

## Review Draft

# The Role of Cannabinoids for Control of Chemotherapy-Induced Nausea and Vomiting in Palliative Care

## Summary/Abstract

Vomiting and nausea are ranked among the top most distressing side effects of chemotherapy by cancer patients, yet appear to be underappreciated by care givers. Despite significant progress in recent years in developing more effective and better-tolerated measures to address chemotherapy-induced nausea and vomiting (CINV), a significant number of patients still develop CINV during later treatment phases. Cannabinoids have a mechanism of action that is unique among antiemetics and provides relief to patients who fail to respond adequately to conventional therapy. A trial is currently being conducted to directly address the issue of cannabinoid therapy in refractory CINV using nabilone. As illustrated by two case reports, these medications continue to maintain an important role in CINV treatment, and may also become increasingly important to palliative care in cancer patients in other roles.

## Introduction

One of the more important tasks in palliative care is achieving adequate control of symptoms associated with advanced disease and its treatment. Nausea and vomiting are common side effects of cancer chemotherapy that, for more than two decades, have been ranked by patients as two of the most distressing (Coates, 1983; Griffin, 1993). Despite this, evidence suggests that chemotherapy-induced nausea and vomiting (CINV) are not reported by patients, recognized by doctors, or treated to the extent that they occur (Grunberg, 2004). Unresolved, this can result in a decrease in both quality of life and treatment efficacy due to issues such as malnutrition, psychological stress, and non-compliance (Wiser, 2005; Neymark, 2005).

Patients who are under the age of 50, female, with a history of low alcohol consumption, motion sickness, and/or anxiety are at higher risk for CINV (Schwartzberg, 2006). Risk is also contingent on type and dose of chemotherapeutic agents used, with cisplatin considered to be the most emetogenic agent, inducing emesis in more than 90% of patients in the absence of preventive antiemetic therapy (Hesketh, 1997).

CINV has been classified into five categories (Table 1, The Five Types of Chemotherapy-Induced Nausea and Vomiting (CINV), from ONS Presentation5.5.06.ppt ) based on the time of onset and pattern of occurrence in relation to the time of chemotherapy administration (NCCN, 2006). Most research has concentrated on the acute phase that occurs within the first 24 hours after chemotherapy, and better control of acute emesis has been achieved with newer agents such as the serotonin 5-HT<sub>3</sub> receptor antagonists. However, delayed emesis, which occurs more than 24 hours after chemotherapy, is often not as well controlled with the antiemetics proven effective in the acute phase. Even after antiemetic treatment, nausea and vomiting have been observed in 60% and 50% of patients receiving highly emetogenic agents, respectively, and 52% and 28% of patients receiving moderately emetogenic agents, respectively (Grunberg, 2004). Therefore, the control of emesis in the delayed phase remains a therapeutic challenge.

## Cannabinoids for Treatment of CINV

### *History*

Medicinal interest in cannabis dates back as early as 2737 B.C., when it was prescribed for a variety of ailments, including pain relief for earaches and childbirth. The drug's popularity as a medicine spread throughout Asia, and by the late 18th century, American medical journals were recommending hemp seeds and roots for the treatment of inflamed skin, incontinence and venereal disease.

The therapeutic properties of cannabinoids continue to be of interest in the palliative care of oncology patients, with purported medical benefits that include appetite stimulation, alleviation of moderate neuropathic pain, and reduction of nausea and vomiting (Joy, 1999). Because the mechanism of action differs from other agents, cannabinoids may be used to benefit patients with CINV who either fail to respond or experience side effects using conventional agents. Further, synergistic effects have been observed between cannabinoids and prochlorperazine (Cunningham, 1985; Lane, 1991); combining cannabinoids with other antiemetic medications with non-overlapping toxicities may be an optimal approach to CINV management in some cases.

### *Pharmacology, Metabolism, and Mechanism of Action*

The constituent responsible for the pharmacologic activity of cannabis is  $\Delta^9$ -tetrahydrocannabinol, otherwise known as THC (Gaoni, 1964). THC is metabolized primarily in the liver through the cytochrome P450 2C9 isoenzyme (Bornheim, 1992), and the various metabolites are slowly excreted in the feces and urine. In blood plasma, THC is almost immediately bound to lipoproteins and subject to metabolism (Lemberger, 1971). With regular use, THC and its metabolites accumulate in the fat and brain (Kreuz, 1973).

