Utah Department of Health

Guidance on the Suggested Use of Medical Cannabis

Epilepsy

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.

This document details the guidance on the use of medical cannabis for chronic pain. This document does not include general instructions on the use of medical cannabis, contraindications, warnings, precautions and adverse reactions to using cannabis and drug-to-drug interactions which could be found in the extended guidance document titled *Guidance on the Suggested Use of Medical Cannabis.* The extended guidance document can be found on the Utah Department of Health Center for Medical Cannabis website (www.medicalcannabis.utah.gov).

About the authors: This document was authored by the Utah Cannabinoid Product Board and Utah Department of Health staff.

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 Institutional Review Board (IRB) or was conducted and approved by the federal government.

DISCLAIMER

The following information on the use of medical cannabis serves as a suggested use guide for those participating in the Utah Medical Cannabis Program. This document has been vetted and approved by the Utah Cannabinoid Product Board under Utah Health Code 26-61-202.

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.

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. **Medical cannabis is NOT a first line therapy for most medical conditions.**

The information in this document is intended to help as far as available data allows 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 outcomes in patients using 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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IMPORTANT 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. To avoid unwanted psychoactive side effects, **"start low and go slow"** especially when using cannabis products for the first time or using new dosages or types of products.

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.

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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 (Suraev et al., 2017).

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.

Cannabidiol

A recently published review and meta-analysis of CBD's efficacy based upon 13 completed clinical trials and 9 clinical trials in progress concluded that CBD used in combination with prescription anti-seizure medications appears to decrease seizure frequency (Stockings et al.,

2018). In another study, CBD administration was shown to improve quality of life in patients with epilepsy without affecting seizure frequency or severity.

Based upon the safety profile of CBD and the weight of clinical evidence, use of CBD as adjuvant therapy in conjunction with prescription anticonvulsant medications in patients with poorly controlled epilepsy appears to be justified, but due to potential for drug-drug interactions, the use of CBD should be coordinated and monitored by the healthcare provider managing the epilepsy. If using artisanal hemp extracts as a source of CBD, batch testing results from independent laboratories should be consulted for CBD and THC content of oral and sublingual dose forms as well as vape pen cartridges. Artisanal hemp extract products labeled as "full spectrum" often contain small amounts of THC, usually less than 1 part of THC per 20 parts of CBD. However, depending on the dose of CBD, there may be clinically significant THC exposure which may or may not be desirable depending on individual patient factors.

Cannabidiol-enriched medical cannabis (chemotype III or equivalent) verses pure CBD
Robust data from well-designed blinded controlled clinical trials documenting the efficacy of medical cannabis containing THC for the treatment of epilepsy are lacking; however, there are reports including a 2018 review with meta-analysis of observational data (Pamplona et al., 2018) suggesting efficacy of cannabidiol-enriched medical cannabis (chemotype III) in the treatment of pediatric and adult epilepsy that may be more effective than purified CBD. In this meta-analysis involving a total of over 600 patients, the average daily dose of CBD ranged between 1 and 50 mg/kg, with treatment length from 3 to 12 months (mean 6.2 months). Two thirds of patients reported improvement in the frequency of seizures (399/622, 64%). There were more reports of improvement from patients treated with CBD-rich extracts (318/447, 71%) than patients treated with pure CBD (81/175, 46%), with statistical significance ($p < 0.0001$). Nevertheless, when the standard clinical threshold of a *"50% reduction or more in the frequency of seizures"* was applied, only 39% of the individuals were considered "responders," and there was no difference ($p = 0.52$) between treatments with CBD-rich extracts (122/330, 37%) and purified CBD (94/223, 42%). Patients treated with CBD-rich extracts reported substantially lower average daily doses of CBD (6.0 mg/kg/day) than those using purified CBD (25.3 mg/kg/day). The reports of mild adverse events (158/216, 76% vs. 148/447, 33%, $p < 0.001$) and severe adverse events (41/155, 26% vs. 23/328, 7%, $p < 0.0001$) were more frequent in products containing purified CBD than in CBD-rich extracts. The authors of this meta-analysis concluded that CBD-rich extracts seem to present a better therapeutic profile than purified CBD, at least in their population of patients with refractory epilepsy. It should be noted that these are observational data with no blinded controls, or placebo controls, hence the risk of significant bias due to lack of controls for other variables such as specific seizure types, disease refractoriness, self-reporting, self-reporting bias, and placebo effect cannot be excluded.

