Effects of Smoked Cannabis and Oral Δ^9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials

Richard E. Musty
Rita Rossi

ABSTRACT. Background. In 1999 the Institute of Medicine (IOM) issued a report entitled *Marijuana and Medicine* (Joy, Watson and Benson, 1999). It recommended the development of cannabinoid drug delivery systems which might be effective for nausea, vomiting and AIDS wasting syndrome, among other chronic disorders. The report went on to recognize that patients should be allowed to smoke marijuana if they failed to achieve relief from approved symptoms that could be relieved by cannabinoid drugs with rapid onset. Recommended criteria of the report included: access to marijuana within 24 hours of submission by a physician, supervision that allows for assessment of treatment effectiveness, and an oversight strategy comparable to an institutional review board. In this context a review of previously unpublished state-run clinical trials with *Cannabis sativa* (marijuana and/or Δ^9-tetrahydrocannabinol capsules) to test efficacy in reducing nausea and vomiting following cancer chemotherapy is warranted. The impetus for these studies came from individual state legislatures responding to constituents' claims that smoking marijuana reduced or blocked nausea and vomiting.

Methods. Technical reports were obtained from 6 states which had

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conducted clinical trials. Each protocol was examined for the procedure used, the experimental design of the clinical trial and the results obtained. Data were available on 748 patients who smoked marijuana prior to and/or after cancer chemotherapy and 345 patients who used the oral THC capsule.

Results. Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.

Conclusions. On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy.

The development of smokeless inhalation devices could certainly reduce the potential harm from smoking marijuana.

KEYWORDS. Cannabis, cannabinoid, marijuana, cancer, chemotherapy, nausea, vomiting, tetrahydrocannabinol

The first study comparing oral Δ^9-tetrahydrocannabinol (THC) to placebo capsules and marijuana to marijuana placebo cigarettes was published by Chang et al. (1979). In this study 15 patients were given oral doses of THC over several courses of chemotherapy. Each subject received a 10 mg THC capsule beginning two hours prior to chemotherapy and every three hours subsequently. In the event of a breakthrough vomiting episode, those patients were given marijuana cigarettes to smoke for the remaining administrations rather than oral THC. When measured THC blood levels were < 5 ng/ml, 44% of subjects vomited, between 5 ng/ml and 10 ng/ml, 21% vomited, and > 10 ng/ml, 6% vomited. After smoking marijuana, the incidence of vomiting for the same blood levels ranges were 83%, 38% and 0%. Vomiting rates after placebo capsules or smoked placebo marijuana were 72% and 96%, respectively.

In a marijuana-only trial, Vinciguerra et al. (1988) tested 56 patients, non-randomized, who acted as their own controls. Patients rated themselves via subjective assessment of nausea and vomiting. Thirty-four percent of the patients rated smoked marijuana as being very effective, 44% moderately effective, and 22% ineffective. The authors did not report the frequency of nausea and vomiting when marijuana was not smoked.

Technical reports were obtained from 6 states, in which inhaled marijuana was used in patients undergoing cancer chemotherapy. The states had passed legislation to make these studies legal. Usually, studies were designed by researchers in collaboration with State Departments of Health. Each state was required to write a protocol for the research (which was submitted to the Food and Drug Administration (FDA) for approval). Subsequently, a Schedule I license was obtained from the Drug Enforcement Administration (DEA). Finally, rolled marijuana cigarettes and capsules of THC (in sesame oil) were obtained from the National Institute on Drug Abuse (NIDA). These studies will be reviewed individually in this article.

In 1999, the Institute of Medicine (IOM) recommended that marijuana be made available for patients refractory to other medications (Joy, Watson and Benson, 1999). This review provides further support to the Chang and Vinciguerra studies.

TENNESSEE

Background. The State of Tennessee conducted this trial after legislative action in April of 1981 (Board of Pharmacy, 1983).

