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# The emerging role of cannabinoid neuromodulators in symptom management

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A symposium, The Emerging Role of Cannabinoid Neuromodulators in Symptom Management, was held during the Multinational Association of Symptom Care in Cancer 18th International Symposium, June 23, 2006, in Toronto, Ontario, Canada. The following summarizes the presentations of the panel members.

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**Abstract** *Introduction:* The cannabinoids nabilone (Cesamet) and dronabinol (Marinol) are indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in cancer patients who have failed to respond adequately to conventional antiemetic therapy. *Discussion:* The endocannabinoid (CB) system interacts with numerous other systems and pharmaceutical cannabinoids target ubiquitous CB1 and CB2 receptors in the central nervous system and periphery, relieving nausea and vomiting and pain. *Summary:* The benefits of this novel class of medications in cancer may extend beyond CINV, as indicated by data from preclinical studies and animal models.

**Keywords** Cannabinoids · Chemotherapy-induced nausea and vomiting · CB1 and CB2 receptors · Pain

## Introduction

In 2000, there were 10 million new cancer cases globally and the incidence is projected to reach 15 million by 2020, an increase of 50% [24]. This unprecedented rise in cancer is due primarily to an aging population and worldwide trends in smoking prevalence. The impact of cancer on mortality is staggering. Malignant tumors in 2000 accounted for 12% of 56 million deaths [24]. Even in industrialized, more affluent nations, 50% of those diagnosed with cancer will die of the disease. In developing countries, 80% of people present with late stage, incurable disease.

From diagnosis through the course of treatment, cancer patients are at risk for a multitude of symptoms, including side effects from its treatment (Table 1) [1]. One or a combination of symptoms and treatment-related side effects cause distress and limit function. Unfortunately,

**Table 1** Symptoms of cancer and side effects of its treatment [1]

| Symptoms and side effects |
|---|
| Gastrointestinal problems |
| Nausea and vomiting (symptom of the disease, unknown etiology, post-operative nausea and vomiting [PONV] and chemotherapy-induced nausea and vomiting [CINV]) |
| Ascites |
| Diarrhea |
| Bowel obstruction |
| Pain |
| Metabolic abnormalities |
| Anorexia and malnutrition |
| Psychological problems |
| Anxiety, depression |
| Oral problems |
| Candida, treatment-induced mucositis, xerostomia |
| Respiratory problems |
| Dyspnea, cough, hemoptysis, hiccups |
| Skin problems |
| Fungating lesions, pressure ulcers, pruritus |
| Insomnia |
| Weakness and fatigue |
| Eaton–Lambert syndrome, neutropenia, anemia |

clinicians frequently fail to manage symptoms and side effects adequately. For example, two thirds of patients are not given antiemetics according to guidelines and pain is poorly treated in as many as four of every five cancer patients [9]. Managing symptoms and side effects is a complicated process that often involves multiple therapies. An effective strategy would be to target therapy such that one drug treats more than one symptom or treatment-related side effect.

The commercially available cannabinoids, nabilone (Cesamet) and dronabinol (Marinol), target ubiquitous cannabinoid (CB) receptors in the central (CB1) and peripheral (CB1 and CB2) nervous systems. Cannabinoids are established treatment for chemotherapy-induced nausea and vomiting (CINV) and AIDS-related anorexia [5, 12, 20]. $\Delta^9$-Tetrahydrocannabinol 27 mg/ml and cannabidiol 25 mg/ml ($^{N}$Sativex) received an Approval with Conditions from Health Canada in April 2005 as adjunctive therapy for neuropathic pain in multiple sclerosis [17]. Potential benefits in cancer patients extend beyond established uses to include analgesia, anti-tumor effects, mood elevation, muscle relaxation and relief from insomnia [22].

Understanding the mechanism of action of cannabinoids and reviewing what is currently known about symptom benefits in cancer and side effects of therapy can provide a pathway to their judicious use. Current studies assist in providing evidence for potential uses of this class of drugs in supportive care of cancer.

