Cannabinoids in the Treatment of Chemotherapy-Induced Nausea and Vomiting

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Abstract

Before the introduction of the serotonin receptor antagonists (5-HT3 receptor antagonists) in the early 1990s, limited effective options were available to prevent and treat chemotherapy-induced nausea and vomiting (CINV). In 1985, the FDA approved 2 cannabinoid derivatives, dronabinol and nabilone, for the treatment of CINV not effectively treated by other agents. Today, the standard of care for prevention of CINV for highly and moderately emetogenic chemotherapy is a 5-HT3 receptor antagonist, dexamethasone, with or without aprepitant or fosaprepitant. With the approval of safer and more effective agents, cannabinoids are not recommended as first-line treatment for the prevention of CINV and are reserved for patients with breakthrough nausea and vomiting. Because of medical and legal concerns, the use of marijuana is not recommended for management of CINV and is not part of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis. Although patients may like to pursue this treatment option in states that have approved the use of marijuana for medical purposes, its use remains legally and therapeutically controversial. (*JNCCN* 2012;10:487–492)

The management of chemotherapy-induced nausea and vomiting (CINV) has improved over the past 20 years. Before the introduction of 5-hydroxytryptamine (5-HT3) receptor antagonists, treatment options were limited to less-effective and more-toxic agents, such as cannabinoids and neuroleptics. The principle goal of antiemetic therapy is to prevent acute and delayed CINV.[1] In 1991, ondansetron was the first 5-HT3 recep-

tor antagonist approved for CINV and changed how patients undergoing chemotherapy were managed, treated, and studied. The addition of the neurokinin-1 (NK-1) receptor antagonists and new-generation 5-HT3 receptor antagonists (palonosetron) have further improved control of delayed nausea and vomiting.

CINV can be separated into several categories: acute, delayed, anticipatory, and breakthrough.[1,2] Acute CINV usually occurs within a few minutes to several hours after the chemotherapy is given, and resolves within approximately 24 hours. Delayed CINV occurs more than 24 hours after chemotherapy treatment. Acute CINV is managed through prevention using a 2 or 3 drug combination. Delayed CINV is prevented with effective treatment of acute CINV and the addition of aprepitant to the antiemetic regimen. Palonosetron, a new-generation 5-HT3 receptor antagonist, is also effective at preventing delayed CINV. Anticipatory CINV occurs before the patient even receives the chemotherapy dose, and benzodiazepines are recommended for its treatment. Breakthrough nausea and vomiting occurs despite appropriate antiemetic treatment or requires additional antiemetic rescue medications.

Breakthrough CINV continues to be a concern because it can be difficult to treat. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis recommend using an agent from a class other than the one used to prevent acute and delayed CINV (available in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).[1] Several agents are recommended, including cannabinoids, haloperidol, metoclopramide, olanzapine, phenothiazines, and benzodiazepines, for the management of breakthrough nausea and vomiting that target the various neuroreceptors. The NCCN Guidelines recommend synthetic cannabinoids, dronabinol, and nabilone as treatment options for breakthrough nausea and vomit-

ing caused by chemotherapy. ASCO guidelines recommend cannabinoids be reserved for patients intolerant of or refractory to 5-HT3 receptor antagonists, NK-1 receptor antagonists, and dexamethasone.[3] The Multinational Association of Supportive Care in Cancer states that cannabinoids can be considered for refractory nausea and vomiting and as a rescue antiemetic.[4]

In the mid-1980s, synthetic orally administered cannabinoids were approved for the treatment of CINV. With the approval of safer and more-effective medications, the use of these agents with a lower therapeutic index, such as cannabinoids, is not recommended as first-line treatment for prevention of CINV and should be reserved for patients refractory to or intolerant of standard antiemetics.

The use of medical marijuana is very controversial and is not part of the NCCN Guidelines for Antiemesis. Although patients may like to pursue this treatment option in states that have approved the use of marijuana for medical purposes, prescribers and patients must remember that marijuana use is still illegal according to federal law.

