Utah Department of Health

UDOH Guidelines on Suggested Use of Medical Cannabis

About this document: The following Guidelines on the Use of Medical Cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. The intended audience for this document is qualified medical providers, pharmacy medical providers, patients intending to use medical cannabis and/or caregivers of patients intending to use medical cannabis.

About the authors: This document was authored by the Utah Cannabinoid Product Board and UDOH staff. Expertise from outside these two groups include

About the Utah Cannabinoid Product Board: Under Utah Health Code 26-61-201 the Cannabinoid Product Board is a board of medical research professionals and physicians who meet on a voluntary basis to review and discuss any available scientific research related to the human use of cannabis, cannabinoid product or an expanded cannabinoid product that was conducted under a study approved by an IRB or was conducted and approved by the federal government.

DISCLAIMER

This document has been vetted and approved by the Utah Cannabinoid Product Board which has authority to do so under Utah Health Code 26-61-202.

This document is a summary of peer-reviewed literature concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. It is not meant to be comprehensive and should be used as a complement to other reliable sources of information. This document is not a systematic review or meta-analysis of the literature and has not rigorously evaluated the quality and weight of the available evidence. This document includes a 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.

All patrons participating in the Utah Medical Cannabis Program are advised to use this document and any such document produced from this original document as informational and educational. The use of medical cannabis is at one's own risk. All participants must be aware that medical cannabis is NOT a first degree therapy and in some, but not all, cases it is not a second degree therapy.

The information in this document is intended to help Utah health care decision-makers, health care professionals, health systems leaders, and Utah Medical Cannabis patients to make well-informed decisions and thereby improve the quality of health care services regarding medical cannabis use. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process.

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This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the State of Utah applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the State of Utah.

Definitions

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).
6) **Chemotype:** Chemically distinct plant phenotypes defined by content ratios of THC:CBD. Medical cannabis and cannabis-based medicines can be divided into 3 broad chemotype categories based on relative content ratios of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD):[1]
   a) Chemotype I - Δ^9-tetrahydrocannabinol (THC)-predominant with THC:CBD ratio >10:1
   b) Chemotype II - significant quantities of both THC and CBD with THC:CBD ratio <10:1 and >2:10
   c) Chemotype III- cannabidiol (CBD)-predominant with THC:CBD ratio <2:10

General Instructions and Understanding of this Document:

1) The suggested **adult** medical cannabis starting doses outlined in this document are not backed up by clinical trials and may not be appropriate recommendations for all patients or for all conditions being treated, but are included in this document to provide qualified medical providers with some basic considerations when initiating treatment with medical cannabis, especially in cannabis-naïve patients.

2) **Medical cannabis dosing guidance**

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

The medical literature is generally devoid of specific dose recommendations for the use of medical cannabis in the treatment of various disease states. The starting and titrating dose suggestions outlined in this document are adapted from several sources including:

a. Caroline A. MacCallum, and Ethan B. Russo. Practical Considerations in Medical Cannabis Administration and Dosing. *European Journal of Internal Medicine* 40 (2018) 12-19;
b. Dosing recommendations from the United Kingdom package insert for nabiximols/Sativex (cannabis whole-plant extract oral mucosal spray with 2.5mg of CBD and 2.7mg THC per spray).
c. Several observational reports from Israel using chemotype III medical cannabis in the treatment of autism spectrum disorder and epilepsy.[2] [3]

General Instructions for the Use of Medical Cannabis

1) **Cannabis should be stored in a safe place** such as a lock box in the home out of reach of children.

2) **Qualified medical providers must clearly communicate the potential risks of cannabis**, no differently than with any other psychoactive medication.

3) **Differences in Chemotypes** One chemotype may be preferable over another depending on the disease process being treated, desired effects, desired avoidance of side-effects, and prior clinical experience or preference of individual patients. There is a general lack of robust controlled clinical trials addressing therapeutic synergy (the "entourage effect") of various cultivars and chemotypes, and current scientific information regarding therapeutic synergy is often observational in nature with conflicting results. Case-by-case individualization of treatment dosage and chemotype, will remain a significant reality until more robust clinical data are available to help better guide clinical decision making.

