Utah Department of
Health & Human Services
Center for Medical Cannabis

Department of Health and Human Services

Guidance on the Suggested Use of Medical Cannabis

About this document: The following information 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 includes qualified medical providers, pharmacy medical providers, patients intending to use medical cannabis, and caregivers of patients intending to use medical cannabis.

About the authors: This document was authored by the Utah Cannabis Research Review Board and Department of Health and Human Services staff.

About the Utah Cannabis Research Review Board: The Cannabis Research Review Board, created in Utah Health Code 26-61-201, 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 products or an expanded cannabinoid product that was conducted under a study approved by an Institutional Review Board (IRB) or was conducted and approved by the federal government.

DISCLAIMER

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This document is a summary of available peer-reviewed literature concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. With the ongoing nature of cannabis and cannabinoid research, it is not meant to be complete or comprehensive and should be used as a limited 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. There is 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. This document includes warnings and risks related to the use of cannabis including cannabis use disorder, potentially irreversible brain damage/mental illness, and legal liability for DUI and potential for adverse work-related consequences.

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Definitions

Cannabidiol (CBD): a plant-derived cannabinoid that lacks intoxicating or psychoactive properties.

Cannabinoids: biologically active constituents of cannabis, or synthetic compounds that have affinity for, and activity at cannabinoid receptors (e.g. THC, CBD, Dronabinol, Nabilone).

Cannabis-based medicines or cannabis-derived medicines: medicinal cannabis extracts with defined or standardized cannabinoid content, e.g. nabiximols/Sativex (CBD+THC), cannabidiol/Epidiolex.

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 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Hillig & Mahlberg, 2004):

- Chemotype I - delta-9-tetrahydrocannabinol (THC)-predominant with THC:CBD ratio >10:1

- Chemotype II - significant quantities of both THC and CBD with THC:CBD ratio <10:1 and >2:10
- Chemotype III- cannabidiol (CBD)-predominant with THC:CBD ratio <2:10

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).

Entourage Effects: The presence of multiple cannabis compounds being present to create a unique benefit in the body (for more information on the entourage effect, refer to "Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects" by Dr. Ethan Russo).

Delta-9-tetrahydrocannbinol: the primary active component of cannabis that acts at the cannabinoid CB1 receptor to produce a wide-range of biological and behavioral responses (Cooper & Haney 2009).

Epidiolex®: an FDA-approved medication consisting of plant-derived highly purified cannabidiol (CBD), indicated for the treatment of certain types of seizures.

Full Spectrum: A cannabis product that contains a complete spectrum of the plant's compounds, preserving the total range of cannabinoids and terpenes of the cannabis plant. Not all cannabis extracts are considered full spectrum, those that are commonly known as full spectrum include live resin or high terpene full-spectrum extract (HT-F SE).

Herbal Cannabis: the whole plant or parts, or material from the whole plant, e.g. buds/flowers, resin, leaves.

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.

(1) Does NOT include any drug approved by the U.S. Food and Drug Administration (FDA)

(2) Does NOT include CBD-only products

Phytocannabinoid: cannabinoids derived from the plant (e.g. cannabinol (CBN), cannabidiol (CBD), tetrahydrocannabinol (THC), cannabigerol (CBG) and over 100 other known components).

Synthetic cannabinoid: cannabinoids made in laboratories.

Tetrahydrocannabinol (THC): a plant-derived cannabinoid that has psychoactive properties.

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:**

   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 (Schleider et al., 2019 & Tzadok et al., 2016).

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 different 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 (e.g. ingested) medical cannabis products – Chemotypes I and II (significant amounts of THC)**
   a. Bioavailability of orally administered THC and CBD may be increased when administered in conjunction with a fatty meal (Zgair et al., 2016).
   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 two 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

NOTE: *All patients using cannabis and providers recommending cannabis to patients should consider the warnings, precautions and adverse side effects listed in this document before beginning the use of cannabis or increasing dosages of current cannabis use.*

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 oral extracts with a THC:CBD ratio of 1:20 have been used in several clinical trials in Israel for the treatment of autism spectrum disorder and seizures. 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

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 (MacCallum & Russo, 2018):

Table 1. Administration factors in cannabis delivery methods

	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 localized symptoms
Cons	- Dexterity required to load vaporizer - Vaporizer costs - Some vaporizers are not very portable - More frequent dosing required	- Delayed onset of action - Rapid titration for acute symptoms is more difficult - Higher potential for first-time excessive dosing	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