## The endogenous cannabinoid system: an overview

Though there are no silver bullets or panaceas in supportive oncology, using drugs that work through novel pathways and possess a broad range of benefits may allow effective treatment of multiple symptoms or side effects with one medication. There are three types of cannabinoids: botanical, which includes marijuana and hashish; endogenous, including anandamide, 2-arachidonylglycerol (2-AG) and palmitoylethanolamine (PEA); and the pharmaceutical cannabinoids nabilone (Cesamet), dronabinol (Marinol) [5] and $\Delta^9$-tetrahydrocannabinol 27 mg/ml and cannabidiol 25 mg/ml ($^{N}$Sativex) [11]. There is an abundance of scientific information on cannabinoids, which assists in elucidating various aspects of the pharmaceutical products, including their mechanism of action and established and potential uses in humans.

Endocannabinoid systems and signaling were identified in invertebrate species and have, therefore, survived 500 million years of human evolution [6]. Moreover, CB1 receptors are more than tenfold more prevalent in the brain than opioid receptors [4]. Two cannabinoid receptors were identified in humans—CB1 and CB2. CB1 receptors, which are found in the central nervous system (CNS) tissue, are neuromodulatory [8]. The CB2 receptors are located in non-neural tissue with the exception of some expression in the microglia. The highest concentration of these receptors, which are believed to be immunomodulatory, are located in the spleen. The affinity of the endogenous cannabinoid anandamide is weak for both CB1 and CB2 receptors; however, nabilone and dronabinol exhibit greater affinity for both receptors.

The cannabinoid system interacts with several other systems, indicating the broad spectrum of its activity (Table 2) [15]. While these data are derived from animals, potential application to humans is intriguing. For example, cannabinoid interaction with serotonergic receptors may explain, in part, the benefits of cannabinoids on migraine. Although the anti-inflammatory effects of cannabinoids are not well-recognized, they possess 20-fold more anti-inflammatory capacity than aspirin and about twofold more so than hydrocortisone. The potential for synergy between the cannabinoid system and the opioid system, specifically μ and κ opioid receptors, was also demonstrated [7, 18, 21]. In humans, such synergism might translate into improved efficacy at lower doses of both agents.

## Pharmacokinetics and metabolism of oral cannabinoids

The pharmacokinetics of nabilone (Cesamet) and dronabinol (Marinol) are similar with the exception of the number

**Table 2** Interaction between cannabinoids and other systems [15]

| System | Effects of interaction |
|---|---|
| Glutamate | Inhibit release from presynaptic sites |
| GABA | Inhibit release from presynaptic sites |
| Serotonin | Potentiate 5-$HT_{2A}$ and inhibit 5-$HT_{2A}$ |
| Adrenergic | CB1 synergy with $\alpha_2$-agonists |
| Opioid | Interact synergistically with μ+κ receptors |
| Dopamine (D) | Inhibit $D_1$ via CB1 |
| | Activate $D_2$ via CB1 |
| Neuroprotective | Direct anti-oxidant effects |
| | Reduce "excito-toxicity" via CB1 decrease in glutamate release |
| | Inhibits nerve growth factor |
| Anti-inflammatory | Inhibit prostaglandin $E_2$ synthesis |
| | CB1-induced decrease in calcitonin gene-related peptide and nerve growth factor |
| | CB2-induced decrease in histamine and bradykinin |

5-HT=5-hydroxytryptamine

of metabolites and the duration of action (Table 3) [5, 12]. Nabilone has substantially fewer metabolites, which might lower the patient's risk for toxicity and side effects. The duration of action of nabilone is substantially longer than that of dronabinol as well. Due to the longer duration of action, nabilone offers twice-daily dosing, while dronabinol is given every 4 to 6 h [5, 12]. This longer duration of action also might make nabilone a more useful medication for chronic therapy.

Cannabinoids are metabolized principally via the cytochrome P450 (CYP450) 2C9 isoenzyme [13]. Neither nabilone nor dronabinol induces CYP450 isoenzymes; however, dronabinol inhibits the CYP450 3A4 isoenzyme. Thus, the risk for interactions between nabilone and drugs metabolized via the CYP450 3A4 pathway is low. This is important because many of the chemotherapy drugs are metabolized via CYP450 3A4.