Treatment Method. Patients (all of whom were refractory to other anti-emetics) were referred for treatment by the patient's personal physician. Patient records were reviewed by a Patient Qualification Review Board of the State of Tennessee. Those approved were randomized to 3 age groups: less than 20 years old, 20-40 years old, and over 40 years old. Those not having conditions precluding oral administration were administered the THC capsule and those unable to ingest capsules were treated with smoked marijuana cigarettes. Most of the patients had previously been treated with the THC capsule. Thus the report focused on the effects of use of marijuana cigarettes.

Measures. A patient treatment evaluation form was completed for each day of treatment. Recording forms included a record of dose and notes, the patient's assessment of nausea and vomiting, appetite and food intake, physical state, and (marijuana) "high." Forty-three patients were enrolled in the study. Sixteen patients were excluded for various reasons: missing data, abusive drug use, premature death, those who could not tolerate smoking, or patients who declined treatment.

Results. The results of the study are shown in Table 1. Treatment

TABLE 1. Tennessee trial: Patient assessment of the effects of smoked marijuana on nausea and vomiting, side effects and appetite

	Marijuana Effect		Side Effects		Appetite	
	n	%	n	%	n	%
Very Effective	11	(40.1%)	Mild	23 (85%)	Above Average	5 (18.5%)
Moderately Effective	11	(40.1%)	Moderate	3 (11.1%)	Normal	16 (59.3%)
Partially Effective	1	(0.04%)	Severe	1 (0.04%)	Below Normal	5 (18.5%)
Slightly Effective	4	(15%)				
Poor	1	(.04%)				

success by method was also discussed. Success was defined as partially, moderately, or very effective. For those under age 40 years of age, 100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

MICHIGAN

Background. Michigan conducted a study under the direction of the Michigan Department of Public Health after legislative action in 1979. John. R. Ingall of the Detroit Metropolitan Comprehensive Cancer Center was the study coordinator, and the report was complied by the Michigan Cancer Foundation (Department of Social Oncology, Evaluation Unit 1982).

Treatment Method. In order to be eligible for the trial, patients had to meet these criteria: be under active cancer chemotherapy treatment, have a satisfactory medical status such that potential side effects of marijuana or a phenothiazine derivative, thiethylperazine (Torecan®), were not life-threatening or likely to evoke serious mental/behavioral effects, and be free of serious mental or organic disease. Patients were randomly assigned to a marijuana cigarette or thiethylperazine therapy group. If the treatment failed in a 24 hour trial, patients were then crossed over to the other treatment group. For the marijuana group,

patients took one puff per minute until they felt ''high'' 30 minutes prior to chemotherapy. The smoking procedure continued until sometime after chemotherapy was completed. One hundred sixty-five patients completed this trial (78 male and 86 female).

Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

Results. The results for this study are shown in Table 2. Marijuana was marginally more effective as compared to thiethylperazine in controlling nausea and vomiting/retching. As in the previous study, reported side effects were mild.

GEORGIA

Background. The State of Georgia and Emory University collaborated to conduct this trial after legislative action in 1980 (Kutner 1983).

Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea			Vomiting/Retching After Chemotherapy	
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking	
Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

of three treatment groups by age: less than 20 years old, 20-40 years old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and ''high.'' One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

smoking, but standardized smoking yielded somewhat inferior outcomes.

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt "high." No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

REFERENCES

Beck TH, AA Ciociola, SE Jones et al. and the Ondansetron Study Group. 1993. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med* 118:407-13.

Behavioral Health Sciences Division. 1984. *The Lynn Pierson Therapeutic Research Program*. Health and Environment Department: New Mexico.

Behavioral Health Sciences Division. 1983. *The Lynn Pierson Therapeutic Research Program*. Health and Environment Department: New Mexico.