	-Variable blood levels depending upon the depth and duration of inhalation	-Highly variable and poor bioavailability of CBD		

Table 1 Table adapted from Practical Considerations in Medical Cannabis Administration and Dosing (MacCallum & Russo, 2018)

a. **Topical dosing of medical cannabis:** No clinical studies have been published regarding the percutaneous absorption of cannabis-containing ointments, creams, or lotions (Health Canada, 2013). 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 transdermal in preclinical animal studies (Paudel et al., 2010). **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 (Swortwood et al., 2016). The air temperature in the chamber where the plant material is present is particularly important due to at least two separate mechanisms:

- 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) (Wang et al., 2016 & Lanz et al., 2016). 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 (Wang et al., 2016) and complete decarboxylation of all THCA and CBDA may be 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.

- The vaporizer temperature set point also influences what portion of individual cannabinoids and terpenoids get vaporized and inhaled due to the wide range of individual cannabinoid boiling point temperatures and terpenoid vapor pressures at any given temperature (Lovestead & Bruno, 2017; Haynes, 2016). 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.

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 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 (Lanz et al., 2016).

The amount of herbal cannabis administered by a heated vaporizer device required to achieve an inhaled dose of THC that would be comparable to an oral dose of synthetic THC (dronabinol), can be estimated from the table below that was extracted from an

Table 2. Amount of cannabis calculated to contain equivalent amounts of THC to dronabinol (2.5 to 60 mg).

inhaled/smoked cannabis dosing article (Carter et al., 2004).

% of THC in cannabis	Amount of cannabis (g) required to obtain:			
	2.5 mg of THC	10 mg of THC	30 mg of THC	60 mg of THC
5%	0.60	1.24	3.70	7.40
10%	0.30	0.62	1.85	3.70
15%	0.16	0.41	1.23	2.46
20%	0.10	0.31	0.93	1.86
25%	0.08	0.25	0.75	1.50
30%	0.05	0.20	0.62	1.24

Table 2. Table adapted from Medical Cannabis Dosing: Rational Guidelines for Dosing (Carter et al., 2004)

The data in this table applies to inhaled cannabis administered by combustion (smoking) which is not allowed under Utah law. However, a separate clinical trial looking at THC bioavailability comparing smoked cannabis with vaporized whole flower cannabis showed similar results of about 50% bioavailability when using a Volcano® heated air vaporizer device with a temperature set point of 190°C (Abrams et al., 2007). Hence, it is reasonable to assume that the dosing comparisons in this table can be appropriately applied to the quantity of cannabis placed in a heated air vaporizer device assuming a set point temperature of 190°C and an heater air vaporizer device with function comparable to that of a Volcano® vaporizer device.

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 and titration recommendations that will be appropriate for all patients in all treatment circumstances.*

Figure 1. Treatment suggestions for QMPs and cannabis-naïve adult patients on starting and titrating the dosing of vaporized herbal cannabis.

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.

- 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 and the desired approximate dose needed based on experience with prior dosing.
- 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.
- 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.
- 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.
- 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.**
- Higher vaporizer setpoint temperatures (e.g. 210-230°C) will likely result in rapid and more complete decarboxylation of THCA and CBDA, 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.
- **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.**
- 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.

- 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. Unlike herbal cannabis

Figure 2. Treatment suggestions for QMPs and cannabis-naïve adult patients on starting and titrating the dosing of medical cannabis concentrates administered via a vape pen.

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.

Start LOW and go SLOW.

- 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.
- 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.
- 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.
- 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 of 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, the CDC believes that the majority of the cases of severe pulmonary injury and death are due to the presence of vitamin E acetate 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.**

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 sorts 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 above. There is no device-specific dose-finding studies for use of vape pens for the delivery of medical cannabis for the treatment of any specific disease.

Contraindications

1) **Pregnancy - Potential Adverse Effects of Maternal Cannabis Use on Fetal Development and Child/Adolescent Development** (See Health Canada, 2018 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 (Alpar et al., 2016).

   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 (Calvigioni et al., 2014). 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 (Gunn et al., 2016), 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 (Day et al., 1994; Fried & Watkinson, 1990; Fried et al., 1992*a*). In school-aged children, prenatal cannabis exposure was also associated with deficits in attention and presence of impulsivity and hyperactivity (Fried & Watkinson, 1992*b*). 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) (Fried & Watkinson, 1998; Richardson et al., 2002), with these deficits also appearing in 13- to 16-year olds (Fried & Watkinson, 2003) and 18- to 22-year olds (Smith et al., 2006). 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 (Volkow et al., 2017).