## The role of cannabinoids in emesis

Emesis is mediated by multiple neurotransmitters and receptors including serotonin, dopamine, substance P, histamine, endorphins, acetylcholine, gamma-aminobutyric acid (GABA) and cannabinoids [2]. To control vomiting, and perhaps particularly nausea, more than one receptor may need to be blocked. Unlike other systems, the endocannabinoid system works through a retrograde pathway to inhibit neurotransmitters. The term "omnineuromodulation" was used to describe the mechanism of action of pharmaceutical cannabinoids in emesis because they are thought to directly inhibit or modulate neurotransmitters via agonism of ubiquitous CB1 receptors located in the CNS and gut. Cannabinoids directly block emesis via agonism of CB1 receptors and indirectly by inhibiting other neurotransmitter release.

A substantial proportion of patients continue to experience CINV despite taking conventional antiemetic therapy. In a study in which patients received aprepitant, dexamethasone and ondansetron, more than one half (56%) experienced persistent CINV and one half (50%) reported delayed CINV (Fig. 1) [14]. Nausea and vomiting that breaks through standard prophylactic antiemetic therapy is a management challenge, the importance of which is underscored by the adverse impact of refractory CINV on quality of life and function [23]. A major concern is discontinuance of chemotherapy due to the negative effects of persistent CINV (Case Study: part 1 below).

**Table 3** Pharmacokinetic overview of cannabinoids [5, 12]

| | Nabilone (Cesamet) | Dronabinol (Marinol) |
|---|---|---|
| Oral dosing | 1–2 mg 1–3 h before chemotherapy and two times per day for up to 48 h afterwards | 5 $mg/m^2$ 1–3 h before chemotherapy and every 2–4 h afterwards for a total of 4–6 doses per day |
| Source | Synthetic $\Delta^9$-THC analog | Synthetic $\Delta^9$-THC |
| Formulation | Crystalline powder capsule | Capsule formulated with sesame oil, among other ingredients (contraindicated in patients with a hypersensitivity to sesame oil) |
| Onset of action (min) | 60–90 | 30–60 |
| Peak plasma concentrations ($T_{max}$) (h) | 2 | 2–4 |
| Duration of action (h) | 8–12 | 4–6 for psychoactive effects |

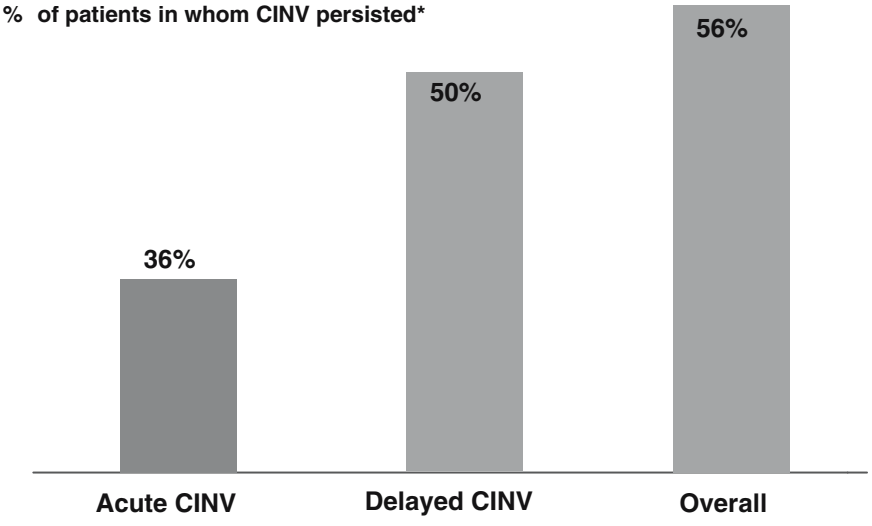


**Fig. 1** Nausea and vomiting persist in a substantial proportion of patients receiving first-line therapy [14]

## Case study: part 1

Challenges in managing symptoms of cancer therapy: persistent CINV

*Patient history*

Four years earlier, a 57-year-old woman was diagnosed as having breast cancer. She underwent right modified radical mastectomy and received 6 cycles of chemotherapy, which she tolerated well. Approximately 3 months ago, the patient complained of lower back "soreness", which had worsened over 2 weeks and some "clumsiness" of her left leg. While she was somewhat concerned, she attributed her symptoms to overtraining for the local marathon. However, 1 month later, the patient awakened with severe back pain and was unable to get out of bed. Her husband brought her to the emergency department (ED) where she was found to have bilateral weakness of both legs (greater in the left leg than in the right leg).