NOTE: *Current Utah law requires batch testing and labeling of THC and CBD content on the package of all medical cannabis products dispensed in Utah.*

4) **Starting dose guidance for oral or sublingual (i.e. ingested) medical cannabis products – Chemotypes I and II (significant amounts of THC)**

[2] 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

[3] 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.

a. Bioavailability of orally administered THC and CBD may be increased when administered in conjunction with a fatty meal.[4]
b. To avoid unwanted psychoactive side-effects, **"start low and go slow"** especially when using chemotype I products.

c. 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.

NOTE: *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.

5) **Starting dose guidance for oral or sublingual administration of medical cannabis products – Chemotype III – CBD predominant**.
   a. Bioavailability of orally administered THC and CBD may be increased if administered in conjunction with a fatty meal.

Chemotype III medical cannabis extracts with a THC:CBD ratio of 1:20 have been used in several clinical trials in Israel. 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:** 1mg THC and 20mg CBD once at bedtime
- **Days 3-4**: 1mg THC and 20mg CBD twice per day
- **Days 5-6+** : Increase dose **if needed** and if tolerated every 2-3 days to **15 mg THC/300mg CBD/24 hours** divided BID-TID

[4] 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.

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

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

8) **Medical Cannabis Dosage Forms – Advantages and Disadvantages** (adapted from Caroline MacCallam and Ethan Russo)[5]

	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-pass 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
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

a. **Topical dosing of medical cannabis:** No clinical studies have been published regarding the percutaneous absorption of cannabis-containing ointments, creams, or lotions.[6] Cannabinoids are highly hydrophobic, making transport across the aqueous layer of the skin the rate-limiting step in the diffusion process but absorption of cannabinoids does occur

[5] Caroline A. MacCallum, Ethan B. Russo; Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine* 40 (2018) 12-19.
[6] Health Canada; Information for Healthcare Professionals - Cannabis (marihuana, marijuana) and the cannabinoids. Feb 2013, page 33.

tansdermally in preclinical animal studies.[7] **Currently there is not enough published clinical data to make any recommendations regarding dosing of transdermal delivery of medical cannabis.**

b. **Vaporization of herbal cannabis for first-time use or when using a new cultivar or chemotype:**

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 herbal preparation.[8] 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) contained in the flower into their more pharmacodynamically active states (THC and CBD).[9] [10] Vaporizer temperature setpoints of 210-230°C result in rapid and near complete decarboxylation of THCA and CBDA. Lower vaporizer temperature set points result in slower decarboxylation rates[11] and complete decarboxylation of all THCA and CBDA is less likely to occur which may result in a clinical response that is significantly different (and in some situations preferable) when compared to what happens 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.[12] At lower vaporizer chamber temperature setpoints, cannabinoids and terpenoids with higher vapor pressures and lower boiling points will generally be more completely vaporized and inhaled than the cannabinoids and terpenoids that have higher boiling points and lower vapor pressures.

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[7] Paudel KS, Hammell DC, Agu RU, Valiveti S, Stinchcomb AL. Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers Intranasal and transdermal delivery of cannabidiol. *Drug Development and Industrial Pharmacy*, 2010; 36(9): 1088–1097

[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] 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

[11] 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

[12]

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.

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 trichromes in the herb. 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.[13]

[13] 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

NOTE: *Due to 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 herbal cannabis.

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).

2. 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 and the desired approximate dose needed based on experience with prior dosing.

3. 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. [1]

4. Dosing intervals using a vaporizer device are usually determined by the need for symptom control and may be as frequent as every 2-4 hours.

5. 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.[1]

6. 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.**

7. Higher vaporizer setpoint temperatures (e.g. 210-230°C) will likely result in rapid and more complete decarboxylation of THCA and CBDA,[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 lower vapor pressures which may result in increased sedation and intoxication. Set point temperatures approaching the temperature of combustion (230°C) may also increase the amounts of pre-combustion products of pyrolysis, and promote degradation of THC into CBN. Due to these effects, higher temperature set points are more likely to result in possibly unwanted side-effects including mental impairment, excessive intoxication, sedation, and euphoria, but may be considered when lower temperature set points do not result in adequate management of symptoms.