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.**

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 (Jaques et al., 2014; Baker et al., 2018). THC concentrations in breast milk in humans may be up to eight-fold higher than

that found in maternal blood (Perez-Weyes & Wall, 1982). In a case-control study 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 (Astely & Little, 1990). 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 (Health Canada, 2013). 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 (Mittleman & Mostofsky, 2011). Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% (Aronow & Cassidy, 1974) and has been associated with a five-fold increased risk of myocardial infarction in the first hour following smoking (Mittleman et al., 2001). This increased risk may be caused by a delta-9-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℃, formation of carbon monoxide.

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 (D'Souza et al., 2004). 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) (Marconi et al., 2016*a*; Di Forti et al., 2009). The risk of schizophrenia associated with cannabis use is especially high in individuals who have a personal or family history of schizophrenia (Radhakrishnan et al., 2014). 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 (Wilkinson et al., 2014).

Cannabis use is associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms (Marconi et al., 2016*b*). 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 (Schoeler et al., 2016). 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 (Wilkinson et al., 2014) 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

Patients using cannabis and providers recommending cannabis to patients should consider the possible effects of cannabis use listed below. A few of the acute effects of cannabis include euphoria, relaxation, dream-like states including vivid dreams, paradoxical insomnia, altered sensory perception and increased appetite (Candrey & Haney, 2009).

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 (Meier et al., 2012; Brumback et al., 2016; Morin et al., 2019). 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 (Wong & Wilens, 2017).

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

2) **Impaired Cognition** (Karlson; 2019)
   - Acute effects of cannabis use are established with strong evidence and include impairment of short-term memory, attention, concentration, executive functioning and visual perception (Health Canada, 2018).
   - 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 (Lenné et al., 2010).

- Some brain imaging studies associate regular (weekly or more frequent) cannabis use with structural changes in gray and white matter in different brain regions (Hartman et al., 2013).
- Early-onset use and use of high-potency, THC-predominant cannabis is associated with a higher degree of impairment (Hartman et al., 2015).
- 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 (Volkow et al., 2016).

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** (Neavyn et al., 2014).
- 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 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 (World Health Organization, 2020). The age of onset of cannabis use is inversely proportional to the incidence of cannabis use disorder (e.g. 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 (Sorensen et al., 2017).

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 (National Academies of Sciences, Engineering, and Medicine, 2017*a*). 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.

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 [e.g., 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 (Patel et al., 2019). 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)) (Tarang et al., 2020).

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 (FDA, 2006). Preclinical data in some animal studies and case reports suggest possible proconvulsant effect of THC but other case reports suggest possible anti-convulsant effects of THC (Rosenberga et al., 2017). Until better clinical data are available, high doses of THC should probably be avoided in individuals with seizure disorder, and THC-predominant cannabis (chemotype I) should be used with significant caution.

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 (Marconi et al., 2016*b*). 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 (Schoeler et al., 2016).

14) Bipolar and Other Mood Disorders

A 2015 systematic review and meta-analysis of six studies of bipolar disorder and cannabis use sampled a total of 2,391 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 (Gibbs et al., 2015). 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 threefold (Odds Ratio: 2.97; 95% CI: 1.80–4.90) increased risk for new onset of manic symptoms (Gibbs et al., 2015).

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 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) (Gobbi et al., 2019). 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 (Childs et al., 2017).

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 (Hancox et al., 2015). There is substantial evidence of a statistical association between cannabis smoking and worse respiratory symptoms and more frequent episodes of chronic bronchitis (National Academies of Sciences, Engineering, and Medicine, 2017*b*). 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 (National Academies of Sciences, Engineering, and Medicine, 2017*b*). 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** (Taylor et al., 2019). 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 twofold increase in the incidence of diabetic keto-acidosis compared to self-reported non-users (Akturk et al., 2019). 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 (Ehrenkranz & Levine, 2019). 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 marijuana use was associated with development of testicular germ cell tumors, although the strength of evidence was low. Evidence regarding other cancers was insufficient (Ghasemiesfe et al., 2019).

