

The Use of
CANNABINOIDS
in the Supportive Care
of Cancer Patients

By Vincent Maida, M.D., A.B.H.P.M.



As clinicians involved in the care of cancer patients, we face daily challenges in managing the symptoms of the disease and the side effects of various treatments. Indeed, the adverse effects of therapy can be as difficult to manage effectively as the disease process itself. Moreover, persistent symptoms and side effects impose a significant burden on the patient, restricting function, impacting negatively on quality of life (QOL), and perhaps leading to nonadherence and noncompliance with chemotherapy regimens, with resultant increased morbidity and mortality. We have a broad range of therapies and algorithms available to manage symptoms and side effects, but all too often these measures fail to provide adequate relief.

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The FDA (Food and Drug Administration)-approved cannabinoids, nabilone (Cesamet™) and dronabinol (Marinol®), offer clinicians an additional and unique pathway to effective symptom and side effect management. Nabilone is indicated for the treatment of the nausea and vomiting associated with chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. Dronabinol is indicated for the treatment of anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

The cannabinoids are characterized by complex modulatory activity in the central nervous system (CNS). Interaction between these agents and cannabinoid (CB) receptors, particularly CB1 receptors, in neural tissues is

largely responsible for their antiemetic effects. CB2 receptors are located mostly in immune tissue such as spleen, tonsil, mast cells, lymphocytes, and microglial cells. Cannabinoid agonism at CB2 receptors is associated with immunomodulatory effects. Nabilone is an oral synthetic Δ^9 -THC analogue and dronabinol is an oral formulation of Δ^9 -tetrahydrocannabinol (Δ^9 -THC). However, there are some important differences between the two in terms of duration of action and dosing. Nabilone exerts activity for eight to 12 hours, in contrast to four to six hours for dronabinol. Nabilone is given one to three hours before chemotherapy and two times daily for up to 48 hours afterward. While dronabinol is also given one to three hours prior to chemotherapy, repeat dosing occurs every two to four hours, for a total of four to six doses daily.

The Role of the Cannabinoids in Managing Chemotherapy-induced Nausea and Vomiting (CINV)

The National Institute of Health (NIH) recommends 5-HT₃ antagonists as the cornerstone of first-line antiemetic therapy, augmented by aprepitant (Emend®) and/or dexamethasone (Decadron®), depending on the emetogenicity of the chemotherapy regimen (Figure 1). The 5-HT₃ antagonists are largely ineffective for treating anticipatory and delayed CINV; however, more than one-third of patients receiving aprepitant-containing antiemetic therapy continue to experience nausea and vomiting during the acute phase. In patients who fail to respond to these regimens, adding an agent with a different mechanism of action may be the optimal approach to the management of CINV, according to



Figure 1. Recommended First-line Antiemetic Regimens for CINV

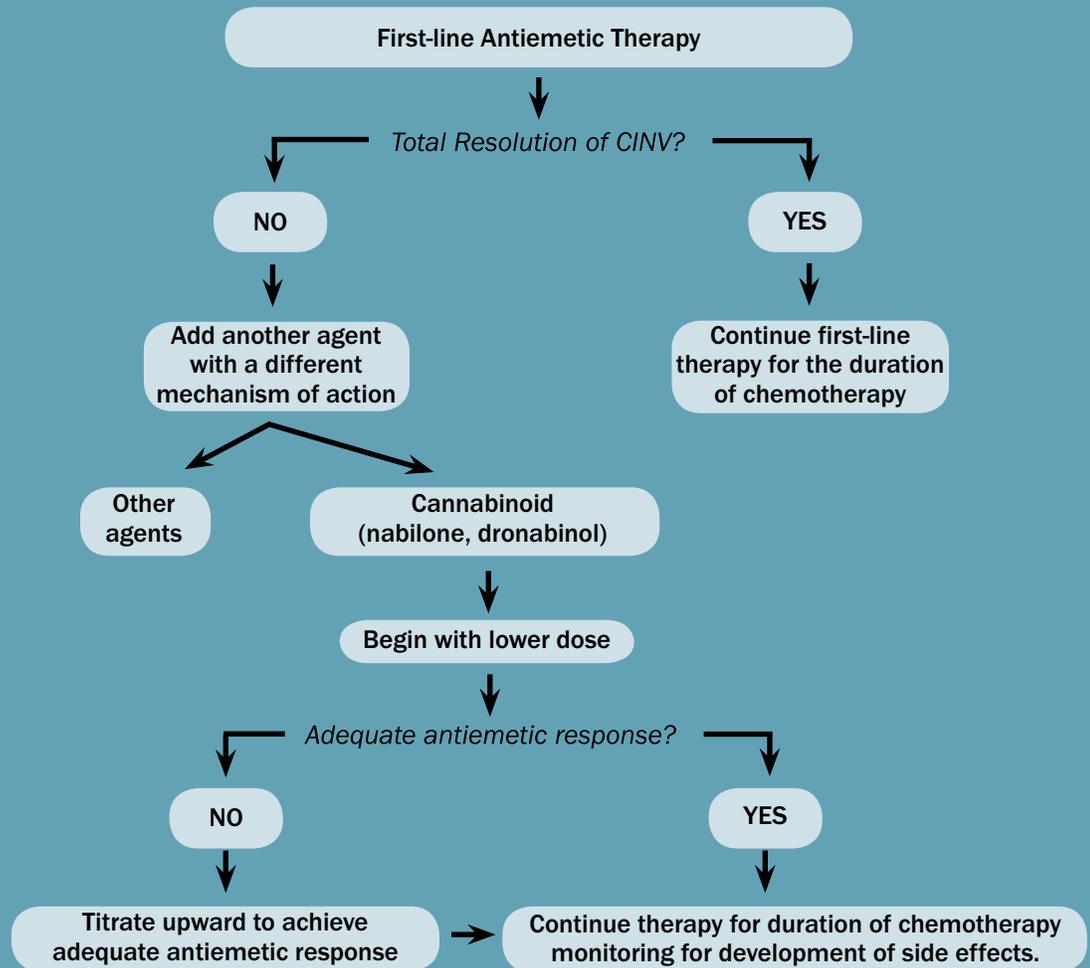
Risk of Emesis	Pre-chemotherapy	24-72 Hours Post-chemotherapy
High	5-HT3 antagonist+aprepitant+ dexamethasone followed by ?	Dexamethasone+aprepitant
Moderate	5-HT3 antagonist+dexamethasone followed by ?	Dexamethasone
Low	5-HT3 antagonist or dexamethasone as needed	As needed
Minimal	No preventive measures (risk <10%)	As needed