8. **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[1].**

9. 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.

3. **Inhalation of medical cannabis concentrates administered via vape pens:**

Medical cannabis vape pens can be used for acute relief of symptoms and can be used on an as-needed basis, or as add-on therapy to oral treatments for breakthrough symptoms when managing chronic problems similar to using herbal cannabis in heated air vaporizer devices. Unlike herbal cannabis vaporization devices, there is no adjustable temperature set point for vape pens.

The **approximate dose of THC and CBD per inhalation** from a vape pen can be estimated based on batch lab-test results for CBD and THC content of the vape cartridge divided by the estimated number of inhalations per cartridge for a specific vape pen. These sort of calculations may be helpful when comparing inhaled doses to oral and sublingual doses, and may help avoid excessive dosing and side effects. However, due to individual variability of inhalation technique and lack of precise dosing due to uncalibrated and non-standardized vape pen devices, it may be more prudent to follow the general symptom-based titration suggestions below. There are no device-specific dose-finding studies for use of vape pens for the delivery of medical cannabis for the treatment of any specific disease.

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 vape pen 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 medical cannabis concentrates administered via a vape pen device.

1. Start LOW and go SLOW.
2. In cannabis naive individuals, start with chemotype II or chemotype III medical cannabis extracts with moderate or low THC content. Chemotype I medical cannabis may be considered but should start with low THC content cartridges to avoid intoxication and other significant reactions.
3. 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.
4. Consider use of vape pen cartridges with lower THC content coupled with less-aggressive dosing frequency if using vape pens to treat children, the elderly and in otherwise compromised adults.
5. Vape pens and cartridges used in vape pens should be purchased at state-inspected and regulated medical cannabis pharmacies with labeled THC and CBD content and then only after review of batch testing results performed by independent laboratories.

WARNING: The CDC has reported a nation-wide large number of cases of severe pulmonary injury with respiratory failure and deaths associated with the antecedent use unregulated black-market cannabis vape pens and cartridges. Analysis of these adverse events has revealed that most affected individuals were using unregulated cannabis extracts in their vape pens and that these extracts had been cut/adulterated/diluted using vitamin E acetate. Based on current data as of January 2020,[1] the CDC believes that the majority of the cases of severe pulmonary injury and death are due to the presence of vitamin E acetate[1] in THC-containing e-cigarettes/vape pens.

There may be some medical cannabis products that are produced and intended for oral ingestion or topical administration that contain vitamin E acetate as a carrier. **Use of a vape pen to administer medical cannabis concentrates that were intended for topical administration, or oral/sublingual ingestion, may result in acute lung injury and possibly death.**

Medical cannabis dose-response variables to consider

The therapeutic effects and side-effects of a specific medical cannabis product, 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. Cannabis and cannabinoid-containing products containing THC and CBD have been shown in some studies to demonstrate a non-linear dose-response curve.[14] Placebo-controlled trials using nabiximols/Sativex® in the treatment of chronic poorly-controlled cancer-related pain[15] and anecdotal clinical observations suggest an inverted U-shaped dose-response curve, meaning that as the doses of THC and/or CBD are increased, the desired clinical effects can sometimes be less than what was observed at lower doses. These observations can be patient-specific and may not be uniform in all patients.
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.[16]
d) Route and technique of administration – 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 orally or sublingually-administered medical cannabis including THC, CBD, and other components of cannabis may be improved if taken in conjunction with a fatty meal. 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).[17] 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.[23]
f) Bioavailability of oral cannabinoids may also be affected due to variables affecting absorption such as carrier components and additives, nanoparticle preparations.[18]
g) In the case of vaporized cannabis, the technique used for inhalation (speed and duration of inhalation) and temperature set points[19] may affect the extent of decarboxylation, vaporization efficacy, and resultant bioavailability.
h) 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, may have variable effects.
i) Drug interactions with other medications affecting pharmacokinetics and pharmacodynamics of cannabis and cannabinoids.
j) Development of tolerance to some effects and side-effects with longer duration of use.
k) Pre-treatment handling of flower/bud

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[14] Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, Gouaux B, Abramson I. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007; 107:785–96. [PubMed: 18073554]

[15] Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright SR, Fallon MT. Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial. *The Journal of Pain*, Vol 13, No 5 (May), 2012: pp 438-449

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

[17] 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.