Board of Pharmacy, State of Tennessee. 1983. *Annual Report: Evaluation of marijuana and tetrahydrocannabinol in the treatment of nausea and/or vomiting associated with cancer therapy unresponsive to conventional anti-emetic therapy: Efficacy and toxicity.*

Buser KS, RA Joss, D Piquet et al. 1993. Oral ondansetron in the prophylaxis of nausea and vomiting induced by cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in women with breast cancer. Results of a prospective, randomized, double-blind, placebo-controlled study. *Ann Oncol* 4:475-9.

Chang AE, DJ Shiling, RC Stillman et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 91:819-24.

Crucitt MA, W Hyman, T Grote et al. 1996. Efficacy and tolerability of oral ondansetron versus prochlorperazine in the prevention of emesis associated with cyclophosphamide-based chemotherapy and maintenance of health-related quality of life. *Clin Ther* 18(4):778-88.

Cupissol DR, B Serrou, and M Caubel. 1990. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high-dose cisplatin-induced emesis. *Eur J Cancer* 26(1):23-7.

Department of Social Oncology, Evaluation Unit. 1982. State of Michigan, *Marihuana Therapeutic Research Project*.

Doblin, R and M Kleiman. 1991. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes *J Clin Oncol* 9(5):1314-19.

Herrstedt J, T Sigsgaard, M Boesgaard, T Jensen, and P Dombernowski. 1993. Ondansetron plus metopimazine compared with ondansetron in patients receiving moderately emetogenic chemotherapy. *N Engl J Med* 328(15):1076-80.

Italian Group for Antiemetic Research. 1995. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *New Engl J Med* 332(1);1-5.

Jones AL, AS Hill, M Soukop et al. 1991. Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 338:483-87.

Joy J, SJ Watson, and JA Benson. 1999. *Marijuana as medicine: Assessing the science base*. Washington DC: National Academy Press.

Kaasa S, S Kvaløy, MA Dicato et al., and the International Emesis Study Group. 1990. A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: A randomized, double-blind study. *Eur J Cancer* 26(3):311-14.

Kutner, MH. 1983. *Evaluation of the use of both marijuana and THC in cancer patients for the relief of nausea and vomiting associated with cancer chemotherapy after failure of conventional anti-emetic therapy: Efficacy and toxicity, as prepared for the Composite State Board of Medical Examiners, Georgia Department of Health, by physicians and researchers at Emory University, Atlanta*.

Markman M, A Kennedy, K Webster et al. 1996. Control of carbonplatin-induced emesis with a fixed low dose of granisetron (0.5 mg) plus dexamethasone. *Gynecol Onco* 60:435-7.

Marty M, P Pouillart, S Scholl et al. 1990. Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 322(12):816-21.

Michigan Cancer Foundation, Department of Social Oncology, Evaluation Unit. 1992. *Michigan Department of Public Health Marijuana Therapeutic Research Project, Trial A 1980-81*.

Olver I, W Paska, A Depierre et al. 1996. A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ann Oncol* 7:945-52.

Perez EA, RM Navari, HG Kaplan et al. 1997. Efficacy and safety of different doses of granisetron for the prophylaxis of cisplatin-induced emesis. *Support Care Cancer* 5:31-7.

Randall RC. 1990. *Cancer Treatment & Marijuana Therapy.* Washington DC: Galen Press, 1990. 225-34.

Research Advisory Panel. 1989. *Cannabis Therapeutic Research Program. Report to the California Legislature*.

Ritter Jr. HL, RJ Gralla, SW Hall et al. 1998. Efficacy of intravenous granisetron to control nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *Cancer Invest* 16(2):87-93.

Roila F, M Tonato, F Cognettti et al. 1991. Prevention of cisplatin-induced emesis: A

double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 9(4):675-8.

Sekine I, Y Nishiwaki, R Kakinuma et al. 1996. A randomized cross-over trial of granisetron and dexamethasone versus granisetron alone: The role of dexamethasone on day 1 in the control of cisplatin-induced delayed emesis. *Jp J Clin Oncol* 26(3):164-68.

Vinciguerra V, T Moore, E Brennan. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *NY State J Med* 88:525-7.