Magnetic resonance imaging (MRI) was performed and demonstrated an L1 pathologic fracture with a soft tissue mass impinging on the cauda equina. Despite surgery and radiation, which re-established neurological function, mild weakness remained. Bone scan and X-rays showed multiple lytic bony lesions consistent with metastatic disease. Work-up, including cerebral MRI, showed no organ disease. The patient began taxane-based chemotherapy 2 weeks later. She was taking conventional antiemetic therapy, zoledronic acid for bony metastases and opioid therapy to control her back pain.

*Effective management of persistent CINV*

Conventional antiemetic therapy was modified due to the patient's continued nausea and vomiting. During the fourth cycle of chemotherapy, modification in the antiemetic regimen failed to adequately control nausea and vomiting and the patient indicated that the side effect was prolonged for 3 days after chemotherapy. Although the patient had remained active throughout previous treatments, the nausea and vomiting associated with her current therapy restricted her activities. Despite limited activity, she had lost weight. During the visit, the patient was listless and voiced concern about the next chemotherapy cycle and her fear of the side effects. She questioned whether the chemotherapy was even worth undergoing, considering the impact of its side effects on her functioning and quality of life.

The cannabinoid, nabilone (Cesamet), was added to the patient's antiemetic regimen. She was given 1 mg the evening before chemotherapy and a second dose 3 h before its administration. She continued to receive nabilone after the subsequent chemotherapy cycle to control nausea and vomiting thought to be secondary to other medications she was taking. At the next visit, the patient reported feeling substantially better. Her spirits were improved and she had gained 3 lbs.

Cannabinoids control refractory CINV. A systematic analysis of 30 randomized, comparative trials of cannabinoids (oral nabilone, 16 trials; oral dronabinol, 11 trials; intramuscular levonatrodol, 1 trial) with placebo or other antiemetics (prochlorperazine, metoclopramide, chlorprom azine, haloperidol, domperidone, and alizapride) confirmed