[18] Cherniakov, Irina & Izgelov, Dvora & Barasch, Dinorah & Davidson, Elyad & Domb, Abraham & Hoffman, Amnon. (2017). Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids: Pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration. Journal of Controlled Release. 266. 10.1016/j.jconrel.2017.09.011.

[19] 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)

(1) Excessive handling of buds/flowers may result in damage to trichromes[20] with possible reduced potency and shortened shelf life due to accelerated oxidation and degradation.

l) Pre-treatment processing/heating
   (1) THC-A and CBD-A undergo decarboxylation when heated. Decarboxylation happens slowly at 100 C and more rapidly at temperatures over 160 C. Without an adequate period of heating during processing or administration, THC-A and CBD-A may not be converted into their more-active decarboxylated states (THC and CBD) and may have significantly diminished clinical effects. However, while controlled clinical trials are lacking, some preclinical and observational data suggest that in some disease states such as epilepsy,[21] inflammatory bowel disease,[22] and chemotherapy-induced nausea and vomiting,[23] THC-A and CBD-A may be effective and helpful with fewer side-effects than decarboxylated THC and CBD.

m) Shelf life and storage conditions of the cultivar or medical cannabis product
   (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 pathfinding. 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. [24]

   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

[20] Roy Upton et al; Cannabis Inflorescence, Cannabis spp. Standards of Identity, Analysis, and Quality Control; American Herbal Pharmacopoeia, Revision 2014, page 31
[21] The current status of artisanal cannabis for the treatment of epilepsy in the United States Epilepsy & Behavior, 70(Pt B), 328-333, May 2017 https://doi.org/10.1016/j.yebeh.2016.12.032
[22] Nallathambi, et al.; Anti-Inflammatory Activity in Colon Models Is Derived from D9-Tetrahydrocannabinolic Acid That Interacts with Additional Compounds in Cannabis Extracts. *Cannabis and Cannabinoid Research* 2017, 2.1 http://online.liebertpub.com/doi/10.1089/can.2017.0027
[23] Health Canada; Information for Healthcare Professionals - Cannabis (marihuana, marijuana) and the cannabinoids. Feb 2018, page 60.
[24] 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.

profile in adulthood. [25] The endocannabinoid system also regulates skeletal development and these effects may account for the observation that small-for-gestational-age babies are associated with 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,[26] 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. [27] [28] [29] In school-aged children, prenatal cannabis exposure was also associated with deficits in attention and presence of impulsivity and hyperactivity.[30] 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),[31] [32] with these deficits also appearing in 13 to 16-year old's[33] and 18- to 22-year old's.[34] 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.[35]

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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[25] 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.

[26] Gunn JK, Rosales CB, Center KE, Nunez A, Gibson SJ, Christ C, Ehiri JE. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ* Open 2016 Apr 5;6(4):e009986,2015-009986.

[27] Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, Cornelius MD, Geva D. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol 1994 Mar-Apr;16(2):169- 75.

[28] Fried PA, Watkinson B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. J Dev Behav Pediatr 1990 Apr;11(2):49-58.

[29] Fried PA, O'Connell CM, Watkinson B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: Cognitive and language assessment. J Dev Behav Pediatr 1992 Dec;13(6):383-91.

[30] Fried PA, Watkinson B, Gray R. A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. Neurotoxicol Teratol 1992 Sep-Oct;14(5):299-311.

[31] Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 1998 May-Jun;20(3):293-306.

[32] 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.

[33] Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003 Jul-Aug;25(4):427-36.

[34] Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: An fMRI study in young adults. Neurotoxicol Teratol 2006 Mar-Apr;28(2):286-95.

