Utah Department of Health

UTAH DEPARTMENT OF HEALTH
Center for Medical Cannabis

Guidance on the Suggested Use of Medical Cannabis

Cancer and Chemotherapy-Induced Nausea and Vomiting

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 cancer and chemotherapy-induced nausea and vomiting (CINV). 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.

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 below.

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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 of the document titled *Guidance on the Suggested Use of Medical Cannabis* found at www.medicalcannabis.utah.gov).

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, 2017). 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.

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 chemotherapy-induced nausea and vomiting (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).

Dronabinol vs. ondansetron

In a study of 61 patients comparing ondansetron to dronabinol in the treatment of CINV, treatment response was similar with dronabinol (54%), ondansetron (58%), and combination therapy (47%) when compared with placebo (20%). Nausea absence was significantly greater in active treatment groups (dronabinol, 71%; ondansetron, 64%; combination therapy, 53%) versus placebo (15%; $p < 0.05$ vs. placebo for all) but there was no added benefit of combining dronabinol to ondansetron compared with either agent by itself. Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Active treatments were well-tolerated (Meiri et al., 2007).

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

1. From a patient perspective, CINV is one of the more distressing aspects of chemotherapy.
2. Preventing acute, delayed, and anticipatory CINV is preferable to attempts at treatment.
3. Oral cannabinoids (dronabinol and nabilone) have been shown to be more effective than placebo in prevention and treatment of acute and delayed CINV.
4. Established first-line antiemetic treatment regimens (e.g. 5-HT3 antagonists, neurokinin-1 antagonists, and corticosteroids) for a given chemotherapy intervention should be used unless contraindicated or not tolerated.

5. Dronabinol or nabilone (oral FDA-approved cannabinoids for treatment of CINV) can be used as monotherapy or in combination with other antiemetics and have the advantage over medical cannabis of possible insurance coverage.
6. There is no controlled study of artisanal medical cannabis preparations or inhaled herbal cannabis that shows superiority over current first-line CINV therapies, or oral FDA-approved cannabinoids (dronabinol and nabilone), but observational studies, and individual patient experience and anecdote suggest that some patients may have a beneficial response with inhaled cannabis or orally-ingested or sublingually administered preparations of medical cannabis as sole treatment or add-on therapy to standard antiemetic therapy in the treatment of CINV (Abrams, 20016).
7. Some observational data suggest that inhaled cannabis (smoked or vaporized) may be more useful in the treatment of CINV than oral dosage forms of synthetic THC and orally administered medical cannabis extracts (Musty & Rossi, 2001).
8. Prior patient experience with first-line therapies and inhaled and/or orally-ingested forms of medical cannabis should be taken into consideration when recommending treatment of CINV using medical cannabis.
9. There are problems with variable absorption and bioavailability with all forms of medical cannabis, especially orally-ingested products taken on an empty stomach with no food, or taken orally during active nausea and vomiting.
10. The antiemetic dose-response curve for use of cannabinoids in the treatment of CINV has not been studied but may not be linear, meaning escalation of dose may or may not result in improved therapeutic response and in some cases, dose escalation could hypothetically result in worsening symptoms of CINV.
11. **Always check for drug-drug interactions** prior using medical cannabis – THC and CBD can affect serum levels of chemotherapeutic agents and other medications metabolized by several of the cytochrome P450 enzymes (See Drug Interactions section of the document titled *Guidance on the Suggested Use of Medical Cannabis* found at www.medicalcannabis.utah.gov).

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

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

1. Start with 5 mg/m^2 THC equivalent, administered 1 to 3 hours prior to the administration of chemotherapy and then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses per day.
2. In elderly patients, and those with unstable vital signs or co-occurring cardiovascular problems, consider initiating THC equivalent at 2.5 mg/m^2 once daily 1 to 3 hours prior

to chemotherapy to reduce the risk of CNS symptoms and cardiovascular adverse outcomes.

3. The dosage can be titrated to clinical response during a chemotherapy cycle or subsequent cycles, based upon initial response, as tolerated to achieve a clinical effect, in increments of 2.5 mg/m^2.
4. The maximum dosage of THC equivalent should not exceed 15 mg/m^2 **per dose** for 4 to 6 doses per day.
5. **Adverse reactions are dose-related and psychiatric symptoms increase significantly at higher and maximal dosages.**
6. Monitor patients for adverse reactions and consider decreasing the dose to 2.5 mg once daily 1 to 3 hours prior to chemotherapy to reduce the risk of CNS adverse reactions.