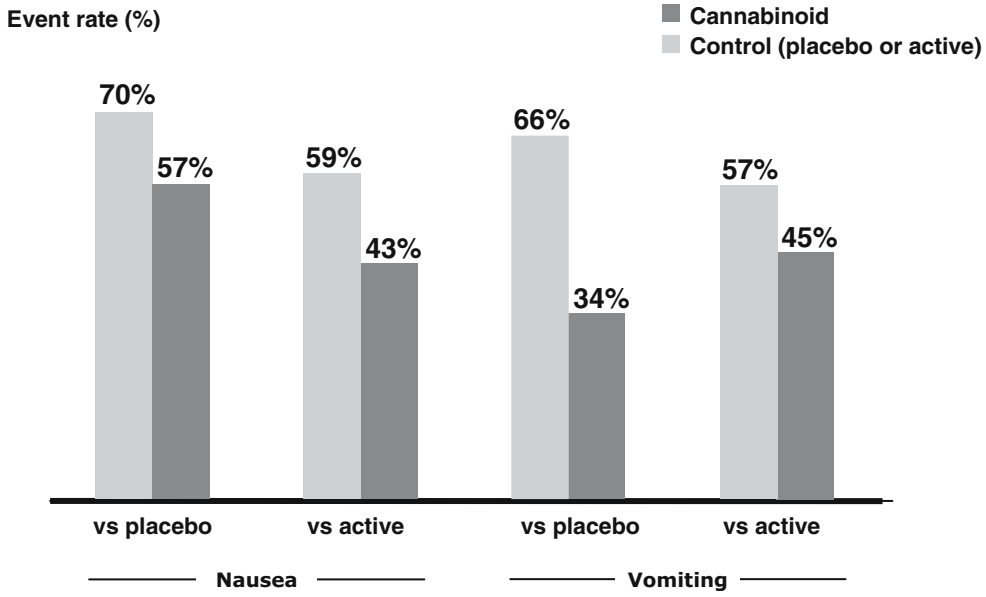


**Fig. 2** Control of nausea and vomiting with cannabinoids: a systematic review [20]

their efficacy in CINV [20]. Composite data of event rates (vomiting or nausea) found lower breakthrough nausea and vomiting with cannabinoids (Fig. 2). The number needed to treat (NNT) for complete control of nausea and vomiting compared with active controls was 6.4 and 8.0, respectively. Patients preferred cannabinoid therapy over both placebo and other antiemetics (NNT, 1.6 and 2.8, respectively).

## The role of cannabinoids in pain

Preclinical investigation has documented the benefits of both CB1 and CB2 receptor agonists in several types of pain (Table 4) [11]. These receptor agonists produce specific biochemical effects in the periphery and CNS in response to tissue injury or inflammation (Table 5) [11]. While much remains unknown about their mechanisms in humans, their analgesic activity in various types of pain and their effects on neurotransmitters provide anti-nociception through multiple pathways and implicate potential benefits in the treatment of one or more types of pain. As an example, CB1 induces a decrease in the nerve growth factor, a factor involved in neuroplasticity and neuropathic pain. Benefits of cannabinoid therapy were demonstrated in patients with multiple sclerosis-related central neuropathic pain in one study. The NNT for 50% pain relief was 3.5 [19].

**Table 4** Preclinical studies: effects of cannabinoids on various types of pain [11]

| Effects showed in preclinical studies | Type of pain | | | |
|---|---|---|---|---|
| | Acute | Visceral | Chronic | Neuropathic |
| Anti-nociceptive | – | – | – | – |
| Hyperalgesia | – | – | CB1 blocks pain facilitation from the RVM and blocks wind-up | Up-regulation of CB1 receptors<br>Animal studies support a role for CB2 receptors in peripheral tissues, microglia |
| Anti-inflammatory | – | – | CB2 receptors play an important role | CB2 receptors play an important role in immunocytes upregulated CB1 on a beta fibers, blocks allodynia at dorsal horn |
| Allodynia | – | | Due to the up-regulation of CB1 receptors | |
| Comparison with opioids | Comparable in potency and efficacy to coma codeine | | Greater potency and efficacy in both inflammatory and neuropathic pain | – |

– = Significant evidence
*RVM* Rostral ventromedial medulla

**Table 5** Effects of cannabinoid receptors in response to tissue injury or inflammation [11]

| CB1 effects | CB2 effects |
|---|---|
| ↓CGRP | ↓Mast cell degranulation |
| ↓NGF | ↓Histamine |
| ↓Plasma extravasation | ↓5-HT |
| ↓Hyperalgesia | ↓NGF sensitization |
| ↓Edema | ↓Neutrophil migration |
| | ↓NO production by macrophages |

CGRP=calcitonin gene-related peptide
5-HT=5-hydroxytryptamine
NGF=nerve growth factor
NO=nitric oxide

## Synergy between cannabinoids and opioids

Studies in animal models have revealed synergy between cannabinoids and opioids, as evidenced, in part, by cross-talk between both receptors [3]. If such synergy is translatable to humans, cannabinoids may be opioid-sparing, reduce the risk for adverse effects and improve opioid-resistant pain. Roberts et al. conducted a study examining the effect of $\Delta^9$-THC plus morphine on sensory pain [16]. In this double-blind, four-treatment, four-period, four-sequence, crossover study, 13 volunteers were given $\Delta^9$-THC 5 mg or placebo, followed by 0.02 mg/kg/IV morphine or placebo 90 min later. The subjects rated pain associated with thermal stimuli to the skin on three visual analogue scales (VAS) 15 min after the administration of morphine or placebo. This study demonstrated synergistic reduction in the affective component to pain with the combination of an opioid and cannabinoid with no serious or unexpected side effects.