THC-predominant medical cannabis (chemotype I)
THC-predominant medical cannabis (chemotype I) has been anecdotally reported as an effective treatment of some people with epilepsy but has not been adequately studied in humans. Preclinical data in some animal models of epilepsy (Karler & Turkanis, 1980) and human observational data suggest that high doses of THC may have pro-convulsant effects (Russo 2017). THC-predominant medical cannabis should probably be considered in treatment-refractory patients only after a very careful risk/benefit analysis of all epilepsy treatment options,

and then only after failure of treatment attempts using pure CBD and CBD-predominant medical cannabis.

Medical Cannabis and Pediatric Epilepsy

One retrospective observational study (Tzadok et al., 2016) looked at 74 pediatric patients, (age range 1-18) with intractable epilepsy resistant to > 7 antiepileptic drugs. More than half of them had also failed a ketogenic diet, vagal nerve stimulator, or both. They were all started on a CBD-enriched medical cannabis extract concentrate dissolved in canola oil containing 20% CBD and 1% THC (20:1 ratio). Patients were treated and observed for a minimum of 3 months but many of them were observed for longer than that (average 6 months). CBD doses ranged from 1-20 mg CBD/kg/day but 81% of them responded to doses less than 10 mg CBD/kg/day. THC dose did not exceed 0.5 mg/kg/day and the maximum absolute dose of CBD was 270 mg per day. Seizure frequency was assessed by parental reports during clinic visits. Most parents (89%) reported a reduction in seizure frequency in their children: 18% reported 75-100% reduction, 34% reported a 50-75% reduction, 12% reported a 25-50% reduction and 19% reported <25% reduction in seizure frequency. Parents of 13 of the 74 patients (7%) reported aggravation of seizures which led to stopping the CBD-enriched medical cannabis extract in 5 patients. Other adverse events included somnolence/fatigue in 22% of patients and mild GI problems in 7%. Positive effects not related to seizure reduction were reported in 44/74 patients including improved behavior and alertness, improved sleep, and improved communication and motor skills.

There are no controlled clinical trials comparing pure CBD (Epidiolex) with CBD-predominant medical cannabis (chemotype III), or CBD-enriched medical cannabis, hence firm conclusions regarding efficacy and safety of CBD-predominant medical cannabis cannot be made at this time. In cases where FDA-approved AED's have been tried and found to be inadequate or not tolerated, and where pure CBD (Epidiolex) has limited FDA-approved indications, some parents of children with inadequately-managed epilepsy may ask a qualified medical provider to consider recommending the use of medical cannabis. Under current Utah law, children and adults under the age of 21, will have to be reviewed and approved on a case-by-case basis by the Compassionate Use Board prior to dispensing medical cannabis.

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

1. <u>Suboptimally-managed epilepsy is a substantial risk by itself for poor clinical outcomes and premature death.</u>
2. Based on clinical trials using pure CBD (Epidiolex), and observational data using CBD-predominant medical cannabis preparations in the treatment of epilepsy, a patient considering use of medical cannabis should probably begin with pure CBD, or chemotype III (CBD-predominant medical cannabis).
3. There is significant uncertainty regarding the clinical effects of THC and THC-predominant cannabis in the treatment of epilepsy in humans. Preclinical animal data suggest that THC may have both proconvulsant and anticonvulsant effects depending on dose, seizure model, and factors of seizure initiation versus seizure spread, and other studies suggest a "rebound" effect to THC with increased seizure activity with THC cessation (Gordon & Devinsky, 2001). Unlike purified CBD, there is insufficient evidence from controlled clinical trials to assess whether or not there are anti-

convulsant effects of Cannabis sativa, CBD:THC combinations, or oral cannabis extracts in the treatment of epilepsy *(Stockings et al., 2018).* However, there are observational reports that suggest the possibility of therapeutic synergy where relatively small amounts of THC are combined with higher doses of CBD to improve the efficacy of CBD in treatment-resistant epilepsy (Pamplona et al., 2018).

