-quality studies, no conclusions about the efficacy of cannabinoids in the treatment of epilepsy could be drawn. An important consideration in the use of cannabinoids in the treatment of epilepsy is the potential for drug-drug interactions. Clobazam and valproic acid, in particular, are two commonly used anti-seizure medications whose metabolic clearance may be affected by the co-administration of cannabinoids.

A recently published review and meta-analysis of CBD's efficacy based upon 13 completed clinical trials and 9 clinical trials in progress concluded that CBD used in combination with prescription anti-seizure medications appears to decrease seizure frequency.[110] In another study, CBD administration was shown to improve quality of life in patients with epilepsy without affecting seizure frequency or severity.

Based upon the safety profile of CBD and the weight of clinical evidence, use of CBD as adjuvant therapy in conjunction with prescription anticonvulsant medications in patients with poorly controlled epilepsy appears to be justified. Patients with epilepsy should be under the care of a neurologist, ideally one with expertise in the diagnosis and treatment of seizure disorders. The use of CBD by a neurologist in conjunction with other anti-seizure medications for the treatment of epilepsy is appropriate.

Extrapolating from the bioavailability of other cannabinoids, 2.5 mg of CBD taken by mouth is approximately equivalent to 1 mg vaped or smoked. Accordingly, patients who prefer vaping should start with 0.5 mg/kg twice a day and increase by 0.5mg twice a day to a maximum of 4 mg twice a day. Patients must be closely monitored for potential drug-drug interactions, and CBD should be gradually discontinued (i.e. do not abruptly terminate CBD) if there is no clear clinical response.

Data from well-designed blinded controlled clinical trials documenting the efficacy of medical cannabis containing THC for the treatment of epilepsy are lacking, however, there are a few reports containing observational and retrospective data without controls that suggest possible efficacy of chemotype III medical cannabis in the treatment of pediatric and adult epilepsy.

Medical Cannabis and Pediatric Epilepsy:

[109] Suraev AS, Todd L, Bowen MT, Allsop DJ, McGregor IS, Ireland C, Lintzeris N. An Australian nationwide survey on medical cannabis use for epilepsy: History of antiepileptic drug treatment predicts medical cannabis use. Epilepsy and Behavior. (2017) 70:334-340.

[110] Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;0:1–13. doi:10.1136/jnnp-2017-317168

One retrospective study[111] looked at 74 pediatric patients, (age range 1-18) with intractable epilepsy resistant to > 7 antiepileptic drugs. More than half of them had also failed a ketogenic diet, vagal nerve stimulator, or both. They were all started on an CBD-enriched medical cannabis extract concentrate dissolved in canola oil (20% CBD and 1% THC) with a CBD:THC ratio of 20:1 administered orally. Patients were treated and observed for a minimum of 3 months but many of them were observed for longer than that (average 6 months). CBD doses ranged from 1-20mg CBD/kg/day but 81% of them responded to doses less than 10mg CBD/kg/day. THC dose did not exceed 0.5mg/kg/day and the maximum absolute dose of CBD was 270mg per day. Seizure frequency was assessed by parental reports during clinic visits. Most parents (89%) reported a reduction in seizure frequency in their children: 18% reported 75-100% reduction, 34% reported a 50-75% reduction, 12% reported a 25-50% reduction and 19% reported <25% reduction in seizure frequency. Parents of 13 of the 74 patients (7%) reported aggravation of seizures which led to stopping the CBD-enriched medical cannabis extract in 5 patients.. Other adverse events included somnolence/fatigue in 22% of patients and mild GI problems in 7%. Positive effects not related to seizure reduction were reported in 44/74 patients including improved behavior and alertness, improved sleep, and improved communication and motor skills.

There are no controlled clinical trials comparing pure CBD (Epidiolex) with CBD-predominant medical cannabis (chemotype III), or CBD-enriched medical cannabis, similar to what was used in the above retrospective observational study. Because there were no placebo controls and due to the inherent potential for bias in parental reporting of seizures, the actual efficacy, or lack or efficacy of medical cannabis with a 20:1 ratio of CBD:THC in the treatment of epilepsy in children cannot be established based on this study. However, in cases where FDA-approved AED's have been tried and found to be inadequate or not tolerated, and where pure CBD (Epidiolex) has limited FDA-approved indications in the treatment of certain rare seizure disorders, and due to the exceptionally high price of Epidiolex and propensity of insurance companies to deny reimbursement for *"off-label use,"*, some parents of children with inadequately-managed epilepsy may ask a qualified medical provider to consider recommending the use of medical cannabis. Under current Utah law, in the case of children and adults under the age of 21, review and approval by the Compassionate Use Board will be needed prior to dispensing medical cannabis.

Things to consider prior to recommending medical cannabis for the treatment of epilepsy:

1. Based on clinical trials using pure CBD (Epidiolex), and observational data using CBD-predominant medical cannabis preparations in the treatment of epilepsy, a patient considering use of medical cannabis should probably begin with pure CBD, or chemotype III or CBD-predominant medical cannabis and should probably avoid attempting treatment of epilepsy with medical cannabis with higher THC content (i.e Chemotype I, or THC-predominant medical cannabis).
2. There are no long-term controlled trials evaluating the potential for negative outcomes in the long-term daily administration of CBD, or CBD-predominant medical cannabis in children or adults. Daily dosing of THC-predominant cannabis or high absolute doses of THC in children and adolescents are associated with a number of negative clinical outcomes outlined in other sections of this document and probably should be avoided in the treatment of epilepsy unless careful assessment of clinical benefit is deemed substantial enough to justify exposing the child/adolescent and adult to the substantial known risks of high daily doses of THC and THC-predominant medical cannabis.
3. **Suboptimally-managed epilepsy is a substantial risk by itself for poor clinical outcomes and premature death.**
4. Pure CBD or CBD-predominant medical cannabis extracts, after consideration of risks and benefits, may be used as primary treatment or as an adjunctive intervention combined with FDA-approved AED's in attempting to achieve optimal management of epilepsy.
5. A patient who is considering use of medical cannabis, and/or a qualified medical provider who is recommending off-label use of pure CBD (Epidiolex) or medical cannabis for the primary or adjunctive treatment of inadequately managed epilepsy, should consider seeking consultation with a neurologist or other specialist with expertise in the acute and long-term management of epilepsy.
6. Stopping CBD and THC during the management of seizures should be done in a gradual fashion over several weeks or months if possible, to reduce the potential for negative clinical outcomes including clinical worsening of epilepsy..

Dosing guidance for treatment of epilepsy in adults:

1. To maintain relatively stable tissue levels needed to prevent seizures, dosing of CBD and medical cannabis should be done at least twice daily using the oral or sublingual route.
2. Careful review of potential drug-drug interactions and clinical effects and adverse effects should carefully followed and documented to help guide dose adjustments

[111] Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, Nissenkorn A, kYosef OE, Hyman E, Granot D, Dor M, Lerman-Sagie t, Ben-Zeev B. CBD-enriched medical cannabis for intractable epilepsy- The current Israeli experience. *Seizure* (2016) 35:41-44.

3. Treatment of breakthrough seizures could be considered using CBD-predominant medical cannabis extract given via the sublingual route or using a vape pen in an adult who is alert and awake, but there are no clinical trials to provide guidance regarding efficacy or harm, or appropriate doses of medical cannabis for the acute treatment of breakthrough seizures.
4. Based upon labeling for Epidiolex, in adult patients with no liver disease, initial oral dosing of pure CBD is 1.25 mg/kg administered twice daily (i.e. for a 50 kg adult: start with CBD 62.5 mg every twelve hours). Dosing can be increased by 2.5 mg/kg on a weekly basis as indicated. Dosing of pure CBD in the treatment of epilepsy should not exceed 20mg/kg/day or 500mg twice daily in a 50kg adult.
5. There are no available clinical dose-finding data to guide dosing and titration of CBD-predominant medical cannabis in the treatment of epilepsy.
6. **Patients should start low and go slow. If titrating doses upwards results in adverse events, or worsening of seizures occurs, reduce dose back down to the most recent best-tolerated dose.**
7. Following the general dosing guidelines in this document for Chemotype III cannabis (CBD-predominant), and starting with a two-times-per-day dosing schedule, and assuming the use a 20:1 CBD:THC concentrated oral or sublingual extract, a suggested adult starting dose for treatment of epilepsy would be:

    Days 1+2:
    0.75 mg - 1 mg THC equivalent and 15 mg - 20 mg CBD taken orally or sublingually twice per day
    (1.5 mg-2 mg THC/24 hours and 30 mg-40 mg CBD/24 hours)

    Days 3+:
    Increase dosing every 2-3 days by increments of 1mg THC equivalent and 20mg CBD taken twice/day as long as tolerated and still having breakthrough seizures, **up to 15mg THC equivalent/24 hrs**.

