EXHIBIT B

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ABSTRACT: A prospective pilot study of the use of inhalation marijuana as an antiemetic for cancer chemotherapy was conducted. Fifty-six patients who had no improvement with standart antiemetic agents were treated and 78% demonstrated a positive response to marijuana. Younger age and prior marijuana exposure were factors that predicted response to treatment. Toxicity was mild and consisted primarily of sedation and xerostomia. This preliminary trial suggests the usefulness of inhalation marijuana as an antiemetic agent. Because of the lack of a randomized placebo control group, the precise role of this agent is unclear. Further studies should include derivatives of this substance in combination with standard effective drugs to control chemotherapy-induced nausea and vomiting.

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A great deal of clinical information has recently been generated concerning the efficacy of various antiemetic agents for patients treated with cancer chemotherapy. (1-3). Without effective control of nausea and vomiting, patient compliance with potentially curative chemotherapy programs diminishes, compromising not only quality but quantity of life. Effective new chemotherapeutic agents could never be successfully tested in clinical trials if they possessed potent emetic side-effects.
Although a number of agents have recently been found to be active, including metoclopramide, (4,5) haloperidol, (6) dexamethasone, (7) and lorazepam, (8) the need to introduce newer agensts and combination antiemetic therapy may be necessary for continued control of symptoms. Also, complete control of nausea and vomiting during anticancer treatment must take into account not only the physical effects but also the psychological ones. Control of anxiety through behavior modification and relaxation is an effective antiemetic treatment of anticipatory nausea and vomiting. (9)

Natural and synthetic cannabinoids are known to be effective antiemetic agents. (10-12) Delta-9-tetrahydrocannabinol (THC) has been found to be superior to prochlorperazine. (13) Also, patients who are refractory to standart antiemetic agents have significant reduction in nausea and vomiting with oral THC. (14) There is little information on the efficacy of inhalation marijuana aside from anecdotal reports from patients who obtained the drug privately.
As a part of a New York State Department of Health program, North Shore University Hospital conducted a preliminary study of the use of inhalation marijuana as an antiemetic agent for cancer chemotherapy. The purpose of this study was to evaluate the efficacy of inhalation marijuana for patients refractory to standard agents, to identify patient characteristics to predict response, and to evaluate toxicity and patient acceptance of this form of treatment.

METHODS

Patients with histologically confirmed malignancies who were actively receiving chemotherapy were entered into the protocol. Eligibility criteria included: 18 years of age or older, refractoriness to conventional antiemetic agents, and absence of severe cardiac or psychiatric disease. Patients had to agree not to drive or operate heavy machinery or a motor vehicle for at least 12 hours after the last dose of marijuana. Central nervous system depressants including alcohol were prohibited during the administration of marijuana.

Marijuana cigarettes were supplied by the National Institute on Drug Abuse (NIDA) to the New York State Department of Health. All patients were instructed on standard smoking procedures. The patient inhales deeply, holds the inhalation for ten seconds, and then exhales. After waiting 10 to 15 seconds, the cycle is repeated. The total dose is completed within five minutes. A flame-proof holder was available to permit delivery of nearly all of the cigarette appropriate to the patient's dosage. The dose schedule, which was calculated to the nearest one-fourth cigarette; was 5 mg THC/m2, starting 6-8 hours prior to chemotherapy and every 4-6 hours thereafter, for a total dose of four doses per day on each day of chemotherapy (one cigarette= 10.8 mg THC). In order to prevent cigarettes from drying out and causing harsh smoke, patients were instructed to keep the cigarettes in the refrigerator or humidified.
This was a nonrandomized study where patients served as their own controls. Patients were asked to self-rate their status by completing a patient evaluation form after each therapeutic episode. Nausea was graded on a scale from 1 (none) to 4 (severe), vomiting was graded from 1 (none) to 5 (10+ times), appetite was graded from 1(none) to 5 (above normal), and physical state was graded from 1 (very weak) to 4 (above normal), and mood was graded from 1 (very depressed to 5 (very happy). Based on the degree of nausea, vomiting, food intake, physical state, and over-all mood, patients rated the overall effectiveness of marijuana as none, moderately effective, and very effective.
Physician investigators were approved by the Hospital's Patient Qualification Review Board. Physicians utilized the official New York State triplicate prescription form as their research order for medication. Informed consent was obtained from all patients and the procedures followed were approved by an institutional research committee.

RESULTS

Seventy-four patients entered the study and 56 were evaluable. Eighteen patients who had initially agreed to be treated with marijuana later decided not to participate. Eighteen patients rated the marijuana very effective (34%) and 26 patients rated it moderately effective (44%) for an overall response rate of 78% (44/56). Twelve patients (22%) noted no benefit.