Chemotherapy-induced emesis may be the result of several neurotransmitters activating receptors on the chemoreceptor trigger zone, vomiting center, and gastrointestinal tract. The neuroreceptors involved in emesis include serotonin (5-HT3) and dopamine receptors. Acetylcholine, corticosteroid, histamine, cannabinoid, opiate, and NK-1 receptors are also involved in the emetic response. These receptors may also be drug targets for antiemetic therapy. The 2 known cannabinoid receptors are CB1 and CB2. In contrast with the receptors listed earlier, blocking of CB1 and CB2 results in emesis. Cannabinoids act as an agonist on the CB1 receptors, resulting in their pharmacologic effect.[5] Parker et al.[6] provides a more detailed review of the mechanism of action of cannabinoids in the regulation of nausea and vomiting.

Delta-9-tetrahydrocannabinol (THC) is the major psychoactive component of cannabis and has been shown to have antiemetic properties. Studies with dronabinol and nabilone were performed in the 1970s and 1980s, before the approval of 5-HT3 receptor antagonists, and often included a placebo arm, which is something that would not occur today. Their side effect profile and the availability of safer and more-effective agents for CINV prevention have limited the use of oral cannabinoids.

Tramer et al.[7] published a meta-analysis on the use of cannabinoids for CINV control. The investigators screened 198 reports and analyzed data from 30 randomized controlled studies from 1975 to 1997; 16 studies were with nabilone, 13 with dronabinol, and 1 with intramuscular levonantradol. Of the 30 studies, 10 used a placebo as the comparator, and prochlorperazine was prescribed in 12 trials. Other antiemetic controls included metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride. Of the 30 studies, 25 were crossover designs. The authors found that cannabinoids were more effective with moderately emetogenic chemotherapy regimens than all of the active controls, but were not more effective with very high or low emetogenic regimens. When asked, patients preferred the cannabinoid over the control antiemetic. More side effects were associated with the cannabinoid treatment, and patients were more likely to withdraw from therapy. Beneficial side effects, such as euphoria, a "high" sensation, drowsiness, sedation, or somnolence, were observed in the cannabinoid arms. However, harmful events, such as dysphoria, depression, hallucinations or paranoia, and arterial hypotension (> 20% decrease in blood pressure), were also more common.

Rocha et al.[8] published a meta-analysis on data from 13 studies of cannabinoids versus another antiemetic. In 10 studies, the comparator was prochlorperazine. None of the studies compared the cannabinoid with a 5-HT3 receptor antagonist. The analysis showed that dronabinol was better than prochlorperazine. Nabilone was not superior to the neuroleptic antiemetics studied. They also reviewed 18 studies for patient preference. Patients preferred cannabinoid therapy over control. Side effects were more problematic in the cannabinoid arms. The side effects occurred more frequently and were more intense in patients receiving cannabinoids than the control. Paranoid delusions, hallucinations, dysphoria, and depression were almost exclusively associated with cannabinoid therapy. Some of the side effects were considered beneficial, such as a high sensation, sleepiness, sedation, and euphoria.

Nabilone

Nabilone is an orally active synthetic cannabinoid approved by the FDA in December 1985. Nabilone is a schedule II controlled substance because of the

high potential for abuse. It is approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have not experienced adequate response to conventional antiemetic treatments. This restriction is because of the risk of disturbing psychomimetic reactions associated with this agent. Nabilone is not intended for use on an as-needed basis or as the first-line antiemetic treatment.

