Utah Department of
Health & Human Services
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, 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 Department of Health and Human Services Center for Medical Cannabis website (www.medicalcannabis.utah.gov).

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: Under Utah Health Code 26-61-201, the Cannabis Research Review 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.

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Guidance: There is substantial evidence to support the conclusion that medical cannabis or cannabinoids are effective or ineffective treatments for cannabis-induced nausea and vomiting.

[a] Developed using level of evidence categories from the 2017 National Academies of Sciences, Engineering, and Medicine report on cannabis (National Academies of Sciences, Engineering, and Medicine, 2017d).

Important note: In the event of significant adverse effects, stop use of medical cannabis until adverse effects have resolved, and then reduce to previous, best-tolerated dose. To avoid unwanted psychoactive adverse effects, "start low and go slow", especially when using cannabis products for the first time or using new dosages or types of products.

Smoking cannabis is not permitted under the Utah health code. Any mention of smoking in this document refers to the method used for a particular study and is stated for your information only. The Department of Health and Human Services, the Cannabis Research Review Board, and the State of Utah do not promote smoking as a method of cannabis use.

There is **limited evidence** to support the conclusion that medical cannabis or cannabinoids may effectively treat 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 the use of orally-administered chemotype II medical cannabis extract resulted in a significant reduction in pain compared to placebo. Use of chemotype I (THC-predominant) medical cannabis extract with little or no CBD for treating cancer-related pain was not statistically different from the placebo (Johnson et al., 2010).

There is **insufficient evidence** to support or refute the conclusion that medical cannabis or cannabinoids may effectively treat neuropathic pain due to nerve damage from chemotherapy. Although medical cannabis has been shown to be effective in relieving 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 significantly reduced reported pain with active treatment. (Lynch et al., 2014). Three phases 3, randomized, double-blind, placebo-controlled trials examined adjunctive nabiximols spray (27 mg/mL THC: 25 mg/mL CBD starting at 1spray/day and titrated by one spray/day to a maximum of 10 sprays/day) among adults with advanced cancer and chronic pain despite optimal opioid therapy. These trials did not demonstrate a significant difference in change in average daily patient-reported

pain scores for nabiximols versus placebo. However, one trial demonstrated significant improvements in secondary quality-of-life outcomes, and the other two trials demonstrated some improvement in patient function, all favoring nabiximols. (Fallon et al., 2017; Lichtman et al. 2018)

There is **insufficient evidence** to support or refute the conclusion that medical cannabis is effective in treating 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 treating 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 the direct anticancer effects of cannabinoids in some types of cancer (Rocha et al., 2014). Accumulating evidence from these vitro and 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 several 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 unknown, but in vitro data suggest cannabinoids induce cancer cell apoptosis (Velasco et al., 2016). Cannabinoids may also inhibit tumor angiogenesis and 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). However, caution is advised, as tumor-promoting effects have been described less frequently (Hart et al., 2004 & Cudaback et al., 2010). The reason for this conflict is unknown, but it may be related to the achieved concentration of cannabinoids, the expression level of cannabinoid receptors, or the 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 treating 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 nine 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 daily 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 cancer management, 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 the 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 can 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**.**

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A 2016 Cochran review of 23 randomized controlled trials looking at cannabinoids for chemotherapy-induced nausea and vomiting (CINV) found that fewer people who received cannabis-based medicines experienced nausea and vomiting than those who received a 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 and conventional medicines, 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's perspective, CINV is one of the more distressing aspects of chemotherapy.
2. Preventing acute, delayed, and anticipatory CINV is preferable to attempt at treatment.
3. Oral cannabinoids (dronabinol and nabilone) have been shown to be more effective than placebo in preventing and treating 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 the 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). However, observational studies and individual patient experience and anecdotes suggest that some patients may have a beneficial response to inhaled cannabis or orally-ingested or sublingually administered preparations of medical cannabis as the 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 treating 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 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 the use of cannabinoids in the treatment of CINV has not been studied. However, it may not be linear, meaning escalation of dose may or may not result in improved therapeutic response. In some cases, dose escalation could hypothetically result in worsening symptoms of CINV.
11. **Always check for drug-drug interactions** prior to 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 treating 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 before 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 with unstable vital signs or co-occurring cardiovascular problems, consider initiating THC equivalent at 2.5 mg/m2 once daily, 1 to 3 hours before chemotherapy, to reduce the risk of CNS symptoms and adverse cardiovascular 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 before 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 clinical trials using actual medical cannabis preparations. They are intended only to be used as dosing suggestions for treating severe CINV that has not adequately responded to first line therapies.*

These dosing suggestions are based on dronabinol and do not consider 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 minimal 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 higher doses of THC in chemotypes I and II medical cannabis products. In cannabis naïve patients who are elderly or significantly compromised, THC equivalent doses lower than the above suggestions should be considered.

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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 Cannabis Research Review 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.**

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