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 reactions from the use of cannabis may include, but are not limited to, fatigue, insomnia, diarrhea, nausea, potential for "hang-over," and decrease in appetite. For medical providers, determining a patient's use of cannabis before procedural sedation can be important for planning patient care and assessing both*

medication needs and possible risks related to increased dosage requirements during endoscopic procedures (Twardowski et al., 2019).

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 (Ghasemiesfe et al., 2019). 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 (MacCullum & Russo, 2018). 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 (Cox et al., 2018). **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 an extended version of cannabis drug interactions available on the Department of Health and Human Services website for medical cannabis (www.medicalcannabis.utah.gov). Useful resources on this topic include 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.

NOTE: *Patients taking blood thinners or medications with sedative effects should talk to their doctor before using 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:

- 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
- Multiple 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 two 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 Two Weeks – "Chronic Pain"**
   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 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 (National Academies of Sciences, Engineering, and Medicine, 2017*c*). 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* (National Academies of Sciences, Engineering, and Medicine, 2017*d*). 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 adequately responded to treatment attempts using FDA-approved conventional treatments and interventions (Health Canada, 2018).

2) **Chemotherapy-Induced Nausea and Vomiting (CINV)**
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.

A 2016 Cochran review 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 (Smith et al., 2015). 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.

Meta-analysis of trials using dronabinol (synthetic THC) suggests that low-moderate dosing of THC (7mg/m^2) to prevent CINV may be more effective than higher doses of THC or attempting to treat CINV once it is established (Plasse et al., 1991).

3) **Multiple Sclerosis or Persistent Debilitating Muscle Spasms**
Summary: There is s*ubstantial 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 (National Academies of Sciences, Engineering, and Medicine, 2017*d*).

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

The 2017 National Academy of Sciences and Engineering literature review on the medical effects of cannabis and cannabinoids concluded that there is conclusive evidence for patient-reported improvement in multiple sclerosis-related spasticity (National Academies of Sciences, Engineering, and Medicine, 2017*d*). An extensive literature review conducted by the government of Canada (Health Canada, 2013) 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 (Pryce et al., 2015) support the use of medical cannabis in the early treatment of MS. However, a single placebo-controlled study of pure synthetic THC (dronabinol) administered to 498 patients with chronic and progressive MS (Zajicek et al., 2013) failed to demonstrate an improvement in disability or neuropathology.

One cross-sectional study reported that prolonged use of ingested or inhaled cannabis was associated with poorer performance on various cognitive domains (e.g. information processing speed, working memory, executive function, and visuospatial perception) in patients with MS (Honarmand et al., 2011).

In summary, clinical evidence supports the use of medical cannabis for symptomatic treatment of MS-associated spasticity of both striated and smooth muscles, pain, and sleep disturbances in patients with MS. Preclinical data from MS models in animals suggest the possibility that medical cannabis may also be effective in MS as a disease-modifying agent and may have neuroprotective effects, but clinical trials using medical cannabis as a disease-modifying agent are lacking (Chiurchiù et al., 2018).

When recommending medical cannabis for treatment of MS, inform the patient of possible adverse reactions including the possibility of decreased cognitive performance associated with long-term use of cannabis, and do appropriate clinical monitoring of cognitive function.

For dosing guidance for treatment of MS, please refer to the general dosing suggestions at the beginning of this document.

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

Summary: **Although controlled clinical trial data are lacking, adjunctive use of medical cannabis may be helpful in managing a number of symptoms experienced by a patient suffering with a terminal condition and should probably be considered, especially when symptoms of a terminal condition are not adequately managed with conventional treatments or conventional treatments are not tolerated.**

Treatment of an individual with a terminal illness usually focuses on managing symptoms with the goal of improving quality of life. Symptom management may include efforts to control pain, improve sleep, manage nausea, reduce anxiety, and in extreme cases, manage agitation. There are uncontrolled observational data suggesting that medical cannabis can be used to successfully manage many of these symptoms (Bar-Sela et al., 2013).

One observational study out of Israel involved 2970 patients with various stages of different cancers (Schleider et al., 2018). Pain intensity levels in this study were initially reported as very high (8–10 out of 10 in the VAS scale) in over 50% of the patients while after 6 months of medical cannabis treatment < 5% of patients reported such high levels. Only 19% of patients reported good quality of life prior to treatment initiation while 69% reported good quality of life at 6 months ($p < 0.001$). In addition to improvement in management of pain, other reported improved symptoms were nausea and vomiting, sleep disorders, restlessness, anxiety and depression, pruritus, and headaches.