NOTES:

1. Maximum recommended daily oral or sublingual doses of THC in CBD-predominant, chemotype III medical cannabis in the treatment of epilepsy in unknown.
2. The dose-response curve using medical cannabis in the treatment of epilepsy is unknown, is likely non-linear, and may vary from patient-to-patient and from one medical cannabis extract/cultivar/chemotype to another. Because of these variables, dose escalation may not always result in improved seizure control.
3. Some preclinical and observation human data suggest that unlike CBD, THC by itself may, in some circumstances actually lower the seizure threshold in certain types of seizures,[112] and higher doses may result in increased risk of breakthrough seizures and worsening of unmanaged epilepsy.
4. However, anecdotal and observational reports also suggest a possible therapeutic synergy in treatment of epilepsy when relatively small doses of THC are combined with, or added to higher doses of CBD to improve the efficacy of the CBD and clinical outcomes in treatment-resistant epilepsy.[113]
5. Caution must be exercised in treatment-resistant cases of epilepsy, because dose escalation of CBD-predominant cannabis may eventually result in relatively high daily doses of THC with possible worsening control of seizures due to the adverse effects of relatively high doses of THC.
6. Adults being treated for epilepsy with oral medical cannabis preparations should probably avoid high doses of THC and Chemotype I cannabis or medical cannabis products and probably should not exceed 20mg THC equivalent/24 hours and 400mg CBD/24 hours.
7. This general guidance may not be appropriate for all individuals with unmanaged epilepsy, and titration of doses and ratios of CBD:THC may need substantial individual adjustments and adaptations depending on historical and current clinical response to various treatment attempts..

6. Persistent Nausea and Vomiting/Cachexia

[112] BRUST JC, NG KC, HAUSER A, SUSSER M. MARIJUANA USE AND THE RISK OF NEW ONSET SEIZURES *Epilepsia*, 42(10):1266–1272, 2001

[113] Fabricio A. Pamplona,, Lorenzo Rolim da Silva, and Ana Carolina Cone. Potential Clinical Benefits of CBD-Rich *Cannabis* Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. Front. Neurol., 12 September 2018 | https://doi.org/10.3389/fneur.2018.00759

7. Post-traumatic Stress Disorder (PTSD): Author MD

Summary: There is insufficient evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective treatments for PTSD or symptoms of PTSD.

PTSD may be caused by exposure to actual or threatened death, serious injury, or sexual violence by directly experiencing traumatic event(s), or witnessing in person the event(s) as it/they occurred to others. Conventional treatments for PTSD usually include psychotherapy along with optional use of prescription medications to help manage ongoing and emerging symptoms while undergoing therapy. Cannabis has been anecdotally reported to be useful in managing anxiety, sleep disturbances, nightmares, and other symptoms in individuals suffering from PTSD. There are a number of pre-clinical observations involving the endocannabinoid system and CB1 receptor density in certain areas of the brain in individuals with PTSD[114] [115] that lend credence to an hypothesis that cannabis and cannabinoids could have some effect on symptoms of PTSD. However there is currently significant clinical uncertainty regarding the potential benefits, and also the possible harms of using cannabis or cannabinoids as treatment for PTSD or symptoms of PTSD. Several systematic reviews of this topic are outlined below:

1. A systematic review was conducted and reported in Annals of Internal Medicine in 2017 that looked at systematic reviews, clinical controlled trials, and observational studies with control groups that reported PTSD symptoms with and without use of plant-based cannabis, and adverse effects of plant-based cannabis.[116] Two systematic reviews, 3 observational studies, and no randomized trials were found. This review reported insufficient evidence to draw conclusions about benefits and harms, and the observational studies found that compared with non-use [of cannabis], cannabis did not reduce PTSD symptoms. Authors reported that the clinical trials reviewed had medium and high risk of bias, and overall evidence was judged insufficient to draw any conclusions regarding benefit or harms of using plant-based cannabis as treatment for PTSD.
2. A systematic review regarding medicinal use of cannabis was reported in 2017 by a team at the Portland Oregon Veterans Hospital as part of treatment policy development effort by the VA system.[117] One of the questions addressed in this review is, *"What are the effects of cannabis on health outcomes and healthcare utilization for adults who have PTSD?"* They found insufficient evidence examining the effects of cannabis in patients with PTSD with no blinded controlled studies. They reported 2 observational studies with untreated controls that showed that cannabis use was not associated with improved outcomes in either study when compared to untreated controls.
3. The 2017 report on *The Health Effects of Cannabis and Cannabinoids*[118] from the National Institutes of Science, Engineering, and Medicine was unable to identify any good or fair-quality systematic review that reported on medical cannabis as an effective treatment for PTSD symptoms and determined that there was only one fair-quality small double-blind placebo controlled study that looked at nabilone (a synthetic cannabinoid) and found it to be helpful in managing symptoms of PTSD.

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4. A literature review published in *Depression and Anxiety*, February, 2017 regarding treatment of PTSD using cannabis[119] concluded that treatment outcome studies of whole plant cannabis and related cannabinoid effects on PTSD are limited and not methodologically rigorous, precluding conclusions about their potential therapeutic effects. The authors raised the concern that cannabis use has been linked to adverse psychiatric outcomes, including conditions commonly comorbid with PTSD such as depression, anxiety, psychosis, and substance misuse. They also noted that cannabis use is associated with worse treatment outcomes in PTSD naturalistic studies, and with maladaptive coping styles that may maintain PTSD symptoms. Their ultimate conclusion was that known risks of cannabis use currently outweigh unknown benefits of cannabis for treatment of PTSD.

There is currently no placebo-controlled trial data to guide or recommend the use of medical cannabis or cannabinoids as first-line agents in the treatment of PTSD or comorbid symptoms. Some anecdotal reports and observational studies suggest possible short-term benefits in some individuals with PTSD[120] [121] [122] but there are also longitudinal 10-year data in 2276 US veterans that demonstrate worse outcomes in individuals using cannabis to treat PTSD, including worse outcomes in PTSD symptom severity, increase in violent behaviors, and increase in measures of alcohol and drug use.[123]Cross-sectional studies have found a direct correlation between more severe PTSD symptomatology and increased motivation to use cannabis for coping purposes, especially among patients with difficulties in emotional regulation or stress intolerance.[124] These uncertainties and sometimes contradictory observations need to be addressed with robust randomized placebo-controlled clinical trials. Of note, there are currently at least two randomized trials and 6 other studies examining outcomes of cannabis use in patients with PTSD that are ongoing and are expected to be completed within 3 years.

Because of the current lack of randomized blinded placebo-controlled clinical trials, and current very significant clincal uncertainty regarding risks and benefits of medical cannabis in the treatment of PTSD, the use of medical cannabis to treat PTSD should generally be considered only if:

1. The diagnosis of PTSD has been made or confirmed by a board-certified psychiatrist or a PhD-level therapist with a degree in psychology or social work, or a psychiatric APRN (required by Utah Code 26-61a-104), and;
2. The individual with PTSD has not tolerated or adequately responded to robust clinical attempts using traditional treatment interventions including psychotherapy, and FDA-approved pharmacologic interventions, and;
3. The individual fully understands the known and potential unknown risks of using cannabis or cannabinoids to manage symptoms of PTSD including the potential for worse PTSD treatment outcomes, and;
4. The individual and qualified healthcare provider working together have arrived at the conclusion that the potential risks of using medical cannabis to treat PTSD may be justified by the possible benefits of using cannabis to treat PTSD, combined with the assessed risks of continuing on with symptoms of PTSD that are not adequately managed despite robust attempts using traditional interventions.