[35] 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.[36] [37] THC concentrations in breast milk in humans may be up to eight-fold higher than that found in maternal blood.[38] In a case-control study[39] 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**

Cannabis is known to cause peripheral vasodilatation, postural hypotension, and characteristic conjunctival reddening after smoking, but the most consistent acute physiological effect of cannabis is dose-related tachycardia.[40] While cannabis-induced tachycardia is not usually considered dangerous for healthy young users, it may be dangerous to those already suffering from cardiac disorders or angina.[41] Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50%[42] and has been associated with a five-fold increased risk of myocardial infarction in the first hour following smoking.[43] This increased risk may be caused by a Δ9-THC-related increase in cardiac output, myocardial oxygen demand, catecholamine levels, and in the case of combustion of cannabis which typically happens at temperatures > 230°C, formation of carbon monoxide (carbon monoxide poisoning).

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[36] Jaques SC, Kingsbury A , Henshcke P , Chomchai C , Clews S , Falconer J , Abdel-Latif ME , Feller JM, Oei JL. Cannabis, the pregnant woman and her child: weeding out the myths. *Journal of Perinatology* (2014) 34, 417–424.
[37] Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem RR, Hale TW. Transfer of Inhaled Cannabis Into Human Breast Milk. *Obsetrics and Gynecology* 2018;131:783-788.
[38] Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med* 1982; 307(13): 819–820.
[39] Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol 1990 03;12(0892-0362; 2):161-8.
[40] Health Canada; Information for Healthcare Professionals - Cannabis (marihuana, marijuana) and the cannabinoids. Feb 2013, page 162.
[41] Mittleman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: Preventive strategies. *Circulation* 2011 07/19;124(1524-4539; 0009-7322; 3):346-54.
[42] Aronow WS, Cassidy J. Effect of marihuana and placebo-marihuana smoking on angina pectoris. *N Engl J Med* (1974) 06/11;291(0028-4793; 2):65-7.
[43] Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001 06/12;103(1524-4539; 23):2805-9

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.[44] 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).[45] [46] The risk of schizophrenia associated with cannabis use is especially high in individuals who have a personal or family history of schizophrenia.[47] 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.[48]

Cannabis use is associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms.[49] 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[50]. The overall weight of evidence suggests that the association between cannabis exposure and schizophrenia is modest but consistent.

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[44] D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology 2004; 29: 1558–72.

[45] 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.

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

[47] 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.

[48] 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.

[49] 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

[50] 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

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[51] 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, and Adverse Reactions

1) **Use in Children, Adolescents, and Adults Under the Age of 26**
   Use in this age category may result in altered brain development and function with possible long-term negative consequences including negative mental health outcomes and long-term cognitive impairments.[52] [53] [54] 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 patient's guardian(s). A recent systematic review of the use of medical cannabis in children may be helpful when considering the use of medical cannabis in the pediatric population.[55]

NOTE: *Under current Utah code all individuals using cannabis under age 21 will need approval from the Compassionate Use Board.*

2) **Impaired Cognition**[56]
   - Acute effects of cannabis use are established with strong evidence and include impairment of short-term memory, attention, concentration, executive functioning and visual perception.

[51] 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.
[52] 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.
[53] Brumback T, Castro N, Jacobus J, Tapert S. Effects of marijuana use on brain structure and function: Neuroimaging findings from a neurodevelopmental perspective. *Int Rev Neurobiol* 2016;129:33-65.
[54] Morin JG, Afzali MH, Bourque J, et al. A population-based analysis of the relationship between substance use and adolescent cognitive development. *Am J Psychiatry* 2019;176:98-106
[55] Wong SS and Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. Pediatrics. 2017;140(5):e20171818
[56] Katherine L. Carlson, MD, FASAM. Monograph on Central Nervous System Adverse Effects of Cannabis. Submitted to the Utah Cannabinoid Product Board 7/10/2019

- 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.
- Some brain imaging studies associate regular (weekly or more frequent) cannabis use with structural changes in gray and white matter in different brain regions.
- Early-onset use and use of high-potency, THC-predominant cannabis is associated with a higher degree of impairment.
- 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.