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Partially Effective	1 (0.04%)	Severe	1 (0.04%)	Below Normal	5 (18.5%)
Slightly Effective	4 (15%)				
Poor	1 (.04%)				

100% success was achieved with marijuana cigarettes. For those over 40, 83.3% success was achieved. Only 6 patients used the THC capsule alone and 100% success occurred in those under 40 years of age, and in 33% for those over 40. Side effects were predominantly mild, and appetite improved in about 1 out of 5 patients.

MICHIGAN

Background. Michigan conducted a study under the direction of the Michigan Department of Public Health after legislative action in 1979. John. R. Ingall of the Detroit Metropolitan Comprehensive Cancer Center was the study coordinator, and the report was complied by the Michigan Cancer Foundation (Department of Social Oncology, Evaluation Unit 1982).

Treatment Method. In order to be eligible for the trial, patients had to meet these criteria: be under active cancer chemotherapy treatment, have a satisfactory medical status such that potential side effects of marijuana or a phenothiazine derivative, thiethylperazine (Torecan®), were not life-threatening or likely to evoke serious mental/behavioral effects, and be free of serious mental or organic disease. Patients were randomly assigned to a marijuana cigarette or thiethylperazine therapy group. If the treatment failed in a 24 hour trial, patients were then crossed over to the other treatment group. For the marijuana group, patients took one puff per minute until they felt ‘‘high’’ 30 minutes prior to chemotherapy. The smoking procedure continued until some-

time after chemotherapy was completed. One hundred sixty-five patients completed this trial (78 male and 86 female).

Measures. Measures were recorded by patient self-report as well as physician/nurse observations.

Results. The results for this study are shown in Table 2. Marijuana was marginally more effective as compared to thiethylperazine in controlling nausea and vomiting/retching. As in the previous study, reported side effects were mild.

GEORGIA

Background. The State of Georgia and Emory University collaborated to conduct this trial after legislative action in 1980 (Kutner 1983).

Treatment Method. Cancer patients who were unresponsive to usual anti-emetics, but who were able to employ the oral route of administration were eligible for this trial. Patients were randomly assigned to one of three treatment groups by age: less than 20 years old, 20-40 years

TABLE 2. Michigan Trial: Frequency of Nausea, Vomiting/Retching and Side Effects

	Nausea			Vomiting/Retching After Chemotherapy	
	Marijuana	Torecan*		Marijuana	Torecan*
None	14 (15.0%)	8 (15.7%)	None	19 (18.1%)	10 (14.9%)
Mild	31 (33.3%)	16 (31.4%)	Less than 4 h	25 (23.8%)	19 (28.4%)
Moderate	22 (23.7%)	14 (27.5%)	Between 4-12 h	25 (23.8%)	19 (28.4%)
Severe	19 (20%)	12 (23.5%)	Between 12-24 h	14 (13.3%)	10 (14.9%)
Unknown	7 (7.5%)	1 (0.02%)	Over 24 h	9 (8.6%)	4 (6.0%)
			Unknown	13 (12.4%)	5 (7.5%)

Side Effects of Marijuana Smoking

Sleepiness	21/113 (18.5%)
Sore Throat	13/113 (11.5%)
Headache	7/113 (6.2%)

* Thiethylperazine (Torecan®)

old, and over 40. The treatment groups were: oral THC capsules, standardized cannabis smoking, or patient controlled smoking.

Measures. At each treatment a form was completed containing information on effectiveness of treatment, side effects and the patient's assessment of nausea, vomiting, appetite, physical status, mood and "high." One hundred nineteen patients completed the study.

Observations included patient self-reports and physician summaries. Patient satisfaction was assessed for each treatment. Success was judged by the patient reporting as to whether he/she was satisfied, or very satisfied with the treatment. If the patient was not sure of effectiveness on the first cycle of treatment, but was satisfied or very satisfied on subsequent cycles, this was also considered to be a success. Failure was defined when the patient was dissatisfied on the initial cycle, the patient dropped out of the study, or changed treatment method.