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8. Crohn's or Ulcerative Colitis - Draft submitted by Brian Zehnder, MD

Summary: There is insufficient evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective for the general treatment of Ulcerative Colitis and Crohn's Disease.

Ulcerative Colitis. Cannabis and cannabinoids are often promoted as treatment for many illnesses and are widely used among patients with ulcerative colitis (UC). Few studies have evaluated the use of these agents in UC. Further, cannabis has potential for adverse events, and the long-term consequences of cannabis and cannabinoid use in UC are unknown.

A Cochrane IBD Group published a summary in Issue 6, 2019 (Cochrane Database Syst Rev. 2018 Nov 8;11:CD012954. doi: 10.1002/14651858.CD012954.pub2). This included MEDLINE, Embase, WHO ICTRP, AMED, PsychINFO, the Cochrane IBD Group Specialized Register, CENTRAL, ClinicalTrials.Gov and the European Clinical Trials Register from inception to 2 January 2018. Conference abstracts and references were searched to identify additional studies. Randomized controlled trials (RCTs) comparing any form or dose of cannabis or its cannabinoid derivatives (natural or synthetic) to placebo or an active therapy for adults (> 18 years) with UC were included.
Two authors independently screened search results, extracted data and assessed bias using the Cochrane risk of bias tool. The primary outcomes were clinical remission and relapse (as defined by the primary studies). Secondary outcomes included clinical response, endoscopic remission, endoscopic response, histological response, quality of life, C-reactive protein (CRP) and fecal calprotectin measurements, symptom improvement, adverse events, serious adverse events, withdrawal due to adverse events, psychotropic adverse events, and cannabis dependence and withdrawal effects. We calculated the risk ratio (RR) and corresponding 95% confidence interval for dichotomous outcomes. For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CI. Data were pooled for analysis when the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). Data were analyzed on an intention-to-treat basis. GRADE was used to evaluate the overall certainty of evidence.
Two RCTs (92 participants) met the inclusion criteria. One study (N = 60) compared 10 weeks of cannabidiol capsules containing up to 4.7% delta-9-tetrahydrocannabinol (THC) with placebo capsules in participants with mild to moderate UC. The starting dose of cannabidiol was 50 mg twice daily increasing to 250 mg twice daily if tolerated. Another study (N = 32) compared 8 weeks of therapy with two cannabis cigarettes per day containing 0.5 g of cannabis, corresponding to 23 mg THC/day to placebo cigarettes in participants with UC who did not respond to conventional medical treatment. No studies were identified that assessed cannabis therapy in quiescent UC. The first study was rated as low risk of bias and the second study (published as an abstract) was rated as high risk of bias for blinding of participants and personnel. The studies were not pooled due to differences in the interventional drug. The effect of cannabidiol capsules (100 mg to 500 mg daily) compared to placebo on clinical remission and response is uncertain. Clinical remission at 10 weeks was achieved by 24% (7/29) of the cannabidiol group compared to 26% (8/31) in the placebo group (RR 0.94, 95% CI 0.39 to 2.25; low certainty evidence). Clinical response at 10 weeks was achieved in 31% (9/29) of cannabidiol participants compared to 22% (7/31) of placebo patients (RR 1.37, 95% CI 0.59 to 3.21; low certainty evidence). Serum CRP levels were similar in both groups after 10 weeks of therapy. The mean CRP in the cannabidiol group was 9.428 mg/L compared to 7.638 mg/L in the placebo group (MD 1.79, 95% CI -5.67 to 9.25; moderate certainty evidence). There may be a clinically meaningful improvement in quality of life at 10 weeks, measured with the IBDQ scale (MD 17.4, 95% CI -3.45 to 38.25; moderate certainty evidence). Adverse events were more frequent in cannabidiol participants compared to placebo. One hundred per cent (29/29) of cannabidiol participants had an adverse event, compared to 77% (24/31) of placebo participants (RR 1.28, 95% CI 1.05 to1.56; moderate certainty evidence). However, these adverse events were considered to be mild or moderate in severity. Common adverse events included dizziness, disturbance in attention, headache, nausea and fatigue. None (0/29) of the cannabidiol participants had a serious adverse event compared to 13% (4/31)

of placebo participants (RR 0.12, 95% CI 0.01 to 2.11; low certainty evidence). Serious adverse events in the placebo group included worsening of UC and one complicated pregnancy. These serious adverse events were thought to be unrelated to the study drug. More participants in the cannabidiol group withdrew due to an adverse event than placebo participants. Thirty-four per cent (10/29) of cannabidiol participants withdrew due to an adverse event compared to 16% (5/31) of placebo participants (RR 2.14, 95% CI 0.83 to 5.51; low certainty evidence). Withdrawals in the cannabidiol group were mostly due to dizziness. Withdrawals in the placebo group were due to worsening UC. The effect of cannabis cigarettes (23 mg THC/day) compared to placebo on mean disease activity, CRP levels and mean fecal calprotectin levels is uncertain. After 8 weeks, the mean disease activity index score in cannabis participants was 4 compared with 8 in placebo participants (MD -4.00, 95% CI -5.98 to -2.02). After 8 weeks, the mean change in CRP levels was similar in both groups (MD -0.30, 95% CI -1.35 to 0.75; low certainty evidence). The mean fecal calprotectin level in cannabis participants was 115 mg/dl compared to 229 mg/dl in placebo participants (MD -114.00, 95% CI -246.01 to 18.01). No serious adverse events were observed. This study did not report on clinical remission, clinical response, quality of life, adverse events or withdrawal due to adverse events.

CONCLUSIONS. The effects of cannabis and cannabidiol on UC are uncertain, thus no firm conclusions regarding the efficacy and safety of cannabis or cannabidiol in adults with active UC can be drawn. There is no evidence for cannabis or cannabinoid use for maintenance of remission in UC. Further studies with a larger number of patients are required to assess the effects of cannabis in UC patients with active and quiescent disease. Different doses of cannabis and routes of administration should be investigated. Lastly, follow-up is needed to assess the long term safety outcomes of frequent cannabis use.

Crohn's Disease. Crohn's disease (CD) is a chronic immune-mediated condition of transmural inflammation in the gastrointestinal tract, associated with significant morbidity and decreased quality of life. The endocannabinoid system provides a potential therapeutic target for cannabis and cannabinoids and animal models have shown benefit in decreasing inflammation. However, there is also evidence to suggest transient adverse events such as weakness, dizziness and diarrhea, and an increased risk of surgery in people with CD who use cannabis.

A Cochrane IBD Group published a summary in Issue 6, 2019 (Cochrane Database Syst Rev. 2018 Nov 8;11:CD012853. doi: 10.1002/14651858.CD012853.pub2). This included MEDLINE, Embase, AMED, PsychINFO, the Cochrane IBD Group Specialized Register, CENTRAL, ClinicalTrials.Gov, and the European Clinical Trials Register up to 17 October 2018. Conference abstracts and references were also searched to identify additional studies.

Two authors independently screened search results, extracted data and assessed bias using the Cochrane risk of bias tool. The primary outcomes were clinical remission and relapse. Remission is commonly defined as a Crohn's disease activity index (CDAI) of < 150. Relapse is defined as a CDAI > 150. Secondary outcomes included clinical response, endoscopic remission, endoscopic improvement, histological improvement, quality of life, C-reactive protein (CRP) and fecal calprotectin measurements, adverse events (AEs), serious AEs, withdrawal due to AEs, and cannabis dependence and withdrawal effects. We calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes. For continuous outcomes, we calculated the mean difference (MD) and 95% CI. Data were combined for analysis when the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). Data were analyzed on an intention-to-treat basis and the overall certainty of the evidence supporting the outcomes was evaluated using the GRADE criteria.