4. Until results of clinical trials dictate otherwise, adults being treated for epilepsy with oral medical cannabis preparations should generally avoid the use of high doses of THC or chemotype I medical cannabis products.
5. There are no controlled trials evaluating the potential for negative outcomes in the long-term daily administration of CBD, or CBD-predominant medical cannabis in children. Daily dosing of THC-predominant cannabis or high absolute doses of THC in children and adolescents are associated with a number of potential negative clinical outcomes outlined in other sections of this document and probably should be avoided in the treatment of epilepsy unless careful assessment of clinical benefit is deemed substantial enough to justify exposing the child/adolescent and adult to the substantial risks of high daily doses of THC and THC-predominant medical cannabis.
6. Stopping CBD or medical cannabis during the management of seizures should be done in a gradual fashion over several weeks if possible, to reduce the potential for negative clinical outcomes including clinical worsening of epilepsy.
7. To better understand the complexities encountered when using medical cannabis for the treatment of epilepsy, refer to a 2017 observational report (Sulak et al., 2017) entitled *"The current status of artisanal cannabis for the treatment of epilepsy in the United States"* found at https://www.ncbi.nlm.nih.gov/pubmed/28254350.

Dosing guidance for treatment of epilepsy in adults

1. When possible, patients with epilepsy that is refractory to FDA-approved AED's should be under the direct or consultative care of a neurologist with expertise in the diagnosis and treatment of seizure disorders.
2. To maintain relatively stable tissue levels needed to prevent seizures, dosing of CBD and CBD-predominant medical cannabis should be done at least twice daily using the oral or sublingual route if possible.
3. Careful pre-treatment review of potential drug-drug interactions should be undertaken. Clobazam and valproic acid, in particular, are two commonly used anti-seizure medications whose metabolic clearance may be affected by the co-administration of cannabinoids.
4. Documentation of therapeutic effects and side effects should be done to help guide dose adjustments
5. Based upon package insert labeling for Epidiolex, in patients >2 years of age with no liver disease, a suggested starting dosage for pure CBD is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, pure CBD can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).
6. There are no available clinical dose-finding data to guide dosing and titration of CBD-predominant medical cannabis in the treatment of epilepsy.

7. The dosing guidance outlined below is based on the concept of **"*start low and go slow*"** and limited observational reports using chemotype III cannabis (CBD-predominant) for treatment of epilepsy in children (Tzadok et al., 2016 & Sulak et al., 2017). This guidance assumes the following:
    - Use of a 20:1 CBD:THC oral or sublingual cannabis extracts (although other ratios of CBD:THC have been used in the treatment of epilepsy).
    - The effective dose range for 20:1 CBD:THC medical cannabis is 1-10 mg CBD/kg/day in greater that 80% of children with epilepsy.
    - A slow upward titration similar to that used in Epidiolex beginning at 50% of the lowest observed effective dose of 1 mg CBD/kg/day (i.e. 0.5 mg CBD/kg/day) should be considered (Tzadok et al., 2016).

    The above assumptions are based only on observational data and are not based on any controlled trials. Because of this limitation, the dosing guidance below including the 20:1 CBD:THC ratio may not be appropriate for all adult or pediatric patients with epilepsy in all treatment situations. This guidance is provided to give the qualified medical provider an idea of what might be a reasonable approach to starting and titrating medical cannabis for the treatment of epilepsy.