3) **Altered Mental Status**

Use of cannabis, especially in cannabis-naive patients or in patients who use higher doses of THC, may cause acute problems with altered mental status, confusion and disorientation and sometimes more serious reactions such as psychotic reactions and suicidal ideation. 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 medical cannabis.

4) **Psychomotor Performance and Driving**

- 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.
- 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.**[57]
  - Effects of oral ingestion on psychomotor function and driving skills are usually delayed in onset compared with inhaled doses of cannabis, but 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. Additional caution may be needed during initiation of treatment in treatment-naive individuals or when making a change in medical cannabis product or dosage.**
- Period of driving impairment may persist for several days after last use in some individuals who use cannabis on a regular basis (weekly or more frequently). This effect may be due to the gradual release back into the bloodstream of fat-soluble

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

cannabinoids that were deposited and built up in fatty tissues during regular or heavy use of cannabis.

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

5) **Alcohol Use**
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.**

6) **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.

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

8) **Cannabis Use Disorder (CUD)**
CUD 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)[58] 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.

9) **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 temporarily relieve the symptoms. Treatment with antiemetics is usually not effective. The most successful treatment consists of stopping cannabis use completely.[59]

10) **Cardiovascular Risk and Cerebrovascular Risk:**
There is evidence of a statistical association between cannabis use and ischemic stroke, subarachnoid hemorrhage, and the triggering of acute myocardial infarction.[60] Use of cannabinoids may cause tachycardia, substantial changes in blood pressure, and episodes of postural hypotension. Cannabis and cannabinoids should not be used in patients with unstable vital signs, congestive heart failure, angina, myocardial infarction, known/suspected structural or vascular heart disease, or known cerebrovascular disease.

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[58] https://www.who.int/substance_abuse/publications/cannabis_report/en/index5.html
[59] Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA. Cannabinoid Hyperemesis Syndrome: Diagnosis, Pathophysiology, and Treatment—a Systematic Review. *J. Med. Toxicol.* (2017) 13:71–87.
[60] 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, Chapter 6.

11) **Cardiovascular and Cerebrovascular Risk Among Otherwise Healthy Young Adults**
Cannabis use may be a risk factor for acute myocardial infarction and stroke even among otherwise healthy young adults. In a systematic review of case-series, 62 cases of MI occurred among adults with a mean age of 27.7 years who reported either regular marijuana use (n = 36), synthetic marijuana use [eg, spice] (n = 21) or a combination of both (n = 5). From the cases reporting the onset of AMI symptoms, the average time was within 5 hours after last marijuana use.[61] A cross-sectional observational study reported on the risk of stroke among young adults ages 18-44. They found 1.82 higher odds of stroke (adjusted OR 1.82 (95%CI 1.08 - 3.10)) compared to nonusers of marijuana. The odds of stroke were higher among frequent users of marijuana (>10 days/month) compared to nonusers (adjusted OR 2.45 (95%CI 1.31-4.60)).[62]

12) **Seizures and People with Epilepsy**
Seizure and seizure-like activity have been reported in patients receiving MARINOL® capsules during marketed use of the drug and in clinical trials but a causal relationship has not been established.[63] Preclinical data in some animal studies and case reports suggest possible proconvulsant effect of higher doses of THC[64] but other case reports suggest possible anti-convulsant effects of THC.[65] Until better clinical data are available, high doses of THC should generally be avoided in individuals with seizure disorder, and THC-predominant cannabis (chemotype I) should be used with significant caution and only after failed treatment attempts using other treatment options.

13) **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, the use of cannabis is associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms.[66] 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.[67]

14) **Bipolar and Other Mood Disorders**

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[61] Patel RS, Kamil SH, Bachu R, Adikey A, Ravat V, Kaur M, Tankersley WE, Goyal H. Marijuana use and acute myocardial infarction: A systematic review of published cases in the literature. *Trends Cardiovasc Med*. 2019 Aug 14. S1050-1738(19)30112-4. doi: 10.1016/j.tcm.2019.08.003.