Three studies (93 participants) that assessed cannabis in people with active CD met the inclusion criteria. One ongoing study was also identified. Participants in two of the studies were adults with active Crohn's disease who had failed at least one medical treatment. The inclusion criteria for the third study were unclear. No studies that assessed cannabis therapy in quiescent CD were identified. The studies were not pooled due to differences in the interventional drug. One small study (N = 21) compared eight weeks of

treatment with cannabis cigarettes containing 115 mg of delta-9-tetrahydrocannabinol (THC) to placebo cigarettes containing cannabis with the THC removed in participants with active CD. This study was rated as high risk of bias for blinding and other bias (cannabis participants were older than placebo). The effects of cannabis on clinical remission were unclear. Forty-five per cent (5/11) of the cannabis group achieved clinical remission compared with 10% (1/10) of the placebo group (RR 4.55, 95% CI 0.63 to 32.56; very low certainty evidence). A difference was observed in clinical response (decrease in CDAI score of >100 points) rates. Ninety-one per cent (10/11) of the cannabis group achieved a clinical response compared to 40% (4/10) of the placebo group (RR 2.27, 95% CI 1.04 to 4.97; very low certainty evidence). More AEs were observed in the cannabis cigarette group compared to placebo (RR 4.09, 95% CI 1.15 to 14.57; very low certainty evidence). These AEs were considered to be mild in nature and included sleepiness, nausea, difficulty with concentration, memory loss, confusion and dizziness. This study did not report on serious AEs or withdrawal due to AEs. One small study (N = 22) compared cannabis oil (5% cannabidiol) to placebo oil in people with active CD. This study was rated as high risk of bias for other bias (cannabis participants were more likely than placebo participants to be smokers). There was no difference in clinical remission rates. Forty per cent (4/10) of cannabis oil participants achieved remission at 8 weeks compared to 33% (3/9) of the placebo participants (RR 1.20, 95% CI 0.36 to 3.97; very low certainty evidence). There was no difference in the proportion of participants who had a serious adverse event. Ten per cent (1/10) of participants in the cannabis oil group had a serious adverse event compared to 11% (1/9) of placebo participants (RR 0.90, 95% CI 0.07 to 12.38, very low certainty evidence). Both serious AEs were worsening Crohn's disease that required rescue intervention. This study did not report on clinical response, CRP, quality of life or withdrawal due to AEs. One small study (N= 50) compared cannabis oil (15% cannabidiol and 4% THC) to placebo in participants with active CD. This study was rated as low risk of bias. Differences in CDAI and quality of life scores measured by the SF-36 instrument were observed. The mean quality of life score after 8 weeks of treatment was 96.3 in the cannabis oil group compared to 79.9 in the placebo group (MD 16.40, 95% CI 5.72 to 27.08, low certainty evidence). After 8 weeks of treatment, the mean CDAI score was 118.6 in the cannabis oil group compared to 212.6 in the placebo group (MD -94.00, 95%CI -148.86 to -39.14, low certainty evidence). This study did not report on clinical remission, clinical response, CRP or AEs.

CONCLUSIONS. The effects of cannabis and cannabis oil on Crohn's disease are uncertain. Thus no firm conclusions regarding the efficacy and safety of cannabis and cannabis oil in adults with active Crohn's disease can be drawn. The effects of cannabis or cannabis oil in quiescent Crohn's disease have not been investigated. Further studies with larger numbers of participants are required to assess the potential benefits and harms of cannabis in Crohn's disease. Future studies should assess the effects of cannabis in people with active and quiescent Crohn's disease. Different doses of cannabis and delivery modalities should be investigated.

8. Cancer

Summary: There is insufficient evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective for the general treatment of malignant neoplasms.

Note: The decision to use cannabis or cannabis-based medicines for primary treatment or palliative treatment of a malignant neoplasm should generally be made through consultation with an oncology professional who is able to explore all potential treatment options with the patient.

Cannabinoids and anti-neoplastic properties.

Author, PharmD, MS

Accumulating evidence from in vitro and/or pre-clinical studies supports the antineoplastic properties of cannabinoids and a supporting rationale via dysregulation of the endocannabinoid system in a number of cancers.[1,2] Elevated levels of endocannabinoids and their receptors (CB1 and CB2) have been observed in a number of cancers (lymphomas, hepatocellular carcinoma, leukemia, glioma, and pancreatic, prostate, and breast cancers); in some cases, increased expression of the cannabinoid receptors correlated with disease severity.[1]

The exact mechanism through which cannabinoids exert antineoplastic effects is not known, but in vitro, cannabinoids induce cancer cell apoptosis.[1] Cannabinoids may also inhibit tumor angiogenesis, limit cancer cell migration and metastasis.[1] Cannabidiol has been shown to specifically inhibit cancer cell invasiveness in various pre-clinical animal models.[1] Caution is advised, however, as less frequently, a tumor-promoting effects have also been described.[3,4] The reason for this conflict is not known, but it may be related to the achieved concentration of cannabinoids, expression level of cannabinoid receptors, or immunosuppressive effects.[2-4] Antineoplastic properties in vitro have typically been observed at very high doses that may not be achieved in clinical practice.[5]

The efficacy of cannabinoids as anti-tumor agents has not been sufficiently studied in clinical studies. The limited existing clinical studies of cannabinoids have been for the treatment of recurrent gliobastoma multiforme (GBM), an aggressive primary brain tumor with a poor prognosis.[6,7] Case studies describing patient-administered inhaled cannabis (among 2 children with pilocytic astrocytomas) or orally administered hemp oil (in 1 child with terminal acute lymphoblastic leukemia [ALL]) reported a regression in tumors and reduction blast cell counts, respectively, during the time period of administration of the cannabinoids.[8,9] One phase I/II trial of Δ^9-tetrahydrocannabinol (THC) solution (>95.6% THC) administered intracranially 3-6 days post-surgery at 0.3 ml/min (delivered via a syringe pump for an average of a 10-day cycle length) to achieve a daily dose of 60-80 μg to 9 patients with recurrent GBM. Patients included in this trial had failed standard therapies included surgery, external-beam radiotherapy and two patients had received adjuvant temozolomide. Overall intracranially administered THC was well tolerated; one patient had a mild episode of bulimia, hypothermia and euphoria that resolved. All patients experienced cerebral edema, which is typical after a craniotomy. Median survival was approximately 24 weeks, and 2 patients survived for >1 year. In vitro testing showed that THC inhibited cancer cell proliferation, and expression of cannabinoid receptors did not correlate with survival.[6] Additional studies of cannabis for recurrent or newly diagnosed GBM are underway. Unpublished information directly from the pharmaceutical company of Sativex (interpret information cautiously) reported preliminary information about the effect of the CBD:THC oromucosal spray as an add-on to dose dense temozolomide versus placebo (n=9) in 12 patients with recurrent GBM. CBD:THC significantly increased one-year survival compared to placebo (83% vs. 44%, P = 0.042). Survival (50% survival at 2 years) at two-years and median survival time (662 days vs. 369 with placebo) were also numerically greater with the CBD: THC group compared to placebo. The CBD:THC was reportedly well tolerated.[7]

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10. HIV or AIDS

11. ALS. – Author MD

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal adult neurological disease resulting from the death of anterior horn motor neurons. The cause of this disorder is not known and there is no known treatment. Very limited evidence from pre-clinical studies of ALS suggests that certain cannabinoids modestly delay disease progression and prolong survival in animal models of ALS, while the results from a very limited number of clinical studies are mixed. Due to the small number of studies and equivocal results, evidence-based recommendations for the use of medical cannabis cannot be made. Because of the bleak prognosis for patients with ALS, a therapeutic trial of medical marijuana in ALS patients is reasonable.

9. Autism: Author MD

Summary: There is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are an effective or ineffective treatment for symptoms of Autism or autism spectrum disorder. The medical literature as of 2019, is devoid of results from randomized blinded placebo-controlled clinical trials to guide the use of cannabis or cannabinoids in children or adults for the treatment of autism spectrum disorder (ASD). There are however 3 recently-published short-duration observational studies from Israel that show possible benefit from the use of a CBD-predominant (chemotype III) cannabis extract preparation in the treatment of ASD. Review of these three studies may be helpful for a qualified medical provider when considering the use of cannabis or cannabinoids in the treatment of ASD and its comorbid conditions.