Results. The overall results are shown in Table 3 and by age group in Table 4. Examining the data (in percentages) by age groups reveals success rates were very similar across age groups. These data show success rates were about the same for oral THC and patient controlled smoking, but standardized smoking yielded somewhat inferior outcomes.

TABLE 3. Georgia Trial: Overall Success with All Treatments by Age

	Age			
	< 20	20-40	> 40	Total
Success	10 (71.4%)	30 (75%)	47 (72.3%)	87 (73.1%)
Failure	4 (28.6%)	10 (25%)	18 (27.7%)	32 (26.9%)
Total	14	40	65	119

TABLE 4. Georgia Trial: Success by Treatment Oral THC (PO), Standardized Smoking (SS) and Patient Controlled Smoking (PCS) of Marijuana

	PO	SS	PCS	Total
Success	57 (76%)	17 (65.4%)	13 (72.2%)	87 (73.1%)
Failure	18 (24%)	9 (34.6%)	5 (27.8%)	32 (26.9%)
Total	14	40	65	119

Reasons for failure in patients who failed treatment with oral THC were as follows: 8 patients experienced severe nausea and vomiting, 6 had adverse reactions, 2 were dissatisfied, 1 had breakthrough vomiting, and 1 had no effect. For those who smoked marijuana, 6 patients experienced smoking intolerance, 1 had an adverse reaction, 1 had severe nausea and vomiting, 2 had breakthrough vomiting, and 4 had other side effects.

NEW MEXICO (1983)

Background. This program of Research was conducted by the Lynn Pierson Therapeutic Research Program for the New Mexico Health and Environment Department after authorization by the legislature in 1978 (Behavioral Science Division, 1983).

Treatment Method. Patients enrolled in the program were randomly assigned to one of two treatments: THC capsule or marijuana cigarettes. Doses were matched so that each patient received approximately 15 mg of THC. Patients were administered the treatment before a cycle of chemotherapy. After chemotherapy, patients could continue taking the marijuana or THC for 5 days. Forty female patients and 27 male patients received marijuana cigarettes, while 50 female patients and 25 male patients received THC capsules.

Measures. Observations were made by patients with a self-report scale called the Target Problem Rating Scale. For nausea and vomiting, improvement was defined when patients reported less nausea or vomiting compared with previous anti-emetics. No improvement was defined as no change compared with previous anti-emetics.

Results. The data are shown in Table 5. Patients who smoked marijuana achieved improvement overprevious antiemetic drugs, with those smoking the drug exceeding 90% success.

TABLE 5. New Mexico Trial (1983)

Group	Oral THC	Inhaled Marijuana
Improvement	57 (74.83%)	58 (90.39%)
No Improvement	9 (25.17%)	3 (9.6%)

NEW MEXICO (1984)

Background. The Lynn Pierson Therapeutic Research Program continued in 1984 (Behavioral Science Division 1984).

Treatment Method. The program was similar to that in 1983, with the exception that some patients received only one treatment and others received an average of six treatments after chemotherapy. Patients were randomly assigned to the same treatment groups as in the 1983 protocol. The protocol also allowed patients options to begin in one treatment group and switch to another, to refuse to be in the smoking group, or to try both routes of administration sequentially. Success was defined as a reduction in nausea and vomiting, and failure was defined as no reduction. Table 6 shows the results. It is important to note that few patients continued with the oral THC treatment, while those who smoked marijuana achieved over 90% success. Summarizing side effects of both THC and marijuana reported over the two years, treated patients often fell asleep. Of those who did not (approximately 90 patients), 50% reported sleepiness and 45% felt "high." No other side effects were noted in the report.

CALIFORNIA

Background. After legislation passed by the State of California Legislature in 1979, a Cannabis Therapeutic Program was carried out between 1983 and 1989 under the supervision of the California Research Advisory Panel (1989).