While no randomized, controlled studies in pain management have used opioids with cannabinoids, anecdotal evidence suggests synergistic analgesia, particularly in patients with central and peripheral neuropathic pain (Case Study: part 2 below).

## Case study: part 2

Cannabinoids and pain management in the cancer patient

The patient complained of new-onset pain in her feet and lower legs, which began after the first cycle of taxane chemotherapy and grew more intense. She described the pain as "burning" and "tingling" and said it seemed to worsen at night. The pain, similar to the nausea and vomiting, was impacting her quality of life significantly. Because the pain worsened with walking, the patient was unable to do even light housekeeping or go shopping. Opioid therapy appeared to provide little relief for the patient's neuropathic pain.

Nabilone was titrated to 2 mg bid over 1 week. At her next visit, the patient reported significant decrease in her neuropathic pain. She was able to complete the full course of chemotherapy. At follow-up, metastatic disease was stable. The patient continued to take zoledronic acid, but the morphine was tapered and finally discontinued. She continued to take nabilone at the therapeutic dosage. Her attitude was upbeat and she reported a return to her usual activities.

The case study demonstrates the benefits of cannabinoids in the management of multiple symptoms. Nabilone controlled both treatment-related CINV and taxane-induced peripheral neuropathy. While it was not indicated for the treatment of neuropathic pain in cancer patients, nabilone alleviated her neuropathic pain. The relief of her symptoms and side effects allowed her to resume activities, resulted in weight gain and improved her outlook. It is important to note that she was able to complete the full course of chemotherapy and receive the benefits of tumor response.

## Evidence-based medicine: supporting the use of cannabinoids for symptom management

Indications for cannabinoids other than CINV and AIDS-related cachexia require evidence of their therapeutic benefits, tolerability and safety. Current studies evaluating the use of nabilone in cancer patients are looking for multiple benefits. These include, among others, improved sleep, pain, nausea and synergy with opioids. Phase IV studies, which are underway in the US, should elucidate the incremental benefits that are attained when adding nabilone to the treatment regimen.

## Nabilone (Cesamet) phase IV studies

A proof-of-principle investigation is being conducted in patients with refractory CINV. This multicenter study, involving 10 sites in the International Oncology Network (ION), will enroll 80 patients receiving moderately emetogenic chemotherapy for the first time. Patients with non-small cell lung cancer (paciltaxel plus carboplatin), breast cancer (cyclophosphamide plus doxorubicin) and colorectal cancer (FOLFOX) will be enrolled. During the first chemotherapy cycle, patients will complete a baseline VAS for nausea and pain and then record the number and time of emetic episodes, use of rescue medications, VAS for nausea and pain, side effects, and a quality-of-life questionnaire daily for 5 days and after chemotherapy. All patients will initially receive guideline-recommended antiemetic therapy, consisting of a 5-$HT_3$ antagonist plus

**Table 6** Primary and secondary endpoints of phase IV chemotherapy-induced nausea and vomiting study

| Endpoints of phase IV chemotherapy-induced nausea and vomiting |
|---|
| Primary |
| Complete response |
| No emesis and no rescue medication for 5 days post-chemotherapy |
| Secondary |
| Percentage of subjects with no: |
| Emesis |
| Nausea (VAS<5 mm)/significant nausea (VAS<25 mm) |
| Time to first emesis |
| Decrease in: |
| Pain |
| Analgesia |
| Quality of life (FLIC questionnaire) |

FLIC=functional living index-cancer

dexamethasone [10]. During cycle 2, nabilone, 1 mg 3 to 4 h before chemotherapy and 1 mg in the evening, will be added to the day 1 regimen of patients who experience at least one vomiting episode and/or significant nausea. On days 2 through 4, the nabilone dose will be increased by 1 mg/day up to 2 mg twice daily, as tolerated. Patients will complete the same questionnaires and rating scales as for cycle 1. The primary and secondary endpoints are listed in Table 6.