National Cancer Institute. *Nausea and Vomiting PDQ*. Last modified: 11/21/2005. Available at: <http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/healthprofessional>.

the NIH guidelines. Cannabinoids have been shown to effectively decrease the frequency of emesis and reduce the severity of nausea in cancer patients who are refractory to first-line regimens. In accordance with guidelines, these agents may be added to the existing regimen (Figure 2). To minimize the risk for side effects of therapy, nabilone should be initiated at the lower dose, i.e., one mg, and titrated upward until the desired patient response is achieved. The usual nabilone dosage is one to two mg twice daily.

It is important to continue nabilone therapy during the entire chemotherapy course and up to 48 hours after completion of treatment. Similar to nabilone, dronabinol should be initiated at the lowest dosage and titrated upward. Most patients respond to five mg, taken three or four times daily. Some patients may experience drowsiness with cannabinoid therapy; thus, taking nabilone one to two mg the evening before chemotherapy may be beneficial.

Figure 2. The Role of Cannabinoids in the Management of CINV



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Expanded Role for Cannabinoids in the Future

Another promising attribute of the cannabinoids relates to their intrinsic analgesic properties. A significant body of preclinical evidence clearly demonstrates analgesia mediated through anti-nociceptive, anti-hyperalgesic, and anti-inflammatory mechanisms. Such analgesic effects are mediated through both CB1 and CB2 agonism. In addition, a number of pre-clinical studies also have demonstrated synergistic sensory analgesia when combining opioids and cannabinoids. Importantly, such combination therapy may permit prescribing opioids at lower doses, thereby translating into reduced risk for opioid related side effects.

A cannabinoid in use in Europe and Canada, sativex, a buccal spray that is a combination of Δ^9 -THC and cannabidiol, received approval for conditional use as adjunctive treatment for the symptomatic relief of neuropathic pain in adults with multiple sclerosis (MS) in Canada in 2005. Data from a few published studies using other cannabinoids support this indication. In addition to planned U.S. studies with nabilone in patients with neuropathic pain resulting from cancer, diabetic neuropathy or MS, a U.S. Phase III clinical trial in MS with sativex is in the planning stage. These developments are important to the cancer patient, who is at risk of developing complex pain syndromes, as well as chemotherapy-induced peripheral neuropathic pain.



Addressing Concerns of Cannabinoid Therapy

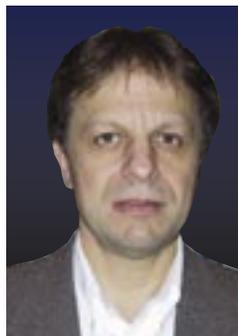
To ensure appropriate use of cannabinoids, similar to all medications, therapy should be individualized to meet the needs and limitations of each patient. In addition to patient response to other therapies, impact of CINV on the patient's functioning, QOL, and comorbidities, the patient history may indicate whether cannabinoid therapy is appropriate. Similar to opioid therapy, caution is warranted when considering the use of a cannabinoid in a patient with a history of substance abuse or a psychiatric disorder.

Informing the patient about expectations for treatment effects is also important. Patients receiving cannabinoids should be advised about the importance of avoiding alcohol,

psychotomimetic substances, and any drugs not prescribed by the physician. Concern regarding the potential for addiction might cause some clinicians to have reservations about prescribing a pharmaceutical cannabinoid. Importantly, true addiction, characterized by such aberrant behavior as loss of control, compulsive use, and continued use despite harm, is believed to occur only rarely in patients receiving these drugs, according to the Drug Enforcement Administration (DEA).

Summary

Supportive care of the cancer patient focuses on comprehensive treatment of the disease and management of comorbidities, symptoms of the disease, and side effects of treatment. Often, first-line therapies do not completely relieve symptoms or side effects. We are then confronted with deciding how to modify treatment to achieve the desired response. The cannabinoids employ unique mechanisms of action that provide additive antiemetic effects. Emerging data also support their observed analgesic and orexigenic effects. With appropriate, individualized, and emerging treatment modalities, the supportive care of the cancer patient may be optimized, translating into prolonged life expectancy and improved QOL. 🌐



Vincent Maida, M.D., A.B.H.P.M., serves as chief of palliative medicine at the William Osler Health Centre in Toronto, Canada. He is also assistant professor at the University of Toronto.