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

These dosing suggestions are based on dronabinol and do not take into consideration variations in bioavailability or any possible additional pharmacodynamic effects or side-effects of medical cannabis extracts due to possible therapeutic synergy related to other cannabinoids and terpenoids that may be present in a given oral or sublingual medical cannabis preparation. Although there are no clinical trial results and very limited observational data in humans, preclinical animal data suggest that it is possible that cannabinoids in addition to decarboxylated Δ-9 THC may have significant clinical effects on CINV symptoms in humans.

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

References

1. Abrams, D. (2016). Integrating cannabis into clinical cancer care. Current Oncology, 23, 8. doi: 10.3747/co.23.3099
2. Cudaback, E., Marrs, W., Moeller, T., & Stella, N. (2010). The Expression Level of CB1 and CB2 Receptors Determines Their Efficacy at Inducing Apoptosis in Astrocytomas. PLoS ONE, 5(1). doi: 10.1371/journal.pone.0008702
3. Foroughi, M., Hendson, G., Sargent, M. A., & Steinbok, P. (2011). Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas—possible role of Cannabis inhalation. Childs Nervous System, 27(4), 671–679. doi: 10.1007/s00381-011-1410-4
4. Guzmán, M., Duarte, M. J., Blázquez, C., Ravina, J., Rosa, M. C., Galve-Roperh, I., … González-Feria, L. (2006). A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. British Journal of Cancer, 95(2), 197–203. doi: 10.1038/sj.bjc.6603236
5. GW Pharmaceuticals: Cannabinoid Research & Medicines. (2017). Retrieved from https://www.gwpharm.com/healthcare-professionals/research/therapeutic-areas#
6. Hart, S., Fischer, O. M., & Ullrich, A. (2004). Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor α-Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor. Cancer Research, 64(6), 1943–1950. doi: 10.1158/0008-5472.can-03-3720
7. Health Canada. (2018). Information for Health Care Professionals - Cannabis (marihuana, marijuana) and the cannabinoids. Retrieved from https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf
8. Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D., Potts, R., & Fallon, M. T. (2010). Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain. Journal of Pain and Symptom Management, 39(2), 167–179. doi: 10.1016/j.jpainsymman.2009.06.008
9. Lynch, M. E., Cesar-Rittenberg, P., & Hohmann, A. G. (2014). A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain. Journal of Pain and Symptom Management, 47(1), 166–173. doi: 10.1016/j.jpainsymman.2013.02.018
10. Meiri, E., Jhangiani, H., Vredenburgh, J. J., Barbato, L. M., Carter, F. J., Yang, H.-M., & Baranowski, V. (2007). Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Current Medical Research and Opinion, 23(3), 533–543. doi: 10.1185/030079907x167525
11. Musty, R. E., & Rossi, R. (2001). Effects of Smoked Cannabis and Oral δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy. Journal of Cannabis Therapeutics, 1(1), 29–56. doi: 10.1300/j175v01n01_03
12. Pisanti, S., Malfitano, A. M., Grimaldi, C., Santoro, A., Gazzerro, P., Laezza, C., & Bifulco, M. (2009). Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. Best Practice & Research Clinical Endocrinology & Metabolism, 23(1), 117–131. doi: 10.1016/j.beem.2009.02.001

13. Pisanti, S., Malfitano, A. M., Grimaldi, C., Santoro, A., Gazzerro, P., Laezza, C., & Bifulco, M. (2009). Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. Best Practice & Research Clinical Endocrinology & Metabolism, 23(1), 117–131. doi: 10.1016/j.beem.2009.02.001
14. Plasse, T. F., Gorter, R. W., Krasnow, S. H., Lane, M., Shepard, K. V., & Wadleigh, R. G. (1991). Recent clinical experience with dronabinol. Pharmacology Biochemistry and Behavior, 40(3), 695–700. doi: 10.1016/0091-3057(91)90385-f
15. Rocha, F. C. M., Júnior, J. G. D. S., Stefano, S. C., & Silveira, D. X. D. (2014). Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. Journal of Neuro-Oncology, 116(1), 11–24. doi: 10.1007/s11060-013-1277-1
16. Singh, Y., & Bali, C. (2013). Cannabis Extract Treatment for Terminal Acute Lymphoblastic Leukemia with a Philadelphia Chromosome Mutation. Case Reports in Oncology, 6(3), 585–592. doi: 10.1159/000356446
17. Smith, L. A., Azariah, F., Lavender, V. T., Stoner, N. S., & Bettiol, S. (2015). Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews. doi: 10.1002/14651858.cd009464.pub2
18. The National Academies of Sciences, Engineering, and Medicine. (2017d). The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. doi: https://doi.org/10.17226/24625
19. Velasco, G., Hernández-Tiedra, S., Dávila, D., & Lorente, M. (2016). The use of cannabinoids as anticancer agents. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 64, 259–266. doi: 10.1016/j.pnpbp.2015.05.010