The FDA-approved dosage of nabilone is 1 to 2 mg orally twice daily, with the first dose given 1 to 3 hours before the start of chemotherapy. The recommendation is to start at the lower dose to minimize side effects. Patients may also take a dose the evening before chemotherapy. However, nabilone is not recommended as a treatment option in the NCCN Guidelines for preventing CINV, but rather is recommended at 1 to 2 mg every 12 hours for breakthrough nausea and vomiting (available in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Nabilone is associated with significant adverse events and is not recommended as a first-line agent for CINV. Some of the adverse events are seen as beneficial to the patient. Events such as a feeling of being high or euphoria and drowsiness are seen as potentially beneficial side effects of this agent. Other side effects that are not considered beneficial and are more problematic include ataxia, anxiety, disorientation, hallucinations, depression, and psychosis. Adverse events may persist for a variable and unpredictable period, with adverse psychiatric reactions persisting 48 to 72 hours after the last dose. Orthostatic hypotension has been reported. Nabilone should not be taken with other agents that cause central nervous system (CNS) depression. Because of the significant CNS effects, patients should be cautioned not to drive, operate machinery, or participate in any hazardous activity while taking nabilone. Until patients know how they will respond to treatment with nabilone, it is recommended that they be supervised by a responsible adult.

Studies involving nabilone were conducted before the 5-HT3 receptor antagonists were approved, and the sample sizes were often small. Ahmedzai et al.[9] randomized 34 patients with lung cancer undergoing a chemotherapy regimen that included 3 days of therapy with a combination of cyclophosphamide and doxorubicin on day 1 and etoposide on day 1 to 3 in a double-blind, double-dummy crossover design

to nabilone or prochlorperazine. Patients received 2 mg of nabilone orally every 12 hours starting the evening before day 1 or 10 mg of prochlorperazine orally every 8 hours, with the first dose 4 hours before the start chemotherapy. Patients were crossed over to the other treatment in the next cycle. For the third and subsequent cycles, patients were allowed to select the antiemetic regimen they wanted to receive. Only 26 were able to complete the crossover and were evaluable. Nabilone was significantly better at controlling nausea and retching on day 1 than prochlorperazine, but was not significantly better at controlling vomiting on day 1 (22% vs. 30%, respectively). On days 2 and 3, nabilone was significantly better than prochlorperazine at controlling nausea and vomiting. CNS side effects were more common in the nabilone arm. Nabilone was preferred by 16 patients, but only 12 wanted to receive it again because of side effects. Side effects associated with nabilone were more common than with prochlorperazine. Commonly reported side effects were drowsiness (57%), postural dizziness (35%), and lightheadedness (18%).

Crawford and Buckman[10] conducted a double-blind study of 1 mg of nabilone every 8 hours versus intravenous metoclopramide in patients with ovarian cancer or germ cell tumors undergoing treatment with combination chemotherapy that included higher doses of cisplatin (100–120 mg/m^2). Thirty-two patients were to receive 4 cycles of 1 mg of nabilone orally every 8 hours, with a 2-mg dose given before chemotherapy, and placebo metoclopramide intravenously, and then crossed over to placebo nabilone and 1 mg/kg of metoclopramide intravenously every 3 hours in random order. Only 7 patients received all 4 cycles. No difference was seen in efficacy between the groups; 12 patients preferred nabilone, whereas 10 patients preferred metoclopramide. The side effect profiles of the agents were different. More instances of diarrhea occurred in the metoclopramide arm, and drowsiness was reported more often in the nabilone arm. The investigators noted no significant differences in reports of dizziness or euphoria.

In another study, nabilone was compared with domperidone in a randomized, double-blind study.[11] Thirty-eight patients receiving highly emetogenic chemotherapy were randomized to receive either 1 mg of nabilone orally the night before and every 8 hours on the day of chemotherapy, or 20 mg of dom-

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peridone orally following the same administration schedule for 2 cycles of chemotherapy. Three patients in the nabilone and 4 in the domperidone arm did not receive the planned 2 cycles. Significantly fewer episodes of vomiting were seen in the nabilone arm in cycle 1. No difference was seen in the nausea scores between the arms. Both groups frequently reported drowsiness and dry mouth. Dizziness and postural hypotension were more common in the nabilone arm. Euphoria (11%) and other CNS effects, such as drunk feeling, confusion, and difficulty speaking (5% or 1 patient), were only reported in the nabilone arm.