The effects of cannabinoids are mediated by two types of receptors, CB1 and CB2 (Howlett, 1995). Both are G-protein-coupled receptors found in membranes of nerve cells. CB2 receptors are expressed exclusively in the periphery, primarily in immune function. CB1 receptors are located predominantly in the central nervous system; they constitute the only type of cannabinoid receptor expressed in the brain, where they are extraordinarily abundant. This abundance is greater than for most other G protein-coupled receptors, and ten times that of the *mu* opioid receptors responsible for the effects of morphine.

Specific, saturable and high affinity CB1 binding sites are widely spread in basal ganglia, cerebellum, hippocampus, and cerebral cortex; this distribution is consistent with the effects of cannabis on motor function, cognitive processes, memory, and senses (Iverson, 2003; Martin, 2004). The relative absence of cannabinoid receptors in the brainstem explains why high doses of cannabinoid drugs are rarely lethal (Iverson, 2003).

The presence of an endogenous ligand, or endocannabinoid, was validated more than a decade ago with the isolation of anandamide (arachidonoyl ethanolamide) (Devane, 1992) and later, 2-arachidonyl glycerol (2-AG) (Mechoulam, 1995). The information accumulated with regard to these two endocannabinoid families has led to the development of selective CB1 and CB2 receptor ligands. Two cannabinoid CB1 receptor agonists, dronabinol (Marinol®, Solvay) and nabilone (Cesamet™, Valeant), are currently approved in the United States for clinical use as appetite stimulants and/or antiemetics. Dronabinol, synthetic THC, has been available since 1985 for restricted medical use. Nabilone, a synthetic THC analogue, has been in use in Canada for more than 20 years and has recently been approved for emesis treatment

in the United States. (Table 2, Pharmacokinetic Overview of Available Cannabinoids, from ONS Presentation5.5.06.ppt)

In addition to metabolism by the 2C9 isoenzyme, both dronabinol and nabilone are metabolized to a lesser degree by 3A4. However, unlike dronabinol, nabilone has not been found to date to exert an inhibitory effect on any of the isoenzymes. It therefore competes metabolically with very few medications, including opioids (Nahas; Cannabinoid Metabolism slide, from ONS Presentation5.5.06.ppt).

#### *Therapeutic Role*

Nausea and vomiting are both produced by excitation of one or a combination of triggers in the gastrointestinal tract, brain stem, and higher brain centers (Figure 1, Neuroanatomy and Neurochemistry of Emesis from ONS Presentation5.5.06.ppt) (Miller, 1999). Numerous cannabinoid receptors are located in the nucleus of the solitary tract (NTS), which is important in the control of emesis (Herkenham, 1990). The exact neurophysiology of CINV remains unclear. The NTS receives information regarding emetics in the blood or cerebrospinal fluid from the chemoreceptor trigger zone, or from abdominal irritants via the vagal afferents. The NTS neurons then project to a brain stem central pattern generator, stimulating CINV. Cannabinoids are thought to control CINV through CB1 agonist activity in these areas, a mechanism unique among antiemetic agents.

Reports of nausea relief from recreational cannabis smokers receiving cancer chemotherapy lead to research that found oral THC statistically superior to placebo in cancer patients resistant to conventional anti-emetics (Sallan, 1975). Since then, collective studies have strongly supported a role for cannabinoids in the control of CINV. In a systematic review of 30 randomized, comparative studies of cannabinoids with placebo or other antiemetics, Tramer and colleagues found oral nabilone (16 studies) and dronabinol (13 studies) more effective in complete control of nausea or vomiting in a medium emetogenic setting than conventional antiemetics, including prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride (Figure 2, Control of Nausea and Vomiting with Cannabinoids, from ONS Presentation5.5.06.ppt) (Tramer, 2001). Furthermore, data gathered at the end of 18 crossover trials indicated that between 38% and 90% of patients preferred cannabinoid treatment. Side effects occurred more often with cannabinoid treatment; these were noted as potentially beneficial to the patient (such as a “high” sensation, euphoria, drowsiness/sedation/somnolence) or harmful (such as dizziness, dysphoria/depression, hallucination, paranoia, hypotension, and withdrawal).