Three 15-week, phase IV, multicenter open-label pain studies will be conducted in specific patient populations. All three trials will have the same design, objective and methods (Table 7). Patients will be on stable doses of analgesics during a screening period, which will be followed by a 3-week titration period during which nabilone will be increased from 1 to 2 mg twice daily based upon response. The primary criterion for entry into these studies is pain severity of at least 40 mm on a 100-mm pain VAS. The primary endpoint of all three studies is the average pain score at target site. Secondary endpoints include:

- Worst pain score
- Pain at night score
- Quality of life
- Patient satisfaction
- Safety—adverse events and vital signs

**Table 7** Nabilone (Cesamet) pilot pain studies: design, objective and methods

| Nabilone (Cesamet) pain studies |
|---|
| Design |
| 15-week, phase IV, multicenter, open-label (n=23) |
| Objective |
| Safety and efficacy of nabilone |
| Methods |
| Nabilone 1 mg/day, titrated up to 2 mg bid based on patient response |
| Two-phased |
| Screening/pre-treatment |
| Treatment |

## Summary

The findings from these studies should help more fully elucidate the benefits, distinct advantages and any disadvantages of cannabinoids. Patient tolerability and safety will be assessed in all studies. This information will be instrumental in establishing the roles of cannabinoids in symptom management of the cancer patient.

**Table 8** Safety overview of cannabinoids [5, 12]

| Nabilone (Cesamet) | Dronabinol (Marinol) |
|---|---|
| Contraindications | |
| History of hypersensitivity to any cannabinoid | History of hypersensitivity to any cannabinoid or sesame oil |
| Most commonly occurring adverse effects | |
| Drowsiness | Asthenia |
| Vertigo | Palpitations |
| Dry mouth | Tachycardia |
| Euphoria | Vasodilatation/facial flush |
| Ataxia | Abdominal pain |
| Headache | Nausea |
| Concentration difficulties | Vomiting |
| | Amnesia |
| | Ataxia |
| | Confusion |
| | Depersonalization |
| | Dizziness |
| | Euphoria |
| | Paranoid reaction |
| | Somnolence |
| | Thinking abnormal |

Cannabinoids should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances

## Questions and comments

The symposium concluded with questions from the audience regarding the use of cannabinoids in symptom management. The responses of the panel and their insights are below.

Q: Are there any differences between nabilone (Cesamet) and dronabinol (Marinol) that would suggest the use of one over the other?

Three differences that might influence the decision-making are: the number of metabolites, duration of action and CYP450 inhibition. The longer duration of action associated with nabilone allows this medication to be given twice daily. Generally, the dosing strategy should be "start low and go slow", meaning begin therapy at 1 mg and titrate upward depending upon each patient's response. Generally, nabilone can be titrated quicker in younger vs older patients. It is important to note that all patients should be monitored initially—by healthcare professionals or other responsible adults who have received information on the drug. The lack of CYP450 inhibition associated with nabilone and no observation of any significant drug–drug interactions to date is important in cancer patients who are often receiving several different medications.

Q: What are the side effects/toxicities associated with cannabinoids?

A: It is important to keep in mind that all medications have side effects, including cannabinoids. The most common occurring side effects of these medications are drowsiness, vertigo, dry mouth, euphoria (feeling "high"), ataxia, headache and concentration difficulties (Table 8) [5, 12]. As there is a potential for hypotension and reflex tachycardia, these medications should be used with caution in elderly, frail patients and other at-risk patients. It is interesting to note that tolerance develops to the side effects, especially in patients with a history of cannabis experience, but not to the beneficial effects of cannabinoids.

Regarding the potential for psychotomimetic effects, Dr. Maida related his review of 25 years of cannabinoid use in Canada. Of more than 250,000 prescriptions, approximately only seven were associated with psychotomimetic effects and all of these resolved within 24 h.

Q: Are there patients who do not respond to cannabinoid therapy?

A: A minority of patients do not respond as favorably to cannabinoid therapy as do the majority. Generally, these patients are older or female, though there are no data to explain why. As with all medications, it is important to individualize treatment and select patients for drug therapy based on their needs and limitations.

Q: Should patients who are taking a cannabinoid for the management of refractory CINV drive a vehicle?

A: Due to the sedative effects of cannabinoids, it is best patients have someone else drive them to and from their chemotherapy appointments. Canadian studies, however, showed little effects of nabilone on driving.

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