STLM
Systematically Testing the Evidence on Marijuana

Cannabis for Chemotherapy Induced Nausea and Vomiting

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Nausea and vomiting are two of the most common side effects of chemotherapy, with over 75% of patients experiencing nausea and 30% experiencing vomiting with chemotherapy.[1] Despite advancements in anti-emetic and anti-nausea medications in recent decades, such as 5-HT3 antagonists, neurokinin-1 antagonists, and corticosteroids,[2] chemotherapy-induced nausea and vomiting (CINV) remain significantly distressing side effects.[3]

Antiemetic Properties of Cannabinoids

- Endogenous cannabinoids, known as endocannabinoids, are a class of neurotransmitters that produce an agonistic antiemetic effect. Endocannabinoids have treatment potential for CINV.
- Cannabinoids may be plant derived or pharmaceutically prepared. They exert their anti-emetic effect by inhibiting 5-HT3 (serotonin) receptors in the area postrema, which regulates vomiting. They also activate cannabinoid (CB1) receptors in the gastrointestinal tract through inhibitory G-protein-coupled receptor effects, resulting in decreased gastrointestinal motility.[4]

- The Food and Drug Administration (FDA) has approved the use of Dronabinol and Nabilone for the treatment of chemotherapy-induced nausea and vomiting after the failure of first line anti-emetics.

Efficacy of Cannabinoids Compared to Standard Antiemetics

There has been growing evidence for the efficacy of cannabinoid use for chemotherapy-induced nausea and vomiting:

- Previous Cochrane and systematic reviews revealed adult cancer patients are more likely to have complete absence of nausea or vomiting when they received synthetic cannabinoids compared with placebo.[5,6]

> Dronabinol and Nabilone are FDA-approved for this indication and should be considered for cancer patients who have failed standard antiemetic regimens.

- A recent systematic review found that cannabinoids are also used for management of CINV in children with cancer without serious adverse events.[7]
- Dronabinol (10-15mg/m2 six times daily) and nabilone (2mg twice daily), compared to prochlorperazine (10mg three times daily), a standard antiemetic, showed no difference in absence of nausea, vomiting, or both in the treatment of CINV; however, patients reported a preference for cannabinoids over prochlorperazine.[5]
- One randomized control trial (RCT) revealed dronabinol to be similarly effective to ondansetron for the treatment of delayed-onset CINV.[8]
- Another randomized control trial (RCT) revealed that a cannabinoid extract (THC/CBD) was an appropriate adjuvant agent to reduce CINV in patients with gynecologic cancer.[9]
- A systematic review revealed that using dronabinol (2.5mg) and nabilone (1-2mg) orally may be more effective than oral placebo, prochlorperazine (10mg), ondansetron (4-8mg), or intravenous metoclopramide (2mg/kg) in mitigating CINV.[10]
- An ongoing clinical trial is examining prophylactic treatment of CINV with 1:1 THC 2.5mg:CBD 2.5mg three times daily. Preliminary findings suggest this regimen was associated with less nausea and vomiting but additional side effects.[11,12]
- Some cannabinoid side effects may be beneficial to cancer patients, such as euphoria, sedation, and appetite stimulation per studies of patient self-report.[5]
- Patients have reported a preference for cannabinoids as an anti-emetic medication when receiving chemotherapy.[5]

Clinical Considerations

- The strongest evidence supports the use of synthetic endocannabinoids, including Dronabinol and Nabilone, rather than medical cannabis obtained at a dispensary.
- Clinicians may consider using the NCCN protocol for antiemetics in their approach of treating CINV, which includes the addition of oral Dronabinol (5-10mg) every 4-6 hours and oral Nabilone (1-2 mg) twice daily for breakthrough CINV management.[13]
- Notable adverse effects of cannabinoids include sedation, fever, sweating, and dry mouth even at low doses, and acute intoxication, tachycardia, and psychoses at higher doses or for those who are naïve to cannabinoids.[15]
- As many patients with cancer diagnoses are older adults, special care should be taken in utilizing cannabinoids for this population given the above adverse effects, particularly if they are cannabinoid naïve.
- Additional caution should be taken for patients who have a history of cannabis use disorder or other substance use disorder.[15,16]
- Though cannabis has anti-emetic effects at low doses, it can be pro-emetic at higher doses and can lead to cannabis hyperemesis syndrome. Clinicians should refrain from

prescribing endocannabinoids long-term and at doses higher than FDA guidelines to avoid this disorder.[17]