The first study was a retrospective feasibility study conducted in Israel and published in 2018 in a peer-reviewed journal, *Neurology,* that assessed safety, tolerability and efficacy of cannabidiol-based medical cannabis as an adjuvant therapy for refractory behavioral problems in children with ASD.[125] Sixty children with ASD (age = 11.8± 3.5, range 5.0–17.5; 77% low functioning; 83% boys) were treated with oral CBD and THC at a ratio of 20:1. The dose was up-titrated to effect (maximal CBD dose = 10mg/kg/d). Following this CBD-predominant cannabis treatment the following outcomes were observed:

- Behavioral outbreaks were much improved or very much improved in 61% of patients.
- Anxiety and communication problems were much or very much improved in 39% and 47% of patients respectively.
- Disruptive behaviors, were improved by 29% from 4.74±1.82 as recorded at baseline on the HSQ-ASD to 3.36±1.56 following the treatment.
- Parents reported less stress as reflected in the APSI scores, changing by 33% from 2.04±0.77 to 1.37±0.59.
- The effect on all outcome measures was more apparent in boys with non-syndromic ASD.
- Adverse events included sleep disturbances (14%) irritability (9%) and loss of appetite (9%).

Based on these promising results, the investigators have launched a large, double blind, placebo controlled cross-over trial with 120 participants (NCT02956226), results are pending.

A second study from Israel is a retrospective summary of routine clinical data collected during an initial evaluation and 6-month follow-up of 188 ASD patients (mean age = 12.9 years) treated with medical cannabis between 2015 and 2017.[126] The treatment in a majority of the patients was based on sublingually administered cannabis extract oil with a 20:1 ratio of CBC to THC. The oil contained 45% olive oil, 30% CBD, 1.5% THC, <1.5% CBC, 0.5% CBG, <0.5% CBDV and <0.1% CBN. Reported starting dose was one sublingual drop three times a day with one oil drop (0.05 ml) containing 15 mg CBD and 0.75 mg Δ9-THC. This was followed by individual titration over weeks to months. Optimal dose at 6 months ranged from 1 drop three times/day to 20 drops three times/day (15mg CBD/0.75mgTHC to 300mg CBD/15mg THC three times/day). Symptoms inventory, patient global assessment and side effects at 6 months were assessed by structured questionnaires. After six months of treatment 82.4% of patients

[125] Adi Aran, Hanoch Cassuto, Asael Lubotzky. Cannabidiol Based Medical Cannabis in Children with Autism- a Retrospective Feasibility Study (P3.318) Neurology, 2018; 90 (15 Supplement)

[126] Lihi Bar-Lev Schleider, Raphael Mechoulam, Naama Saban, Gal Meiri, Victor Novack. Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. www.nature.com/scientificreports (2019) 9:200 | doi:10.1038/s41598-018-37570-y

(155) were still in active treatment and 60.0% (93) were successfully re-assessed. Twenty-eight of the 6-month-assessed patients (30.1%) reported significant improvement, 50 (53.7%) moderate improvement, 6 (6.4%) slight improvement, and 8 (8.6%) had no change in their condition.

Quality of life, mood and ability to perform activities of daily living were assessed before the treatment and at six months.

- Good quality of life was reported by 31.3% of patients prior to treatment initiation while at 6 months good quality of life was reported by 66.8% ($p < 0.001$).
- Positive mood was reported by the parents on 42% before treatment and 63.5% after 6 months of treatment ($p < 0.001$).
- The ability to dress and shower independently was significantly improved from 26.4% who reported no difficulty in these activities prior to the treatment to 42.9% at six months ($p < 0.001$).
- Good sleep and good concentration were reported by 3.3% and 0.0% (respectively) before the treatment and on 24.7% ($p < 0.001$) and 14.0% ($p < 0.001$) after 6 months of active treatment.
- Other improvements noted at 6 months included reduction in seizures. Of the 13 patients with seizures who were using the cannabis extract at six months, 11 patients (84.6%) reported disappearance of the seizures and two patients reported improvement.
- Restlessness and rage attacks were improved in 72 patients (91.0%) and 66 (90.3%) respectively.
- The most common side effects reported at six months by 23 of 93 patients (25.2%, with at least one side effect) were: restlessness 6 (6.6%), sleepiness 3 (3.2%), psychoactive effect 3 (3.2%), increased appetite 3 (3.2%), digestion problems 3 (3.2%), dry mouth 2 (2.2%) and lack of appetite 2 (2.2%)..

A third study out of Israel was a prospective open-label observational study using an orally administered cannabidiol (CBD) predominant oil preparation (CBD/THC 20:1 ratio) in the treatment of 53 children (ages 4-22 – average age 11) with ASD looking at effects on the comorbid behavioral problems associated with ASD.[127] Mean duration of treatment and observation was 66 days (range 30-588 days). The CBD median interquartile range (IQR) daily dose was 90 mg (45–143 mg), and the THC median IQR daily dose was 7 mg (4–11mg) mg. None of the children had experienced any previous treatment attempts using cannabis or cannabinoids. Measured outcomes were based on reports from parents and included the following:

- Self-injury and rage attacks (n = 34) improved in 67.6% and worsened in 8.8%.
- Hyperactivity symptoms (n = 38) improved in 68.4%, did not change in 28.9% and worsened in 2.6%.
- Sleep problems (n = 21) improved in 71.4%and worsened in 4.7%.
- Anxiety (n = 17) improved in 47.1% and worsened in 23.5%.

Adverse effects, mostly somnolence and change in appetite, were mild. This study was not designed to evaluate long-term safety or efficacy of cannabidiol, THC, or other cannabinoids in treatment of children or adults with autism.

IMPORTANT: The above 3 studies suggest the possibility of favorable outcomes from use of CBD-predominant cannabis extract (chemotype III) in the treatment of co-morbid and behavioral challenges associated with ASD but they are limited due to their observational nature as they do not include randomized untreated control groups and hence, **causation as to the benefits and risks of using CBD-predominant cannabis extract in the treatment of ASD cannot be established nor excluded based on these studies.** Long-term safety and efficacy likewise cannot be determined based on the short-duration of these 3 observational studies. Why all 3 studies used CBD-predominant cannabis extract with a CBD/THC ratio of 20:1 is not stated but may be based on pre-clinical experience of the researchers doing the studies. It should be noted that there were no children in any of these observational studies who were under the age of 4 years.

Managing behavioral challenges associated with ASD can be very difficult. Currently there is no randomized placebo-controlled trial to guide the use of cannabis or plant-based cannabinoids as in the treatment of ASD. However, there may be clinical situations where FDA-approved medications and interventions are causing substantial adverse reactions or are not adequately controlling behaviors of concern associated with ASD. In such situations and after careful consideration of possible treatment alternatives, a clinician may decide that the potential benefits of using medicinal cannabis may outweigh the potential risks of medicinal cannabis and/or the potential risks of leaving the individual's severe behaviors unmanaged. This would generally happen after failed attempts using interventions that have been approved by the FDA

If medicinal cannabis is recommended by a qualified medical provider, the following general dosing suggestions (based on observations made in the above 3 reports from Israel) may be a helpful starting point:

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[127] Barchel D, Stolar O, De-Haan T, Ziv-Baran T, Saban N, Fuchs DO, Koren G, Berkovitch M. Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities. *Front. Pharmacol*. (2019) 9:1521. doi: 10.3389/fphar.2018.01521

- **Suggested chemotype:** Chemotype III, CBD predominant – 20:1 CBD:THC
- **Dose form:** Cannabis extract dissolved in olive oil
- **Route:** Sublingual drops
- **Starting Dose:** CBD 15mg/THC 0.75mg administered sublingually 3 times per day followed by careful titration based on individual response to dosage increases. Lower starting doses should be considered in younger children.
- **Titration:** Dose range for efficacy is likely quite variable depending on unknown or unpredictable individual patient factors, and may be as high as 10mg CBD/kg/day.