To date, trials comparing cannabinoids with newer agents have not been conducted. Development of more effective drugs for the treatment of acute emesis from highly emetogenic chemotherapy, including selective antagonists for the 5-HT<sub>3</sub> receptor and the tachykinin receptor, make cannabinoids unpractical for first-line treatment (Van Belle, 2002). However, CINV remains a problem despite these therapeutic advances (Roscoe, 2000; Hickok, 2003), especially with respect to delayed nausea and emesis. Furthermore, effective management of acute and delayed nausea and vomiting is important in prevention of anticipatory nausea and vomiting.

Cannabinoids have historically remediated CINV in a substantial proportion of patients who are refractory after standard antiemetic treatment (Herman, 1977; Lucas, 1980; Cesamet PI, 2006). To directly address the issue of refractory CINV treatment, a multi-center, open-label,

sequential treatment study is currently being conducted with nabilone in 40 oncology patients receiving standard chemotherapy for the treatment of non-small cell lung cancer, breast cancer or colorectal cancer, and have failed to respond adequately to standard anti-emetic regimens. As secondary endpoints, the trial will evaluate the possible incremental benefit of adding nabilone to standard anti-emetic regimens to decrease pain and analgesic use, and the potential improvement in global quality of life, as measured by completed Functional Living Index – Cancer (FLIC) questionnaires and a five day diary to record nausea and pain, use of additional pain medications, and adverse events. The International Oncology Network will oversee the trial.

The following reports illustrate cases in which cannabinoid treatment successfully controlled unremediated severe nausea and vomiting during chemotherapy treatment.

### **Case Studies**

#### *Case Report #1 (“Marcia”, from ONS Presentation5.5.06.ppt)*

A 32-year old female under treatment for metastatic colon cancer became at risk for discontinuation of therapy due to inadequate relief of CINV. Her past medical history included severe hyperemesis gravidarum with several admissions for dehydration, chronic anxiety and depression, and childhood non-Hodgkin’s lymphoma, during which she experienced severe CINV with all regimens. Treatment for her current condition included hydromorphone contin 72 mg/day for pain, both in the thoracolumbar region (related to the retroperitoneal disease) and in the right upper quadrant (related to liver distention).

During initial chemotherapy, acute CINV was controlled with ondansetron and dexamethasone, but anticipatory and delayed nausea and vomiting remained problematic. Initiation of FOLFOX (oxaliplatin, 5-Fluorouracil, and leucovorin) caused unremediated acute, delayed, and anticipatory CINV, during which the level of distress experienced caused the patient to consider treatment discontinuation.

The patient was referred to a palliative care center and began treatment with nabilone 1 mg at bedtime for 7 days, then 1 mg twice daily. Total control of CINV was achieved with the regimen. Additional achievements included a 5 lb gain in weight over the course of 4 weeks, and a 50% reduction in opioid use.

#### *Case Report #2 (“Luke”, from ONS Presentation5.5.06.ppt)*

A 61 year old male under treatment for non-small cell lung cancer, which had metastasized to the mediastinum, bone, and liver, reported severe nausea. His past medical history included radiation therapy, asthma, migraine, right deep vein thrombosis, diabetes mellitus type II, left below knee amputation for diabetic neuropathic foot ulcers and gangrene, and phantom limb pain. For treatment of pain associated with phantom limb and brachial plexopathy, he was receiving hydromorphone contin 144 mg/day, nortriptyline 100 mg/day, neurontin 3600 mg/day, and a laxative regimen.

In relation to opioid treatment, the patient was experiencing severe side effects, including nausea, constipation, and sedation. Additional symptoms included severe anorexia and cachexia. Treatment with MIC (mitomycin, ifosfamide, and cisplatin) also produced CINV, with delayed nausea and vomiting more severe than acute.

The patient was placed on regimen of nabilone 1 mg at bedtime for 7 days, then 1mg twice daily thereafter. Within a week, the patient reported a 50% decrease in phantom limb pain and was able to decrease treatment with hydromorphone contin to 96 md/day. Nabilone was increased to 2 mg twice daily, in 4 weeks resulting in further decreases in pain, nausea and vomiting, constipation, and drowsiness.