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 pure 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 anti-epileptic drugs and combinations of anti-epileptic drugs or have experienced significant side-effects from anti-epileptic drugs and want to try alternative treatments (Suarev et al., 2017).

Multiple case reports, dating back to the 19th century, describe the 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 (Rosenberg et al., 2015). 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 (Gloss & Vickrey, 2014 & Zaheer et al., 2018). These reports as a rule, generally show either a decrease in seizure frequency or no effect. Based on mostly observational data with no controlled clinical trial data, cannabis-naïve patients with seizure disorder may respond favorably to CBD-predominant, low-THC medical cannabis (Chemotype III).

6) Persistent Nausea and Vomiting/Cachexia

Summary: **Unlike other qualifying conditions in the Utah Medical Cannabis Act, "nausea, vomiting and cachexia" (unexplained weight loss), are symptoms of an underlying condition or disease process and are not diagnoses by themselves. Patients presenting with these symptoms should undergo appropriate evaluation to determine the underlying disease process causing their symptoms.**

There is *limited evidence* that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS (AIDS wasting syndrome).

There is *insufficient evidence* to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia cachexia syndrome.

There is *insufficient evidence* to support or refute the conclusion that medical cannabis or cannabinoids are effective in the treatment of anorexia nervosa.

A systematic review published in 2015 identified four randomized controlled trials involving 255 patients with HIV/AIDS wasting syndrome. All four studies included dronabinol, with one investigating inhaled cannabis as well. Three trials were placebo-controlled, and one used the progestational agent, megestrol acetate, as the comparator. The review authors concluded that there was some evidence suggesting that cannabinoids were effective in causing weight gain in patients with HIV/AIDS (Whiting et al., 2015).

In cancer patients with anorexia as well as chemotherapy-induced nausea and vomiting, it is worth noting that cannabis is the only antiemetic that also has the effect of stimulating appetite. Although cannabis provides two potential benefits to the patient with cancer, use of cannabis for appetite stimulation does not always reverse cancer cachexia which is a function of energy wasting in addition to decreased food intake (Abrams & Guzman, 2015).

A 2006 randomized double-blind placebo-controlled trial involving 289 patients with cachexia due to advanced incurable cancer and an average life expectancy of three months compared the effects of three interventions: an oral cannabis extract containing THC and CBD, pure THC, and a placebo. The study did not demonstrate any significant differences in outcomes in appetite, quality of life, or cannabinoid-related toxicity. Improved appetite was reported in 73%, 58%, and 69% of patients receiving cannabis extract, THC, and placebo respectively (Strasser et al., 2006).

A 2002 randomized placebo-controlled study involving 469 patients with advanced cancer compared megestrol acetate, dronabinol (synthetic THC), and the use of both agents together in the treatment of cancer-related cachexia. Patients treated with megestrol acetate reported greater appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% ($P < .0001$) for appetite, and 11% versus 3% ($P < .02$) for > 10% baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight gain compared with megestrol acetate alone (Jatoi et al., 2002).

No studies have examined the use of cannabis on anorexia nervosa and limited information exists on the use of cannabinoids to treat anorexia nervosa. A small, randomized, crossover trial of oral Δ9-THC in 11 female anorexic patients suggested that THC produced a weight gain equivalent to the active placebo (diazepam). Three of the eleven patients administered Δ9-THC reported severe dysphoric reactions, withdrawing from the study (Gross et al., 1983).

NOTE: *Dosage of medical cannabis in the treatment of persistent anorexia, nausea and vomiting/cachexia must be individualized. The dose-response curve may not be linear, and some individuals may experience paradoxical problems with reduced appetite and other side-effects with higher doses of THC-predominant cannabis. Individuals using medical or recreational cannabis who present with new-onset, persistent, or episodic vomiting or significant weight loss, should be evaluated for the possibility of cannabis hyperemesis syndrome and, if applicable, pregnancy, or other medical conditions that may need to be diagnosed and treated with interventions besides medical cannabis.*

7) Post-Traumatic Stress Disorder (PTSD):

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 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 (Greer et al., 2014; Betthauser et al., 2015; Roitman et al., 2014), but there are also longitudinal 10-year data in 2,276 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 (Wilkinson et al., 2015). 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 (Bonn-Miller et al., 2007). These uncertainties and sometimes contradictory observations with negative outcomes suggest a need to exercise substantial caution when considering the use of medical cannabis as a treatment for 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 (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.