Herman et al.[12] reported their results of 2 separate studies of the efficacy of nabilone compared with prochlorperazine in preventing CINV. In one study, patients received 2 mg of nabilone orally every 8 hours or 10 mg of prochlorperazine every 8 hours, with the first 2 doses given before chemotherapy. In the other study, patients received 2 mg of nabilone orally and 10 mg of prochlorperazine orally every 6 hours, with the first dose given 30 minutes before chemotherapy. Patients were crossed over in the next cycle, therefore serving as their own control. A total of 113 patients were evaluable from both studies. The investigators defined complete response as total absence of nausea and vomiting during the entire course of chemotherapy. A partial response was a reduction of 50% or more in the duration or severity of nausea and vomiting compared with a previous cycle of the same chemotherapy. No response was a less than 50% reduction in reported nausea and vomiting. No patients (n = 70) receiving a 5-day cisplatin-based therapy experienced a complete response, and 72% reported a partial response to nabilone compared with prochlorperazine. Of 9 patients with lymphoma receiving either CHOP (cyclophosphamide, mitoxantrone, vincristine, prednisone) or MOPP (mechlorethamine, vincristine, procarbazine, prednisone), 6 experienced complete responses to nabilone therapy. Once again, side effects were a major concern with nabilone therapy, with dry mouth, somnolence, and dizziness reported twice as often. Nine patients stopped treatment because of unacceptable side effects; 4 in the prochlorperazine arm and 5 in the nabilone arm. One patient in the nabilone arm was hospitalized for orthostatic hypotension. More severe side effects were seen in the nabilone arm. Studies comparing nabilone with other inferior agents were all small. However, a significant increase in incidence of CNS side effects was seen across all studies, further limiting the routine prescribing of nabilone for the prevention of CINV.

Dronabinol

Dronabinol is synthetic THC, the active ingredient of *Cannabis sativa L* (also known as marijuana), and was approved in 1985 for the treatment of nausea and vomiting associated with chemotherapy in patients who have not experienced an adequate response to conventional antiemetic treatments. Dronabinol is a schedule III controlled substance. The NCCN Guidelines for Antiemesis recommend dronabinol for the management of breakthrough nausea and vomiting associated with chemotherapy (available in this issue, and at www.NCCN.org).[1]

The approved dosage of dronabinol is 5 mg/m^2 orally 1 to 3 hours before the first dose of chemotherapy, and then every 2 to 4 hours after for a total of 6 doses. The dose may be increased in 2.5-mg/m^2 increments to a maximum dose of 15 mg/m^2. Caution should be used when increasing the dose, because the incidence of disturbing psychiatric events is increased at the higher doses. With the newer, safer, and more-effective agents available today, NCCN does not recommend dronabinol for prevention of CINV, but recommends 5 to 10 mg orally every 3 or 6 hours for breakthrough nausea and vomiting.[1]

In a randomized, double-blind, crossover study of oral THC versus placebo in patients undergoing chemotherapy known to be centrally emetogenic, only 22 subjects were enrolled, 20 of whom were evaluable.[13] The original dosage was 15 mg orally every 4 hours for 3 doses, but was changed to 10 mg/m^2 per dose. Nineteen patients received the 15-mg dose and 3 the 20-mg dose. A complete response to THC was defined as no vomiting in patients for whom the same chemotherapy regimen caused moderate to severe nausea and vomiting when given placebo. A partial response was at least a 50% reduction in vomiting compared with placebo after the same chemotherapy regimen. Ten patients received 29 evaluable courses of drug: 14 courses of placebo and 15 of THC. Five complete responses, 7 partial responses, and 3 no responses were seen in the 15 courses of THC. The authors report that no patient

vomited while experiencing a subjective "high." After the high wore off, nausea and vomiting did occur. No complete or partial responses were seen with placebo. Nine patients received only one course of chemotherapy, 3 of whom received THC; 2 of these patients vomited and withdrew from the study and 1 went off study because of THC toxicity. Side effects were common in the THC arm. Thirteen of 16 patients experienced a "high," and 1 patient reported visual hallucinations lasting 10 minutes and depression for several hours.