Treatment Method. Over the years, several protocols were used. Essentially, the early protocols were conservative, e.g., patients were required to have failed treatment with conventional anti-emetic drugs. Later, a more relaxed protocol was used in which the patient and the physician decided whether or not to try the THC capsule or smoke marijuana.

TABLE 6. New Mexico Trial (1984): Treatment Success After the First Treatment with Inhaled Marijuana or Oral THC

Group	Oral THC	Inhaled Marijuana	Combined
Success	6 (54.5%)	79 (95.2%)	79 (98.8%)
Failure	5 (45.5%)	4 (4.8%)	1 (1.2%)

Measures. Physicians used 5 point rating scales to record nausea and vomiting.

Results. Table 7 shows the combined results of the various protocols combined. In this study, smoked marijuana was consistently more effective than oral THC in blocking vomiting except in the most severe cases (> 6 times). Control of nausea was about the same for both groups. The pattern of side effects did not differ, to any extent, between smoked marijuana and oral THC.

NEW YORK

Background. The New York Department of Health study conducted a large scale (Phase III type) cooperative clinical trial (Randall, 1990).

Treatment Method. The central question addressed was how effective inhaled marijuana was in preventing nausea and vomiting due to chemotherapy in patients who failed to respond to previous anti-emetic therapy. Patients undergoing chemotherapy were allowed to use marijuana distributed through three centers: North Shore Hospital (NSH), Columbia Memorial Hospital (CMH), and a triad of the Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital (JGH). By 1985, the New York program provided marijuana therapy to 208 patients through 55 practitioners. Of those, data on 199 patients were evaluated. These patients had received a total of 6,044 NIDA-

TABLE 7. California Trials: Ratings of Nausea and Vomiting for Smoked Marijuana or the THC Capsule.

	Smoked Marijuana	THC Capsule		Smoked Marijuana	THC Capsule
Nausea			Vomiting		
None	9 (9.2%)	38 (15.1%)	None	19 (19.4%)	89 (35.3%)
Mild	34 (34.7%)	85 (33.9%)	1-3 times	36 (36.7%)	69 (27.4%)
Moderate	36 (36.7%)	73 (29.1%)	4-6 times	18 (18.4%)	35 (13.9%)
Severe	17 (17.3%)	55 (21.9%)	> 6 times	24 (24.5%)	59 (23.4%)
Missing	2 (2%)	6 (2.3%)	Missing	1 (1%)	5 (2.3%)

Side Effects (combined ratings from mild to severe are shown Table 8).

TABLE 8. California Trials: Side Effects Reported by Patients

	Smoked Marijuana n = 98	Smoked Marijuana %	THC Alone n = 257	THC Alone %
Dry Mouth	53	56.5	112	44.8
Tachycardia	6	6.4	25	10.0
Ataxia	16	27.1	31	12.8
Dizziness	31	33.1	67	26.8
Orthostatic	7	7.5	32	12.8
Anxiety	19	20.2	47	18.8
Sedation	49	52.1	160	64.0
Elated Mood	25	26.6	61	24.4
Confusion	23	26.6	79	31.6
Perceptual	15	15.9	57	22.8
Fantasizing	10	10.7	29	11.6
Depressed	17	18.1	33	13.2
Panic/Fear	7	7.5	9	7.6

supplied marijuana cigarettes provided to patients during 514 treatment episodes.

Measures. Observations were made by patient self-report.

Results. North Shore Hospital reported marijuana was effective at reducing emesis 92.9% of the time; Columbia Memorial Hospital reported efficacy of 89.7%; the triad of Upstate Medical Center, St. Joseph's Hospital and Jamestown General Hospital reported 100% of the patients smoking marijuana gained significant benefit.

Analyzing patient evaluations, the report concluded that approximately 93% of marijuana inhalation treatment episodes were effective or highly effective when compared with other anti-emetics. The New York study reported no serious adverse side effects. No patient receiving marijuana required hospitalization or any other form of medical intervention.