## Conclusions

Cannabinoids continue to demonstrate an important therapeutic role in controlling CINV in patients failing to respond adequately to conventional antiemetic therapy. Currently, research is being conducted to directly address the use of nabilone as treatment in refractory CINV. As demonstrated by the discussed case reports, this is particularly relevant to patients in a palliative care setting, for whom quality of life is a primary consideration in treatment.

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Table 1: The Five Types of Chemotherapy-Induced Nausea and Vomiting (CINV)

Type of CINV	Characteristics
<b>Acute</b>	<ul style="list-style-type: none"> <li>◆ Usually occurs within minutes to several hours after chemotherapy administration</li> <li>◆ Commonly resolves within the first 24 hours</li> <li>◆ Intensity peaks after 5-6 hours</li> </ul>
<b>Delayed</b>	<ul style="list-style-type: none"> <li>◆ Develops &gt;24 hours after chemotherapy administration</li> <li>◆ Emesis associated with cisplatin peaks at 48-72 hours; can last 6-7 days</li> </ul>
<b>Anticipatory</b>	<ul style="list-style-type: none"> <li>◆ Occurs before next chemotherapy session after a negative experience with chemotherapy in the past</li> <li>◆ Nausea is more common than vomiting</li> </ul>
<b>Breakthrough</b>	<ul style="list-style-type: none"> <li>◆ Occurs despite prophylactic treatment and/or requires rescue therapy</li> </ul>
<b>Refractory</b>	<ul style="list-style-type: none"> <li>◆ Occurs during chemotherapy cycles after prophylaxis and/or rescue therapy have failed in earlier cycles</li> </ul>

Adapted from: National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. *Antiemesis*. Version 1.2005.