[62] Tarang Parekh , Sahithi Pemmasani, Rupak Desai. Marijuana Use Among Young Adults (18–44 Years of Age) and Risk of Stroke - A Behavioral Risk Factor Surveillance System Survey Analysis. *Stroke* 2020;51:308–310.

[63] FDA Marinol/dronabinol package insert - adverse reactions
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651s025s026lbl.pdf

[64]

[65]

[66] 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

[67] 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

A 2015 systematic review and meta-analysis of 6 studies of bipolar disorder and cannabis use[68] 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.

15) **Depression and Suicidality**

Epidemiologic evidence suggests a link between regular (weekly or more frequent) or high dose cannabis use and suicidality. A 2019 systematic review and meta-analysis of 11 studies comprising 23,317 adolescents[69] 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.

16) **Anxiety**

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.

17) **Pre-existing Substance Use Disorders**

Medical cannabis should generally 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). However, there may be circumstances where a qualified medical provider may determine that this risk may be outweighed by potential benefits of use of medical cannabis in an individual with complex problems that are not adequately managed with usual interventions.

18) **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 bronchitis.[71] Although there are some data suggesting improved airway dynamics with

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[68] 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

[69] 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.

[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.

[71] National Academies of Sciences, Engineering, and Medicine. 2017. *The health*

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.

19) **Vitamin E Acetate**
Any hemp extract, cannabidiol or oral medical cannabis preparation that contains Vitamin E acetate has the potential to cause **severe pulmonary injury and death if administered via the inhalation route.**[72] Vape pens should never be used to administer medical cannabis preparations that were not specifically intended to be used in vape pens.

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

21) **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. Patients with diabetes should be monitored to assure adequate glucose control while using medical cannabis.

22) **Osteoporosis and Metabolic Bone Disease**
Animal and in vitro human studies implicate cannabinoids in age-related bone remodeling, and possible osteopenia and osteoporosis. 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.

23) **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.

24) **Potential Risk of Cancer Associated with Use of Cannabis**
A systematic review and meta-analysis of 25 studies assessing marijuana use and the risk for developing lung, head and neck, urogenital, and other cancers showed that regular

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effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press, Chapter 7-1.

[72] Taylor J, Wiens T, Peterson J, et al. Characteristics of E-cigarette, or Vaping, Products Used by Patients with Associated Lung Injury and Products Seized by Law Enforcement — Minnesota, 2018 and 2019. MMWR Morb Mortal Wkly Rep 2019;68:1096-1100. DOI: http://dx.doi.org/10.15585/mmwr.mm6847e1external icon

marijuana use was associated with development of testicular germ cell tumors, although the strength of evidence was low. Evidence regarding other cancers was insufficient.[73]

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

Note: *Other adverse effects to consider for the use of cannabis include, but are not limited to, fatigue, insomnia, diarrhea, nausea and decreased appetite.*

Cannabis Drug Interactions

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. Pharmacodynamic effects leading to additive toxicity are also possible. It has been suggested that clinically significant drug interactions are unlikely to occur; however, few well-designed clinical studies of drug interaction studies have been conducted.[2] Predictions from in vitro and animal studies suggest a high potential for significant first pass drug interactions after oral administration due to THC and/or CBD inhibition of CYP isoenzymes in the intestine and liver.[3] **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 clinical and adverse effects closely; consider dose adjustments as clinically indicated.**

Clinicians may refer to 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/MainTable.aspx) to estimate possible CYP450 mediated drug interactions with cannabis products.

State-Approved Qualifying Medical Conditions

Qualifying medical conditions stated under the Utah Medical Cannabis Act in Utah Health Code 26-61-104 include:

[73] Ghasemiesfe M, Barrow B, Leonard S, Keyhani S, Korenstein D. Association Between Marijuana Use and Risk of Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2019;2(11):e1916318. doi:10.1001/jamanetworkopen.2019.16318