    Starting dose (based on CBD content of 20:1 CBD:THC oral medical cannabis):
    - Week 1: 0.5 mg CBD/kg/24 hours (administered in 2-3 divided doses per day)
    - Week 2: 1 mg CBD/kg/24 hours (administered in 2-3 divided doses per day)
    - Week 3+: Consider increasing total daily dose by 0.5 mg CBD/kg at weekly intervals if not experiencing side effects and still having breakthrough seizures.
    - Maximum daily dose of 20:1 CBD:THC oral medical cannabis in the treatment of epilepsy is unknown but caution should be exercised for doses exceeding 10mg CBD/kg/24 hours.

NOTE: *If titrating doses upwards results in adverse effects or worsening of seizures, reduce dose to the most recent best-tolerated dose (unless this dose is more than 0.5 mg CBD/kg/24 hours less than the current dose in which case would consider a slower reduction as below).*

If goal CBD dose provides minimal or no benefit to seizure control and/or the decision to stop CBD is made for other reasons (including consideration of other treatment options), the medication should be weaned slowly rather than abruptly stopped. A reduction in the daily dose by 0.5 mg/CBD/kg at weekly intervals (or a longer interval for a slower wean if clinically indicated) should be considered.

References

1. Gordon, E., & Devinsky, O. (2001). Alcohol and Marijuana: Effects on Epilepsy and Use by Patients with Epilepsy. Epilepsia, 42(10), 1266–1272. doi: 10.1046/j.1528-1157.2001.19301.x
2. Karler, R., & Turkanis, S. A. (1980). Subacute Cannabinoid Treatment: Anticonvulsant Activity And Withdrawal Excitability In Mice. British Journal of Pharmacology, 68(3), 479–484. doi: 10.1111/j.1476-5381.1980.tb14562.x
3. Pamplona, F. A., Silva, L. R. D., & Coan, A. C. (2018). Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. Frontiers in Neurology, 9. doi: 10.3389/fneur.2018.00759
4. Pamplona, F. A., Silva, L. R. D., & Coan, A. C. (2018). Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. Frontiers in Neurology, 9. doi: 10.3389/fneur.2018.00759
5. Russo, E. B. (2017). Cannabis and epilepsy: An ancient treatment returns to the fore. Epilepsy & Behavior, 70, 292–297. doi: 10.1016/j.yebeh.2016.09.040
6. Stockings, E., Zagic, D., Campbell, G., Weier, M., Hall, W. D., Nielsen, S., … Degenhardt, L. (2018). Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. Journal of Neurology, Neurosurgery & Psychiatry, 89(7), 741–753. doi: 10.1136/jnnp-2017-317168
7. Sulak, D., Saneto, R., & Goldstein, B. (2017). The current status of artisanal cannabis for the treatment of epilepsy in the United States. Epilepsy & Behavior, 70, 328–333. doi: 10.1016/j.yebeh.2016.12.032
8. Suraev, A. S., Todd, L., Bowen, M. T., Allsop, D. J., Mcgregor, I. S., Ireland, C., & Lintzeris, N. (2017). An Australian nationwide survey on medicinal cannabis use for epilepsy: History of antiepileptic drug treatment predicts medicinal cannabis use. Epilepsy & Behavior, 70, 334–340. doi: 10.1016/j.yebeh.2017.02.005
9. Tzadok, M., Uliel-Siboni, S., Linder, I., Kramer, U., Epstein, O., Menascu, S., … Ben-Zeev, B. (2016). CBD-enriched medical cannabis for intractable pediatric epilepsy. Seizure, 35, 41–44. doi: 10.1016/j.seizure.2016.01.004
10. Tzadok, M., Uliel-Siboni, S., Linder, I., Kramer, U., Epstein, O., Menascu, S., … Ben-Zeev, B. (2016). CBD-enriched medical cannabis for intractable pediatric epilepsy. Seizure, 35, 41–44. doi: 10.1016/j.seizure.2016.01.004