DISCUSSION

Even though slightly different methods and different research designs were used in these studies, it is clear that inhaled marijuana was

effective in reducing or eliminating nausea and vomiting following cancer chemotherapy. In those studies which compared the inhalation route to oral THC, inhalation was equal to or better than oral administration. In almost all of these studies, patients were admitted only after they failed treatment with standard anti-emetics, suggesting the patients may have been under fairly aggressive treatment for their cancers.

With regard to side effects, short term use of marijuana leads to sedation, a high, and smoke intolerance in some patients. At this point in time there is no conclusive evidence that marijuana smoke seriously affects the immune system or is associated with cancer (Joy, Watson and Benson, 1999).

In a 1991 survey, Doblin and Kleiman (1991) reported that more than 70% responding oncologists (n = 1035) reported at least one of their patients had used marijuana as an anti-emetic, and that they had also either observed or discussed the patients' use. In addition, 44% of the respondents reported recommending marijuana to at least one patient. Two hundred seventy-seven respondents felt they had clinical experience with both marijuana and Marinol™ (oral THC): (44% thought marijuana was more effective, 43% thought they were about equally effective, and 13% thought Marinol™ was more effective). These data suggest that physicians at that time continued to discuss or recommend marijuana use to some patients. In this sample of oncologists, it seems they understood the potential efficacy of marijuana use. Whether this situation has changed since 1991 is unknown, but one might argue that the introduction of the anti-emetics of the selective serotonin-3 antagonist class, may have changed this practice.

While there have been no studies which have compared smoked marijuana or Marinol™ with the serotonin receptor type-3 antagonists (granisetron or ondansetron), it is instructive to review published clinical trials with these compounds for the sake of comparison. In 9 clinical trials with ondansetron, anti-emesis was obtained in 40%-81% (mean 63.5%) of patients (Beck et al. 1993; Buser et al. 1993; Crucitt et al. 1994; Hainsworth et al. 1991; Herrstedt et al. 1993; Kaasa et al. 1990; Marty et al. 1980; Olver et al. 1996; Roila et al. 1991). In 5 clinical trials with granisetron, 37.7%-93% (mean 56.6%) anti-emesis was reported (Italian Group for Antiemetic Research 1995; Markman et al. 1996; Perez et al. 1997; Ritter Jr. et al. 1998; Sekine et al. 1996). It is generally known that combining anti-emetic drugs with different

mechanisms of action often improves efficacy (Jones et al. 1991). This suggests that future research should consider combining cannabinoids with other anti-emetics.

The data reviewed here suggest that the inhalation of THC appears to be more effective than the oral route. In order to achieve the IOM recommendation to allow patients access to marijuana, both state and Federal Governments would need to reschedule marijuana from Schedule I to Schedule II, or reinstate the Compassionate Use Program. The development of smokeless inhalation devices would certainly be an advance in the use of THC as an anti-emetic medication. Finally, a large number of synthetic cannabinoid and endocannabinoid agonist analogs have been developed. It would seem that testing of these compounds as potential anti-emetics would also be worthwhile.

REFERENCES

Beck TH, AA Ciociola, SE Jones et al. and the Ondansetron Study Group. 1993. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med* 118:407-13.

Behavioral Health Sciences Division. 1984. *The Lynn Pierson Therapeutic Research Program*. Health and Environment Department: New Mexico.

Behavioral Health Sciences Division. 1983. *The Lynn Pierson Therapeutic Research Program*. Health and Environment Department: New Mexico.

Board of Pharmacy, State of Tennessee. 1983. *Annual Report: Evaluation of marijuana and tetrahydrocannabinol in the treatment of nausea and/or vomiting associated with cancer therapy unresponsive to conventional anti-emetic therapy: Efficacy and toxicity.*

Buser KS, RA Joss, D Piquet et al. 1993. Oral ondansetron in the prophylaxis of nausea and vomiting induced by cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in women with breast cancer. Results of a prospective, randomized, double-blind, placebo-controlled study. *Ann Oncol* 4:475-9.