- There are a limited number of RCTs and studies with comparisons to newer antiemetic regimens, and further investigation into the efficacy of cannabinoids is needed. As many patients with cancer diagnoses are older adults, special care should be taken in utilizing cannabinoids for this population given the above adverse effects, particularly if they are cannabinoid-naïve.
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Society Recommendations

The National Comprehensive Cancer Network (NCCN) includes cannabinoids in their recommended antiemetic protocol as a breakthrough treatment for CINV.[13] The American Society for Clinical Oncology (ASCO) recommends that Dronabinol or Nabilone, both synthetic tetrahydrocannabinols, be used to treat nausea and vomiting not controlled by standard antiemetic therapies.[14] Further information of each drug is in Table 1.

Table 1: Mechanism of Action and Prescribing Guidelines for Dronabinol and Nabilone

Drug	Mechanism of Action	Prescribing Guidelines
Dronabinol	Activates cannabinoid receptors CB1 and CB2. Activation of the CB1 receptor produces cannabis-like effects on psyche and circulation, whereas activation of the CB2 receptor does not. Dronabinol has approximately equal affinity for the CB1 and CB2 receptors.	Capsules: 5 mg/m2 administered 1 to 3 hours before chemotherapy, then give 5 mg/m2/dose every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day; increase dose in increments of 2.5 mg/m2 based on response and tolerability. Maximum: 15 mg/m2/dose. Oral solution: Initial: 4.2 mg/m2 (rounded to the nearest 0.1 mg increment [or to the nearest 0.1 mL measurable increment on the calibrated oral dosing syringe]) 1 to 3 hours prior to chemotherapy and then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day. Titrate dose in 2.1 mg/m2 increments (during a cycle or in subsequent cycles) to clinical response. Maximum: 12.6 mg/m2/dose and 4 to 6 doses/day.
Nabilone	Antiemetic activity may be due to effect on cannabinoid receptors (CB1) within the central nervous system.	Oral: Initial: 1 to 2 mg twice daily; begin with the lower dose in the range and increase if needed; may administer 2 or 3 times per day during the entire chemotherapy course; continue for up to 48 hours after the last chemotherapy dose. Maximum: 6 mg/day divided in 3 doses. A dose of 1 to 2 mg the night before chemotherapy may also be of benefit.

Bottom Line

Although the data on the underlying mechanisms of action and the efficacy of cannabinoids as antiemetics continue to be studied, they appear to be useful in the prophylaxis and management of chemotherapy-induced nausea and vomiting at lower doses. Dronabinol and Nabilone are FDA-approved for this indication and should be considered for cancer patients who have failed standard antiemetic regimens. Cancer patients should be counseled and screened regarding the potential beneficial and adverse side effects of cannabinoids before they are prescribed. Clinicians should be informed regarding the adverse side effects of cannabinoids and closely monitor cancer patients who choose to utilize cannabinoids for management of chemotherapy-induced nausea and vomiting.

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Suggested citation:
Nguyen CGT, Lo JO, Bruegl A. Cannabis for chemotherapy induced nausea and vomiting. The Systematically Testing the Evidence on Marijuana Project; 2022. Updated Nov. 17, 2023. https://www.cannabisevidence.org/clinician-resources/clinician-briefs/cannabis-for-CINV

Acknowledgments:
Thank you to Shannon Nugent, PhD and Jessica S. Merlin, MD, PhD, MBA for critically reviewing this document

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VA | U.S. Department of Veterans Affairs
Veterans Health Administration
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Funding provided by the U.S. Department of Veterans Affairs (VA) Office of Rural Health. Visit www.ruralhealth.va.gov to learn more.