Figure 1: Neuroanatomy and Neurochemistry of Emesis

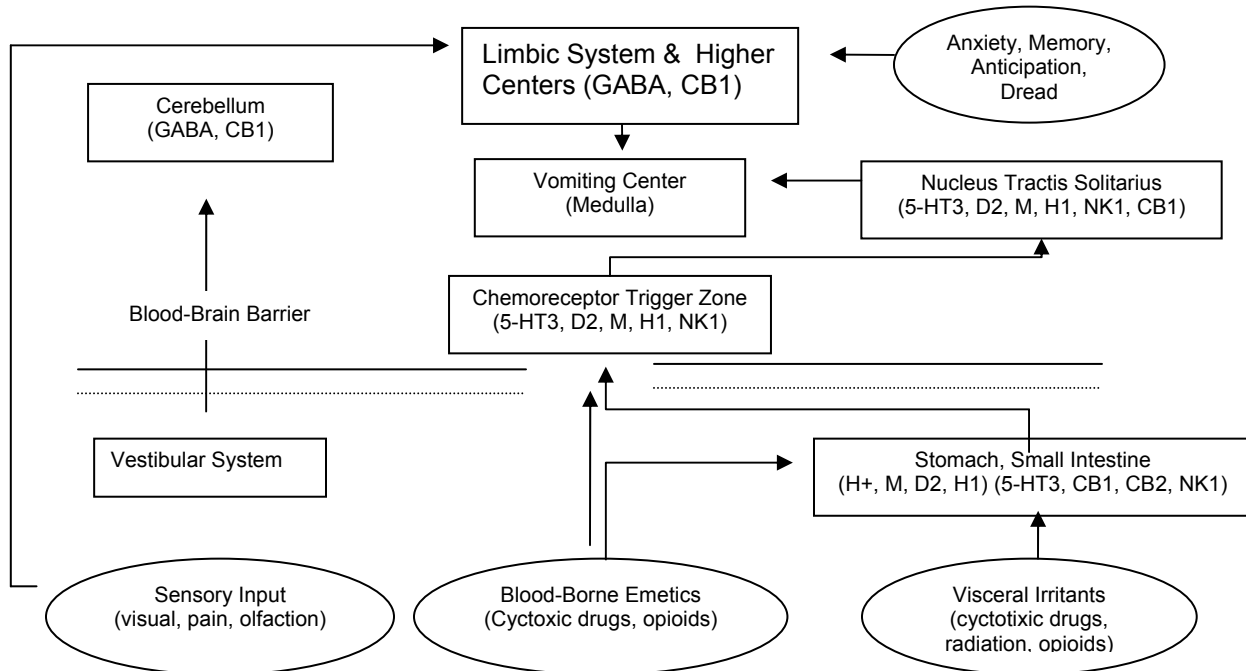


Figure 2, Control of Nausea and Vomiting with Cannabinoids

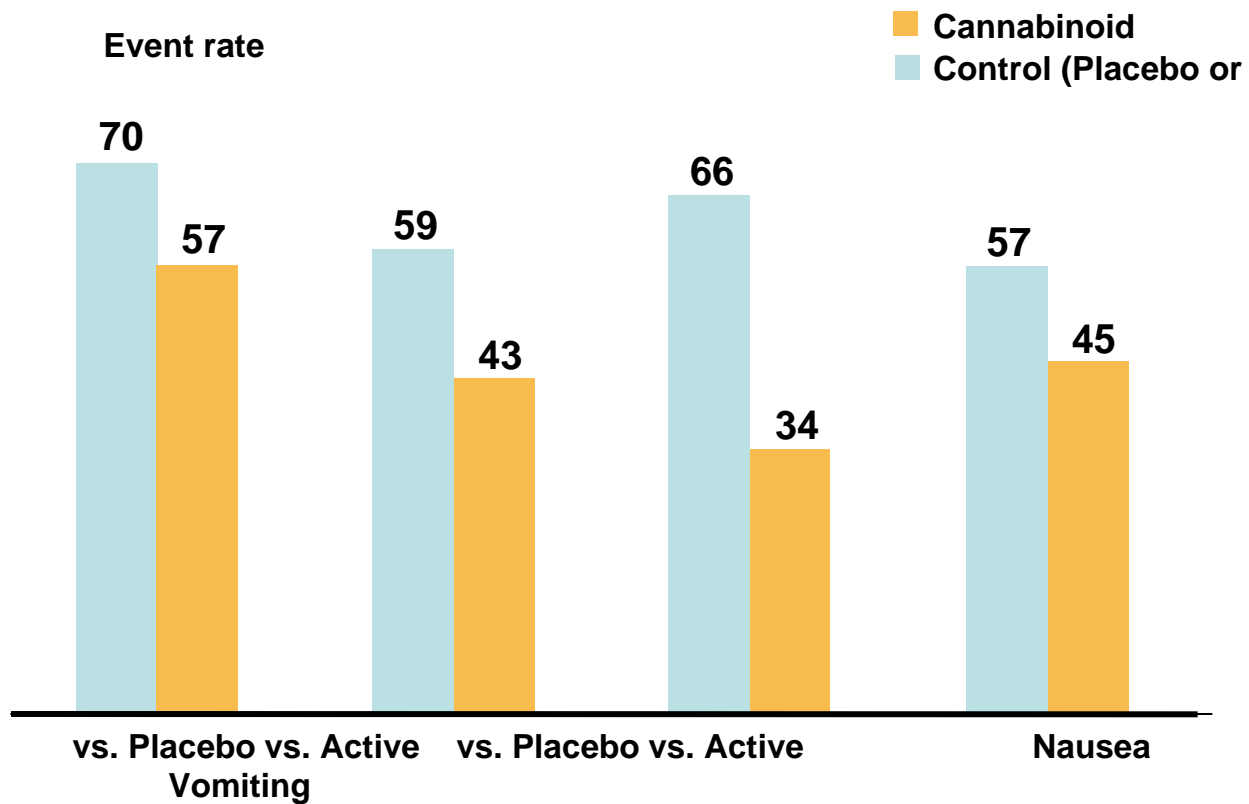


Table 2, Pharmacokinetic Overview of Available Cannabinoids

	<u>Nabilone</u>	<u>Dronabinol</u>	<u>Inhaled Marijuana</u>
<b>Source</b>	Synthetic cannabinoid (THC analogue)	Synthetic cannabinoid (D9-THC)	D9-THC + other cannabinoids
<b>No. of metabolites</b>	2	>21	>60
<b>Distribution volume</b>	Liposoluble (very large)	Liposoluble (very large)	Liposoluble (very large)
<b>Onset of action</b>	60-90 minutes	30-60 minutes	6-20 minutes
<b>Tmax</b>	2 hours	1-4 hours	½ to 2 hours
<b>Duration of action</b>	8-12 hours	4-6 hours	3-4 hours

<b>Half-life:</b>			
<b>Plasma</b>	2 hours	19-56 hours	44-59 hours
<b>Metabolites</b>	35 hours	49-53 hours	