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.

NOTE: The above mentioned section is adapted from the Cochrane Database Systematic Reviews (Kafil et al., 2018a and Kafil et al., 2018b)

9) Cancer

Summary: There is substantial evidence to support the conclusion that medical cannabis or cannabinoids are effective in the treatment of chemotherapy-induced nausea and vomiting (CINV). See *CINV* section above.

There is **limited evidence** to support the conclusion that medical cannabis or cannabinoids may be effective in the treatment of pain due to complications from an invading neoplasm. A 2010 randomized double-blinded placebo-controlled study involving 177 patients with inadequately managed cancer pain despite appropriate use of opioids showed that use of orally-administered chemotype II medical cannabis extract resulted in significant reduction in pain compared to placebo. Use of chemotype I (THC-predominant) medical cannabis extract with little or no CBD for treatment of cancer-related pain was not statistically different from placebo (Johnson et al., 2010).

There is **insufficient evidence** to support or refute the conclusion that medical cannabis or cannabinoids may be effective in the treatment of neuropathic pain due to nerve damage from chemotherapy. Although medical cannabis has been

shown to be effective in relief of pain due to peripheral neuropathy from other causes, there is only one small crossover placebo-controlled trial involving 16 patients that used nabiximols oral-mucosal spray in the treatment of pain due to peripheral neuropathy caused by chemotherapy. Overall neuropathic pain scores in this study were not statistically different between active treatment and placebo, but 5 of the 16 patients had a significant reduction in reported pain with active treatment. (Lynch et al., 2014).

There is **insufficient evidence** to support or refute the conclusion that medical cannabis is effective in the treatment of cancer-associated cachexia (see the Persistent Nausea, Vomiting/Cachexia section above).

There is **insufficient evidence** to support the conclusion that medical cannabis or cannabinoids are effective or ineffective for the general treatment of malignant neoplasms in humans (National Academies of Sciences, Engineering, and Medicine, 2017d). There is, however, an increasing body of preclinical in-vitro and animal-model data suggesting direct anticancer effects of cannabinoids in some types of cancer (Rocha et al., 2014). Accumulating evidence from these vitro and/or pre-clinical studies suggests that antineoplastic effects of cannabinoids occur via dysregulation of the endocannabinoid system (Velasco et al., 2016 & Pisanti et al., 2009).

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 (Velasco et al., 2016).

The exact mechanism through which cannabinoids exert antineoplastic effects is not known, but in vitro data suggest that, cannabinoids induce cancer cell apoptosis (Velasco et al., 2016). Cannabinoids may also inhibit tumor angiogenesis, limit cancer cell migration and metastasis (Velasco et al., 2016). Cannabidiol has been shown to specifically inhibit cancer cell invasiveness in various preclinical animal models (Velasco et al., 2016). Caution is advised, however, as less frequently, tumor-promoting effects have also been described (Hart et al., 2004 & Cudaback et al., 2010). 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 of cannabinoids (Pisanti et al., 2009 & Hart et al., 2004 & Cudaback et al., 2010).

Antineoplastic properties of cannabinoids in vitro have typically been observed at very high doses that may not be achieved in clinical practice (Health Canada, 2018). The efficacy of cannabinoids as antitumor agents has not been sufficiently studied in clinical studies. The limited existing clinical studies of cannabinoids have been for the treatment of recurrent glioblastoma multiforme (GBM), an aggressive primary brain tumor with a poor prognosis (Guzman et al., 2006 & GW Pharmaceuticals, 2017).

Case reports describing patient-administered inhaled cannabis (among two children with pilocytic astrocytomas) or orally administered hemp oil (in one child with terminal acute lymphoblastic leukemia [ALL]) reported a regression in tumors and reduction in blast cell counts, respectively, during the time period of administration of the cannabinoids (Foroughi et al., 2011 & Singh et al., 2013). In a phase I/II trial involving 9 patients with GBM that had failed standard therapies including surgery, external-beam radiotherapy and in 2/9 patients adjuvant chemotherapy, Δ9 THC was administered intracranially directly into the tumor via a catheter that was surgically placed during a second surgery. The THC was infused on a daily basis for up to 10 days per cycle and some patients received multiple cycles (up to 6). 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 two patients survived for >one year (Guzman et al., 2006). Additional studies of cannabis (the nabiximols oromucosal spray, Sativex) for recurrent or newly diagnosed GBM are underway (GW Pharmaceuticals, 2017).