Medical Marijuana

The use of marijuana for medical purposes is a controversial topic. Despite legalization by several states, the use of marijuana is prohibited by federal law; people prescribing or using marijuana for medicinal purposes are at risk of prosecution. *Cannabis sativa L*, also known as marijuana, has been used for centuries for many purposes. People have turned to cannabis for its psychotropic effects and medicinal uses, such as relief of pain and nausea and vomiting. In 1850, cannabis was entered into the U.S. Pharmacopeia, and in 1942 was removed.[14] Physicians could legally prescribe marijuana until 1970, when the Federal Controlled Substances Act classified marijuana as a schedule I controlled substance. An agent classified as schedule I currently has no medically acceptable use in the United States, has a high potential for abuse, and lacks acceptable safety for use of the drug or other substance under medication supervision.[15]

Attempts to reclassify marijuana on a federal level have been unsuccessful. Despite being illegal, patients are still turning to marijuana to control nausea and vomiting caused by chemotherapy, anorexia secondary to cancer, and AIDS and chronic pain. Patients may also use marijuana to treat glaucoma or spasticity secondary to multiple sclerosis. Cannabis may be smoked, inhaled as a vapor, eaten in foods, or applied as a balm. An oral spray (nabiximols, a combination of THC and cannabidiol) is available in several countries, including Canada, for relief of pain and spasticity in patients with multiple sclerosis.

Several states (California, Alaska, Colorado, Hawaii, Maine, Montana, Nevada, Oregon, Vermont, and Washington) have legalized the cultivation, possession, and use of marijuana for medicinal purposes.[16] The U.S. Supreme Court ruled 6 to 3 in

Gonzales v Raich that the federal government had the power to arrest and prosecute patients and their suppliers, because the government has authority under the Federal Controlled Substances Act to regulate interstate commerce in illegal drugs.[17]

In 1997, Schwartz et al.[18] published results of a survey mailed to 1500 oncologists in 1994. Of the 1122 completed responses, only 28% of respondents favored rescheduling of marijuana as a prescription medication, with 48% opposing and 24% uncertain. When asked if marijuana were rescheduled, 30% said they would consider prescribing it for their patients.

A commentary in the May 2005 issue of the *Journal of Clinical Oncology* discusses the use of medicinal cannabis in the Netherlands.[19] Patients in the Netherlands have access to medicinal-grade cannabis, providing a well-defined product and known and constant THC content. Routes of administration include inhalation through smoking or vaporization or orally as a tea. Of 400 physicians surveyed in the Netherlands, 60% to 70% are willing to prescribe medicinal cannabis.[19] However, no controlled clinical studies support the use of medicinal cannabis, and the authors do not recommend its routine use in patients with cancer.

Marijuana is not a completely benign substance.[20] Its use has been reported to be associated with adverse effects on the cardiovascular, respiratory, and central nervous systems. Marijuana smoke contains more carcinogens than cigarette smoke, which may lead to lung cancer and is an important risk factor in the development of respiratory disease.[20] Use may also be associated with an increased risk of head and neck cancer, atrial fibrillation, myocardial infarction, stroke, and chronic bronchitis. Marijuana also has immunosuppressive properties that may be detrimental to patients with cancer. Children whose mothers smoked marijuana during pregnancy may have an increased risk of developing leukemia.[21] No studies of marijuana have been conducted in patients with cancer receiving chemotherapy.[22]

Use of synthetic oral cannabinoids should be limited to the management of breakthrough nausea and vomiting caused by chemotherapy. With safer and more effective agents, synthetic cannabinoids have no place as a first-line treatment for CINV. Medical marijuana, although legal in some states, should not be a treatment option for patients with cancer. Legal issues aside, its safety and efficacy have yet to

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be determined. Routine use of marijuana cannot be recommended until controlled studies are performed and legal issues resolved.

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