13. Alzheimer's disease – Author MD

Alzheimer's disease is the most common cause of dementia in older adults. It is a progressive and fatal disease with no effective treatment. Animal models suggest a role for the endocannabinoid system in the pathogenesis of Alzeimer's disease. A limited number of short-term clinical studies have demonstrated improvement in some clinical manifestations of Alzheimer's disease, such as agitation, insomnia, and disruptive behavior. However, the adverse cognitive effects of chronic cannabis use must be taken into account when using medical cannabis in patients with Alzheimer's disease (2018 CANADA information-health-care-professionals-cannabis-cannabinoids-eng.pdf) .

10. Rare Conditions affecting less than 2% of US population and not adequately managed with conventional treatment attempts

16) Other Medical Conditions Requiring Approval By CUB

1. Anxiety
2. Sleep Disorders
3. Tourette's – Author MD

   Tourette's syndrome is a severe form of tic disorder syndrome. Tic disorders are neurologic diseases of unknown etiology characterized by involuntary movements of muscle groups involved in purposeful motor activity and vocalization. There is no effective treatment for this disease class (Neurology 2019;92:896-906). Some evidence-based reviews conclude that data are insufficient to support or refute efficacy of THC for reducing tic severity (Report of the Guideline Development Subcommittee of the American Academy of Neurology Neurology® 2014;82:1556–1563. https://www.aan.com/siteassets/home-page/policy-and-guidelines/policy/position-statements/medical-marijuana/medical_marijuana_2018.pdf Last accessed on 11 Nov. 2019.), while others conclude that evidence suggests that medical marijuana and THC may be useful for symptom improvement in Tourette's syndrome (National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations
4. Rheumatoid Arthritis
5. Osteoarthritis
6. Substance Use Disorders
7. TBI/Intracranial hemorrhage

8. Parkinson's disease – Author

   Parkinson's disease is a progressive neurological disorder resulting from the death of dopaminergic neurons, in particular those located in the substantia nigra. Treatment options for Parkinson's disease include medications, deep brain stimulation, and physical therapy. Medications used in the treatment of

Parkinson's have significant adverse effects. Deep brain stimulation involves an invasive neurosurgical procedure, with attendant risks and complications, and is not uniformly effective. Physical therapy may be modestly helpful on a short-term basis for some motor manifestations of Parkinson's disease. There is insufficient evidence for the therapeutic utility of medical cannabis in the treatment of Parkinson's disease (need references)

9. Huntington's disease – Author

Huntington's disease is a progressive and fatal neurological disorder involving the basal ganglion. Two small studies failed to show a significant effect of cannabinoids in the treatment of Huntington's disease associated symptoms (European Journal of Internal Medicine 49 (2018) 7–11.).

10. Schizophrenia

1) Pharmacology – Dr. Fine's monograph

DRAFT PREPARED BY PERRY G. FINE MD, PROFESSOR OF ANESTHESIOLOGY, UNIVERSITY OF UTAH, MEMBER UTAH HEALTH DEPARTMENT CANNABINOID PRODUCT BOARD

Cannabis and Cannabinoids: A Brief Historical Overview and Pharmacological Summary

History

Cannabis use as an herbal remedy has a long and storied history dating back millennia, with its newest chapter soon to be written as Utah operationalizes HB 3001 in 2020.

The plant genus *Cannabis* is the naturally occurring and cultivated source of more than 80 identified unique compounds known as phytocannabinoids (1). Several hundred other constituents--many purported to have medicinal benefits—have been isolated from cannabis (2). Hemp and marijuana are both wild and cultivated species within the *Cannabis* genus that are differentiated by their physical properties leading to their respectively varying uses. The key regulatory and pharmacological difference between them is the threshold amount of the psychoactive cannabinoid delta-9-tetrahydrocannabinol (THC) found in marijuana (≥ 0.3% dry weight) [https://www.ams.usda.gov/sites/default/files/media/2018FarmBill.pdf; accessed June 8, 2019]. Generally, hemp has been cultivated as a source of industrial materials (e.g., rope, textiles) and food products (e.g., seeds, oils), whereas marijuana has been used for medicinal purposes and intoxication (3,4).

Human Physiology and the Endocannabinoid System

Endogenously produced cannabinoids play a vital role in human physiology (Table 1).

Table 1 (5). Partial List of Physiological Actions Mediated by Activation or Inhibition of Cannabinoid Receptors.

Antinociception (pain signaling)
Cognition, Learning and Memory
Locomotor Activity
Endocrine Regulation
Temperature Control
Heart Rate
Nausea and Vomiting
Intraocular Pressure
Inflammation
Immune Recognition (including certain types of cancer cells)

The human endocannabinoid system was elucidated throughout the 1990's with discovery of several endogenously produced cannabinoids (endocannabinoids) and identification of receptors expressed on various types of cells throughout the body that differentially bind endogenous and exogenous cannabinoids (6). The endocannabinoid system has myriad and complex regulatory and homeostatic functions that influence almost every bodily system. These include wide-ranging functions including immune competence and inflammation, thermoregulation and metabolism, appetite and pain perception, sleep-wakefulness cycles and mood states (7).

Endocannabinoids

Arachidonic acid is the precursor for endogenous synthesis of endocannabinoids within cellular membranes, triggered by various types of stimuli to meet physiological and homeostatic needs (8). The first endocannabinoid discovered, *N*-arachidonoylethanolamine, is conventionally called anandamide. A few years later, the second member of this class of cannabinoid transmitters, 2-arachidonoylglycerol, called 2-AG was identified. Several other fatty acid amides of ethanol amines and amino acids present in the brain and in the periphery have been identified (e.g., palmitoylethanolamide [PEA], oleoylethanolamide [OEA]). Although they do not bind directly to cannabinoid receptors, as do anandamide and 2-AG, their actions appear to be cannabinoid receptor-dependent (9). These compounds interact in complex and dynamic ways to meet exigent physiological needs.

Endocannabinoid receptors

Two G-protein coupled cannabinoid receptors named CB_1 and CB_2 have been well-categorized and cloned. These receptors are variously expressed in the central and peripheral nervous system and many peripheral organs/tissues/cells, with CB_1 receptors being abundantly present in the central and peripheral nervous systems, and CB_2 receptors having a dominant presence in the immune system. Other than these specific receptor types, cannabinoids bind to and activate a host of other receptors, including G protein-coupled receptor 55 (GPR55), transient receptor potential (TRP) receptors, 5-HT_{1A} receptors, α_2 adrenergic receptors, as well as glycine and adenosine receptors (10).

Although certain specific effects of cannabinoid binding on receptor types have been well elucidated (e.g., THC effects at CB_1 receptors producing psychotropic and cognitive effects), even these interactions are highly complex, and the interplay among endocannabinoids, exogenous cannabinoids and related constituents (i.e., phytocannabinoids, terpenes, and synthetically derived cannabinoids) are not well understood. Therefore it is important for those who choose to ingest cannabis or cannabinoids, and healthcare professionals who prescribe or recommend use of these compounds, to appreciate the critical roles and complexity of the endocannabinoid system both in brain development and in health maintenance and recovery from disease (11, 12).

Cannabis and Its Constituents

Cannabis has been cultivated and bred to express its many chemical constituents in highly variable amounts. Environmental influences and stressors (e.g., heat and light exposure; amount and frequency of watering and nutrients) also influence a given genetic strain's to production of phytocannabinoids and terpenes (2,13). Table 2 is a partial list of the most common and identified constituents of cannabis.

Table 2: Constituents of *Cannabis* by chemical class, modified from Pertwee et al (2)

Chemical Class	**Number of Compounds**
Delta-9-tetrahydrocannabinol (Δ^9-THC)	18
Delta-8-tetrahydrocannabinol (Δ^8-THC)	2
Cannabigerol (CBG)	17
Cannabichromene (CBC)	8
Cannabidiol (CBD)	8
Cannabinodiol (CBND)	2
Cannabielsoin (CBE)	5
Cannabicyclol (CBL)	3
Cannabinol (CBN)	10
Cannabitriol (CBT)	9
Other cannabinoids	22
Total cannabinoids	104
Total noncannabinoids (e.g., flavonoids, terpenes, steroids, biphenyls, phenanthrenes)	441

Of these many compounds, THC and CBD are the best studied. Current commercial and privately grown strains are bred to enhance production of these two cannabinoids in varying ratios for purported therapeutic or intoxicating effects. THC is thought to be responsible for most of the psychoactive effects (and, thus, abuse potential) of cannabis, whereas CBD has no significant psychotropic properties. Hemp, by definition, has low levels of THC but has been bred to contain varying amounts of CBD.