NOTE: *Open discussion should be encouraged between healthcare providers and patients regarding the potential use of medical cannabis in the management of cancer, symptoms due to cancer, and side-effects of chemotherapy. Some patients may consider the use of cannabis outside of the recommendations of their oncology team (Abrams, 2016). The decision to use cannabis or medical cannabis for management of chemotherapy side-effects, pain, or primary treatment/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

Summary: There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of symptoms of painful HIV-associated peripheral neuropathy.

There is *limited evidence* to support the conclusion that medical cannabis is effective in the treatment of HIV/AIDS wasting syndrome

Symptoms associated with HIV infection include pain, headaches, reduced appetite, nausea, vomiting, weight loss, diarrhea, constipation, depression and anxiety. These symptoms occur as both direct and indirect consequences of the HIV infection and as well as side effects of antiretroviral drugs used to treat the disease. Uncontrolled observational questionnaire data involving 143 patients with HIV who also used cannabis suggest substantial subjective benefit from the use of cannabis to manage many of the above symptoms (Woolridge et al., 2005).

Controlled clinical trials showing a positive benefit of the use of medical cannabis to treat symptoms related to HIV are limited to painful peripheral neuropathy, and HIV/AIDS wasting syndrome.

In a 2007 study, 55 patients with HIV-related painful sensory neuropathy were randomized in a blinded fashion to smoke a 0.9 gm cannabis cigarette three times per day over five days containing 3.6% THC (active treatment), or an identical-appearing 0.9 gm cannabis cigarette in which the THC had been chemically extracted (placebo). Patients receiving active treatment reported a 34% reduction in HIV-related neuropathic pain compared to 17% reduction for placebo. (Abrams et al., 2007).

A systematic review published in 2015 identified four randomized controlled trials involving 255 patients with HIV/AIDS wasting syndrome. All four studies included dronabinol, with one investigating inhaled cannabis as well. Three trials were placebo-controlled, and one used the progestational agent, megestrol acetate, as the comparator. The review authors concluded that there was some evidence suggesting that cannabinoids were effective in causing weight gain in patients with HIV/AIDS (Whiting et al., 2015).

11) Amyotrophic Lateral Sclerosis

Summary: 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

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 three recently-published short-duration uncontrolled observational studies from Israel that show possible benefit from the use of a CBD-predominant (chemotype III) cannabis extract in the treatment of ASD (Aran et al., 2018; Schleider et al., 2019; Barchal et al., 2019). Patients treated in these three studies included children and young adults (age range 4-22 years) with behavioral problems that were refractory to standard treatments. Treatment consisted of concentrated cannabis extract with a CBD:THC ratio of 20:1 administered sublingually and titrated up based on effect. Measured outcomes were generally favorable and included reductions in anxiety, disruptive behaviors, hyperactivity, rage attacks, self-injury, and seizures. Improvements were noted in mood, quality

of life, self-care, and sleep. Some patients did not experience clinical improvements. Reported adverse events were generally mild involving somnolence, appetite, and were non-life threatening.

These three 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 or CBD-enriched 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 three observational studies.

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 all 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 positive clinical trial data to support their use and 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 three reports from Israel) may be a helpful starting point:

- **Suggested chemotype:** Chemotype III, CBD predominant – 20:1 CBD: THC
- **Dose form:** Cannabis extract prepared for oral or sublingual use
- **Route:** Sublingual drops
- **Starting Dose:** CBD 15mg/THC 0.75mg administered sublingually three 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

Summary: 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.

Alzheimer's disease is the most common cause of dementia in older adults. It is a progressive and fatal disease with no effective treatment. Preclinical animal models of Alzheimer's disease 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 behaviors. However, the potential for acute side-effects and adverse cognitive effects of chronic cannabis use should be monitored when using medical cannabis in patients with Alzheimer's disease (Health Canada, 2018).

Dosing of medical cannabis in patients with Alzheimer's disease and other forms of dementia has not been adequately studied. Due to increased potential for adverse reactions related to age and other factors, use of high doses of chemotype I cannabis or THC-predominant medical cannabis, should probably be avoided and starting oral or sublingual doses of THC should be relatively low (<2.5mg/dose) (Shelef et al., 2016).

14) Rare Conditions and Diseases

Currently, there are more than 7,000 rare conditions and diseases 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.

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