- HIV/AIDS
- Alzheimer's Disease
- Amyotrophic Lateral Sclerosis (ALS)
- Cancer
- Cachexia
- Persistent Nausea
  that is not significantly responsive to traditional treatment, except for nausea related to pregnancy, cannabis-induced cyclical vomiting syndrome, or cannabinoid hyperemesis syndrome
- Crohn's Disease or Ulcerative Colitis
- Epilepsy or Debilitating Seizures
- Mutiple Sclerosis (MS) or Persistent and Debilitating Muscle Spasms
- Post-Traumatic Stress Disorder (PTSD)
- Autism
- Terminal Illness
- Hospice Care
- A Rare Condition or Disease
- Pain
  pain that is lasting longer than 2 weeks that is not adequately managed
- A Compassionate Use Board Approved Condition

A summarized version of these conditions with the use of medical cannabis is listed here. For a more detailed version of these qualifying medical conditions and the use of medical cannabis, please refer to the Center for Medical Cannabis website to find the individual conditions list.

***Note**: As always, in the event of significant side effects, stop use of medical cannabis until side-effects have resolved, and then reduce to previous, best-tolerated dose.*

1) Pain Lasting Longer Than 2 Weeks – "Chronic Pain"

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 controlled clinical trials 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.[74] 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."*[75] 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.

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[74] 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 4-1)

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

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 adequately responded to treatment attempts using FDA-approved conventional treatments and interventions.

2) Chemotherapy-Induced Nausea and Vomiting (CINV)

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.

A 2016 Cochran review[76] 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.

3) Multiple Sclerosis or Persistent Debilitating Muscle Spasms

There is **substantial evidence** to support the conclusion that cannabis and cannabinoids are effective in improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids). This is based on supportive findings from good-quality studies with very few or no credible opposing findings.

There is **moderate evidence** to support the conclusion that cannabis or cannabinoids are effective in treating neuropathic pain in patients with multiple sclerosis.

There is **insufficient evidence** to support or refute the conclusion that cannabis or cannabinoids are effective in treating spasticity in patients with paralysis due to spinal cord injury.[77]

Multiple sclerosis (MS) is an autoimmune disease in which the immune system attacks myelin sheaths of neurons present in the central nervous system. Resulting damage to myelinated neurons of the central nervous system can result in sensory deficits, neuropathic pain (hyperalgesia and allodynia), motor weakness and paralysis involving both striated and smooth muscles, and upper motor neuron hyper-reflexia and spasticity. A number of biologic-based

[76] 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.

[77] 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.

disease modifying agents, immune antagonists, and symptom-based therapies are approved for the treatment of this chronic and often progressive debilitating disorder.

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

5) Epilepsy/Debilitating Seizures

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. Individuals seeking medical cannabis for management of epilepsy typically have problems with breakthrough seizures despite attempts using multiple AED's and combinations of AED's, or have experienced significant side-effects from AED's and want to try alternative treatments.[78]

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.

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.

6) Persistent Nausea and Vomiting/Cachexia

7) Post-traumatic Stress Disorder (PTSD):

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

[78] 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.

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.

8) Crohn's or Ulcerative Colitis

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

The effects of cannabis and cannabidiol on ulcerative colitis 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.

For patients with Crohn's Disease 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 Crohn's Disease who use cannabis.

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.

9) Cancer

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.*

10) HIV or AIDS

11) Amyotrophic Lateral Sclerosis

There is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are an effective or ineffective treatment for amyotrophic lateral sclerosis (ALS).

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 in the treatment of ALS cannot be made. However, because of the bleak prognosis for patients with ALS, a therapeutic trial of medical cannabis in patients with ALS may be reasonable.

12) Autism

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).

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 phytocannabinoids 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

13) Alzheimer's disease

There is insufficient evidence to support or refute the conclusion that medical cannabis or cannabinoids are an effective or ineffective treatment for Alzheimer's disease or symptoms of Alzheimer's disease and other forms of dementia.

14) Rare Conditions and Diseases

Currently, there are over 7000 rare conditions and disease which are those conditions affecting less than 2% of the US population and are not adequately managed with conventional treatment attempts.

Strength of evidence statements, recommendations for treatment, and medical cannabis dosing suggestions for rare conditions are beyond the scope of this document. Qualified healthcare providers should review pertinent literature if available prior to recommending cannabis for treatment of rare conditions.

16) Pharmacology – Dr. Fine's monograph

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