Heat converts many of these compounds into either bioactive or inactive moieties. Similarly, exposure to an acidic environment, such as stomach acid, can also convert one cannabinoid form into another, and from an inactive compound into one with pharmacological properties. Therefore, routes of administration (e.g., smoking, oral ingestion) have differing effects on similar phytocannabinoid substrates, with resultant pharmacological activity that may be unpredictable. Several substances in cannabis smoke are mutagenic or carcinogenic, similar to tobacco (14).

Little is known about the pharmacological, physiological or pathophysiological effects of the myriad other cannabinoids and noncannabinoids found in various strains of cannabis, whether used short- or long-term. Terpenes, such as β-caryophyllene and β-caryophyllene oxide have demonstrated anti-tumor and anti-inflammatory activity (15). Interactions between phytocannabinoids and terpenes remain poorly studied but an important area of research.

Preclinical and Clinical Pharmacology of Cannabis and Cannabinoids

The two cannabinoids of greatest current clinical interest are THC and CBD. Although other cannabis constituents may emerge as having therapeutic value, there is little human pharmacological evidence to inform clinical use decisions at the current time.

Pharmacokinetics (pK) describe what happens to a drug from the time of its initial contact with the body until it is eliminated (absorption, distribution, metabolism, excretion). These activities

must be known in order to determine, and then predict, what effects that drug and its biotransformed metabolites will have—that is, its pharmacodynamics (pD). More so than most conventionally available medicinal products and United States Food and Drug Administration (FDA) approved drugs, cannabis pharmacology is complicated by the many forms in which it and related products are available. These include whole unprocessed or processed plant portions (e.g., "flower pods") that can be smoked, swallowed, or added—uncooked or cooked-- into foods (heating/cooking will alter cannabinoid chemistry); plant extracts that can be vaporized and inhaled, ingested orally, or mixed with various compounds used for topical application; and, single or combined purified plant extract cannabinoids or synthetically derived cannabinoids available for oral ingestion (liquids, pills, capsules or mixed with foods/beverages) or vaping, or topical application (Figure 1).

Figure 1: Dosage forms for medical cannabis under the Utah Medical Cannabis Act (health.utah.gov/medical-cannabis, accessed 13 June, 2019)

- Tablet
- Capsule
- Concentrated oil
- Liquid suspension
- Topical preparation
- Transdermal preparation
- Gelatinous cube
- Unprocessed cannabis flower in blister pack containing no more than 1 gram of flower pods in each individual blister

- If patient does not respond to two forms listed above, a qualified medical provider may recommend a wax or resin dosage form.
- Smoking of cannabis is not permitted but patients may purchase a medical cannabis device that warms cannabis material into a vapor without use of a flame and delivers cannabis to an individual's respiratory system.
- **SMOKING OF MARIJUANA IS PROHIBITED** under Utah Code 26-61a-102. Edible products (besides gelatinous cubes) such as candies, cookies, brownies, and unprocessed flowers outside of blister packs are also not permitted under Utah Code 26-61a-102 (29).

Various doses of THC and CBD in these many different forms, alone or in combination, are also subject to changes in pK and pD effects based on a host of variables. These include an individual's underlying ethnicity, gender, age, body mass index, kidney and liver function, timing and content of a meal (i.e., stomach contents) for oral preparations, skin location and condition for dermal/topical preparations, and respiratory mechanics (e.g., depth of inhalation and duration of held breath) for inhalational preparations (16).
Furthermore, changes in pK and pD result from concurrent use of other drugs, interactions due to concurrent disease states, and even certain dietary constituents (e.g., grapefruit juice has a major impact on enzymes involved in drug degradation [inhibition of cytochrome P-450 3A4 pathway involved metabolism of THC and CBD). Conversely, there is mounting evidence that THC and CBD alter liver microsomal enzymes so that their use may lead to changes in metabolism of co-administered drugs of many different classes. Since patients with chronic medical conditions are often on one or more types of prescription drugs, thoughtful review and due caution must be exercised when combined with cannabinoids (17,18).
This level of complexity makes it very difficult to make individual patient-based dose-response predictions, and there is not an adequate evidence base to fully inform decisions based on these almost unlimited combinations of variables. If a patient has had previous exposure to cannabis or cannabinoids, their experiences may be helpful in guiding recommendations and anticipating outcomes. Nevertheless, the adage "start low and go slow" while routinely monitoring outcomes on a frequent basis, regardless of formulation or route of delivery, seems to apply as a universal precaution. This principal is especially important in the very young and older individuals, and those with co-morbid health conditions. These fundamental and essential principals of titration and long-term management pertain to cannabis therapy going forward as they do to all more conventional condition management paradigms (e.g., pharmacological treatment of diabetes, heart failure, or chronic pain, etc.).

Pharmacokinetics of cannabis and its constituent cannabinoids THC and CBD

ABSORPTION

Smoked: Absorption of chemical constituents rapidly into the blood stream from the pulmonary capillary bed, and distributed within minutes to the brain and peripheral tissues. Absorption is a function of depth, and duration of inhalation, integrity of lung tissues and cardiac output, all of which can lead to significant variability in blood levels of pharmacologically active constituents such as THC and CBD. This is exemplified by studies demonstrating bioavailability of THC to be between 2-56% (e.g., blood levels of between 7.0 ng/mL and 75 ng/mL within 15 minutes for cannabis cigarettes containing between 14-16 mg THC) (19,20). Absorption of CBD from smoked cannabis is similar to THC, with bioavailability averaging about 31% and mean blood levels in the range of 42-191 ng/ml a few minutes after consuming 19 mg CBD (21). These figures are important for comparative purposes with other dosage forms of either whole plant material, extracts, or purified/synthesized cannabinoids.

Vaporized: Absorption of THC and CBD is rapid with vaping, similar to smoking, with the advantage of less potential toxic bioproducts and carcinogens from vaping versus smoking (22).
Oral: Multiple cross-over studies have demonstrated that peak blood levels of cannabinoids are significantly lower and take far longer to arrive at, and are maintained far longer after oral consumption compared with equal amounts of inhaled (smoking or vaping) cannabis. For example, one study compared cannabis containing THC 51 mg and CBD 1.5 mg. When inhaled,

peak blood concentrations (Cmax) of THC was between 48 and 52 ng/ml (vaping and smoking respectively), and 10 ng/ml after oral consumption. Time to peak blood levels (Tmax) was 7 minutes after inhalation and 2.5 hours after oral ingestion (23). Ingestion of CBD in various oral formulations for a diversity of therapeutic purposes has been popularized over the last several years. The first FDA approved formulation of CBD (100 mg/ml solution) with an indication for treatment of intractable pediatric epilepsy is now available by prescription. Table 3 provides a comprehensive summary of pK parameters for oral CBD, demonstrating the significant variability among formulations and individuals (24-29).