TABLE I. Patient Characteristics (Percent)

Responders Nonresponders P Value
(N=44) (N=12)

Female 64 75
NS*
Mean age (yr) 41 51
(median) (40) (54)
Breast cancer 36 33
NS
Lymphoma 34 25
NS
Prior radiation therapy 30 8
NS
Prior THC 29 20
NS
Prior Marijuana 52 17
0.06
Euphoria 60 36
NS
(high)
Smoker 53 38
NS

*NS= not significant
Standard deviation= 11.9
Standard deviation= 15.6

Characteristics of responding and nonresponding patients are listed in Table I. While no statistically significant differences were noted between responders and nonresponders with regard to sex, type of diagnosis, prior radiation therapy, prior oral THC treatment, incidence of euphoria, or

smoking history, it is important to remember that the sample sizes were small, making interpretation of differences difficult. Patients who responded to marijuana cigarettes were more likely to be younger, median age 40 vs 54 for nonresponders, and had prior marijuana exposure, 52% vs 17% (p= 0.06).
The most common diagnoses for this group of patients were breast cancer, lymphoma, lung cancer, colon cancer, ovarian cancer, testicular cancer, sarcoma, acute leukemia, and myeloma. The most common emetic chemotherapeutic agents were cyclophosphamide, doxorubicin, cis-platinum, procarbazine, methotrexate, dacartazine, and streptozocin, given either singly or in combination. Four of seven patients treated with cis-platinum responded favorably to marijuana cigarettes.
Toxic side effects included sedation in 88%, dry mouth in 77%, dizziness in 39%, and confusion in 13%. Anxiety, headache, and fantasizing were also seen but were less common. There was no toxicity in 13% of patients (Table II).

TABLE II. Percent Toxicity

Sedation	88
Dry Mouth	77
Dizziness	39
Confusion	13
Anxiety	11
Headache	11
Fantasizing	11
None	13

DISCUSSION

The results of this prospective study suggest that inhalation marijuana is active in controlling nausea and vomiting resulting from chemotherapy. Marijuana benefited patients who were treated with a wide range of chemotherapeutic agents including drugs which have considerable emetogenic potential. A prior report by Chang et al (15) documented effectiveness of oral THC and inhaled marijuana against high-dose methotrexate, which normally has mild gastrointestinal toxicity. While most experience indicates that THC is generally ineffective against cis-platinum-induced emesis, benefit was seen in a small number of patients treated in our program with this agent.
Since this was a single arm, nonrandomized, outpatient program, this study lacks a controlled placebo group. Nevertheless, the patients acted as their own controls, having previously failed standard antinausea medications. They evaluated marijuana based on their subjective rating of the severity of nausea, vomiting, appetite and food intake, mood, and physical state after chemotherapy treatment. A placebo-controlled, randomized inpatient study which quantitates all emetic episodes would obviously provide objective and precise information. (16)
Failure to respond to oral THC does not preclude benefit from inhaled marijuana. Twenty-nine percent of patients who failed oral THC responded to the cigarette form. This is not unexpected, since only 5-10% of orally administered THC is absorbed, whereas inhaled marijuana has a five-to tenfold greater bioavailability. (17) Clearly, oral THC is an effective treatment for chemotherapy-induced emesis. Most studies have demonstrated THC to be better than placebo and comparable to prochlorperazine. (18)
The major obstacle related to the oral and inhaled cannabinoids is the route of administration. Patients with anticipatory vomiting do not retain the oral THC. Because of its poor water solubility, parenteral adminstration of cannabinoids has been difficult. The only cannabinoid available for parenteral use, levonantradol, is currently being investigated and has documented activity comparable to THC. (19) Perhaps intranasal or transdermal forms of THC will be developed and found to be clinically useful.
Patient characteristcs were evaluated to identify factors which would predict response to marijuana. There were no significant differences between responders and nonresponders with regard to sex, diagnosis, prior radiation therapy, prior THC ingestion, induced euphoria, and history of cigarette smoking. The only factors that approached significance were young age and prior marijuana intake. Unlike the experience with oral THC, experiencing a euphoric high was not a prerequisite to obtaining the antiemetic effect with marijuana. (20)
The mechanism of the antiemetic action of cannabinoids is unknown. Inhibition of prostaglandin and cyclic adenosine monophosphate has been

suggested. Its major action is more likely related to its effect on the brain, as marijuana causes central nervous system depression and impairment of brain function. At the cellular level, cannabinoids interfere with the synthesis of nucleic acids and chromosome proteins. (21)
Some of the problems encountered in this study which could influence interpretation of the results were the low patient accrual and the fact that nearly 25% of patients who initially consented refused to receive treatment. Reasons for patients' refusal to participate included physician and patient bias against smoking, harshness of smoke from the cigarettes, and preference for oral THC capsules. The major objection was related to the social stigma attached to the use of marijuana. Many patients rejected the idea of "smoking pot" at home and exposing their children to the implications of this type of medication. Should this therapy become available in a different vehicle of administration, patient acceptance would significantly improve.
Our results demonstrate that inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy. A randomized, controlled trial would, however, be necessary to accurately define the exact role of this drug. Toxic effects are well tolerated and the availability of a parenteral form would improve patient utilization of this agent. Future antiemetic protocols should include the active ingredient of marijuana in combination with current effective agents.

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