N	Form	Dose (mg)	T_{max} (hrs)[1]	C_{max} (ng/mL)[2]	AUC_{0-t} (ng*h/mL)[2]	AUC_{0-inf} (ng*h/mL)[2]	Reference
24	Capsule	5.4	0.99[2] (0.5–2)	0.93 (0–2.6)	4.35 (2.7–5.6)		24
12	Capsule	5.4	1.07[2] (0.5–2)	1.13 (0.39–1.9)	4.4 (2.5–5.3)		24
9	Capsule	10	1.0 (0.5–1.5)	2.1 (0.4)	6.9 (1.3)		25
15	Pellets	10	3 (2–4)	3.22 (1.28)	9.64 (3.99)	10.31 (4.14)	26
15	Capsule	10	1.25 (0.5–4)	2.94 (0.73)	9.85 (4.47)	10.52 (4.53)	27
15	Pellets	100	3.5 (1.5–5)	47.44 (20.14)	149.54 (34.34)	153.04 (34.7)	26
8	Capsules	800	3[2] (2–6)	77.9 (1.6–271.9)			28
6	Solution	1500	4 (3–5)	292.4 (87.9)	1517 (78.2)	1618 (74.6)	29
12	Solution	1500	3.5 (2.5–5)	335.4 (81.3)	1987 (53.6)	2198 (48.2)	29
12	Solution	1500	3.0 (1.5–5)	1628 (51.4)	8347 (34.1)	8669 (33.9)	29
6	Solution	3000	5 (3–5)	533.0 (35.1)	2669 (36.4)	2802 (35.5)	29
6	Solution	4500	5	722.1 (52.3)	3215 (50.3)	3426 (48.3)	29
6	Solution	6000	5 (3–5)	782 (83.0)	3696 (79.9)	3900 (79.3)	29

Table 3: Oral Bioavailability Parameters From Healthy Volunteer Studies

previations: Tmax = time to peak blood levels; Cmax = concentration of peak blood levels;
C = area under the curve; [1]Median (range); [2]Mean (SD or range)

Oral Transmucosal: A 1:1 mixture of THC (~10 mg) and CBD (~10 mg) administered as an oral transmucosal spray showed peak blood levels of each cannabinoid (5.5 ng/ml and 3 ng/ml, respectively) between 2-4 hours. These values suggest that absorption characteristics via this route are similar to the oral route (e.g., commercially available and FDA approved synthetic THC), with a high degree of intra- and inter-individual variability (24). Topical: Research into dermal application and absorption of cannabinoids is limited to animal models. Results suggest that THC and CBD are absorbed from intact mammalian skin with or without permeation enhancers at levels comparable to oral absorption. Blood levels can be maintained for days using dermal patches (25).

METABOLISM

Drug metabolism describes what happens to a parent compound once it enters the body. Some drugs when swallowed are degraded into inactive forms in the stomach. Some drugs are

converted into active metabolites in the acidic gastric environment, and this can occur with cannabinoids—most notably acid hydrolysis of CBD into THC. The clinical implications of this are not yet clear. Unaltered orally ingested parent drug that passes into the intestines is absorbed into the portal circulation that leads to liver metabolism via the cytochrome P-450 system (CYP). Cannabinoids that enter into the systemic circulation by way of non-enteric routes (inhalation, topical or oral transmucosal administration) ultimately are processed in the liver, but have access to peripheral and central tissues (i.e. opportunity to cross the blood-brain barrier) before first-pass metabolism through the liver can occur. The majority of cannabinoid metabolism occurs in the liver.

Both THC and CBD undergo extensive biotransformation in the liver, with multiple CYP isoenzymes involved, including CYP 3A4 and 2C19. This is important because these hepatic enzymes are involved in the metabolism of many important drugs, including some opioids and antidepressants. And so the potential for toxic drug-drug interactions must be appreciated, anticipated and monitored. Any patient who chooses to use cannabis or cannabinoids for any purpose should undergo a medication review (OTC and prescription drugs, supplements and herbal preparations) and dose adjustments should be considered based on a full understanding of potential interactions.

EXCRETION

Most cannabinoid metabolites are excreted in the feces (about 2/3) and the urine (about 1/3). The inactive metabolite of THC, 11-nor-9-carboxy THC, has been detected in the blood stream up to a month after cannabis use (33).

Pharmacodynamics of marijuana

Because the psychoactive effects of marijuana, caused by activation of central nervous system (CNS) CB_1 receptors, are so immediate and apparent to those who use it, along with abuse liability concerns by agencies such as the National Institutes of Drug Addiction (NIDA), among others, the CNS pharmacodynamic properties have been studied more thoroughly than other properties. Despite numerous anecdotal reports of postulated medicinal or psychologically beneficial interactions (the “entourage effect”) among phytocannabinoids and other cannabis constituents (e.g., terpenes), there is little evidence that can be drawn upon from which to inform clinical decisions. The only empirically based conclusions that can be predicted are potency-related dose-response effects from the amount of THC in cannabis that is ingested by the smoked or oral route (34). At this time, there is no evidence base from which to draw predictable pK-pD effects for any particular strain of cannabis. Most pD effects reported are from studies involving smoked marijuana, and may not pertain to the oral or topical routes of administration due to slower time to peak blood levels. The following pharmacodynamic effects are listed to help inform health care professionals and their patients, especially those with co-morbid medical or psychiatric conditions that might be affected by acute, intermittent/recurrent, or chronic cannabis use.

CNS effects: euphoria, anxiety, depersonalization, psychosis (paranoia, delusions, hallucinosis), sedation, depression, ataxia (35); distraction from certain types of pain leading to perceived analgesia in some patients with chronic cancer and non-cancer pain syndromes (36); anti-nausea

and anti-emetic effects (37); hyper-emesis syndrome as a component of cannabis use disorder (38); appetite enhancement (39).
Cardio- cerebrovascular effects: tachycardia, atrial and ventricular dysrhythmias (40); vasodilation, conjunctival injection, postural hypotension (41); increased cardiac output with associated increased myocardial oxygen demand, with potential for acute myocardial ischemia and infarction in at-risk patients (42); stroke (43).
Gastrointestinal effects: decreased motility (44); accelerated hepatic steatosis and fibrosis in conjunction with alcohol use (45); acute pancreatitis (46).
Musculoskeletal effects: reduced spasticity associated with multiple sclerosis (47); delayed bone healing (48).
Immune effects: hypersensitivity (allergic) reactions (49).
Reproductive effects: decreased sperm count and motility in men (50); menstrual cycle disruption and infertility in women (51).

Pharmacodynamics of cannabidiol (CBD)
Although there is only one FDA approved CBD product (pediatric epilepsy) now available by prescription in the United States, a wide variety of non-FDA approved CBD formulations are now commercially available. It is important to note that this is a poorly regulated area of commerce, and so health professionals who recommend CBD use, and consumers who are interested in obtaining CBD products, need to be aware that the dose, purity, and source of the product contents may not be accurately reflected in advertising or packaging. As well, like cannabis, dose-response relationships have not been adequately studied in humans, with the exception of CBD for pediatric epilepsy—and even those pK-pD studies and clinical experience demonstrate significant variance among patients in dose-response.

Since cannabidiol is poorly and erratically absorbed after either oral or transmucosal administration, the amount that actually gets absorbed into the systemic circulation by spraying a dose into the mouth, or by swallowing a product containing CBD (e.g., pill, capsule, liquid, "gummy", beverage, etc.) is unpredictable and largely indeterminate on an individual use basis at this time.

Cannabidiol appears to exert its effects through interactions at CB_1 and CB_2 receptors, as well as via other intermediary pathways, including interruption of putative inflammatory processes by as-of-yet poorly defined mechanisms. Apart from well-controlled safety, pharmacokinetics, pharmacodynamics and drug interactions trials in rodents, primates, and in healthy volunteers, the number of well-controlled CBD clinical trials in patients is relatively small considering the scope of its potential use (52). The exception is childhood epilepsy, particularly in Lennox–Gastaut and Dravet syndromes, where CBD was studied more extensively in the process of Epidiolex® drug development (53).

The therapeutic effect of CBD in other disease states, as shown in *in-vitro* and *in-vivo* (animal model) studies, sparked publication of many case reports and only a few controlled studies in various areas such as: psychiatric disorders, Parkinson's disease, cancer, autism, pain, ulcerative colitis, drug dependence, diabetes, and others, with doses as high as 1500 mg/day (54). Oral CBD has been administered in clinical trials to both healthy volunteers and patients with various medical conditions, as single or multiple doses ranging from 10 mg to 6000 mg (55-58). In most

of the studies CBD was well tolerated and no severe or serious AEs were reported. Hence, CBD is generally considered to have a favorable safety profile (59). The most common adverse effects recorded in clinical trials are diarrhea, nausea, headache and somnolence. It is noteworthy, however, that since clinical trials are conducted under widely varying conditions, the observed AE rates are difficult to compare and may not necessarily reflect those observed in practice. The clinical area that appears to have some of the most potential promise is that of neuropathic pain—syndromes, exemplified by painful peripheral diabetic neuropathy, are notoriously refractory to currently available treatments (60).

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