Chang AE, DJ Shiling, RC Stillman et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 91:819-24.

Crucitt MA, W Hyman, T Grote et al. 1996. Efficacy and tolerability of oral ondansetron versus prochlorperazine in the prevention of emesis associated with cyclophosphamide-based chemotherapy and maintenance of health-related quality of life. *Clin Ther* 18(4):778-88.

Cupissol DR, B Serrou, and M Caubel. 1990. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high-dose cisplatin-induced emesis. *Eur J Cancer* 26(1):23-7.

Department of Social Oncology, Evaluation Unit. 1982. State of Michigan, *Marihuana Therapeutic Research Project*.

Doblin, R and M Kleiman. 1991. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes *J Clin Oncol* 9(5):1314-19.

Herrstedt J, T Sigsgaard, M Boesgaard, T Jensen, and P Dombernowski. 1993. Ondansetron plus metopimazine compared with ondansetron in patients receiving moderately emetogenic chemotherapy. *N Engl J Med* 328(15):1076-80.

Italian Group for Antiemetic Research. 1995. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *New Engl J Med* 332(1);1-5.

Jones AL, AS Hill, M Soukop et al. 1991. Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 338:483-87.

Joy J, SJ Watson, and JA Benson. 1999. *Marijuana as medicine: Assessing the science base*. Washington DC: National Academy Press.

Kaasa S, S Kvaløy, MA Dicato et al., and the International Emesis Study Group. 1990. A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: A randomized, double-blind study. *Eur J Cancer* 26(3):311-14.

Kutner, MH. 1983. *Evaluation of the use of both marijuana and THC in cancer patients for the relief of nausea and vomiting associated with cancer chemotherapy after failure of conventional anti-emetic therapy: Efficacy and toxicity, as prepared for the Composite State Board of Medical Examiners, Georgia Department of Health, by physicians and researchers at Emory University, Atlanta*.

Markman M, A Kennedy, K Webster et al. 1996. Control of carbonplatin-induced emesis with a fixed low dose of granisetron (0.5 mg) plus dexamethasone. *Gynecol Onco* 60:435-7.

Marty M, P Pouillart, S Scholl et al. 1990. Comparison of the 5-hydroxytryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 322(12):816-21.

Michigan Cancer Foundation, Department of Social Oncology, Evaluation Unit. 1992. *Michigan Department of Public Health Marijuana Therapeutic Research Project, Trial A 1980-81*.

Olver I, W Paska, A Depierre et al. 1996. A multicentre, double-blind study comparing placebo, ondansetron and ondansetron plus dexamethasone for the control of cisplatin-induced delayed emesis. *Ann Oncol* 7:945-52.

Perez EA, RM Navari, HG Kaplan et al. 1997. Efficacy and safety of different doses of granisetron for the prophylaxis of cisplatin-induced emesis. *Support Care Cancer* 5:31-7.

Randall RC. 1990. *Cancer Treatment & Marijuana Therapy.* Washington DC: Galen Press, 1990. 225-34.

Research Advisory Panel. 1989. *Cannabis Therapeutic Research Program. Report to the California Legislature*.

Ritter Jr. HL, RJ Gralla, SW Hall et al. 1998. Efficacy of intravenous granisetron to control nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *Cancer Invest* 16(2):87-93.

Roila F, M Tonato, F Cognettti et al. 1991. Prevention of cisplatin-induced emesis: A

double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 9(4):675-8.

Sekine I, Y Nishiwaki, R Kakinuma et al. 1996. A randomized cross-over trial of granisetron and dexamethasone versus granisetron alone: The role of dexamethasone on day 1 in the control of cisplatin-induced delayed emesis. *Jp J Clin Oncol* 26(3):164-68.

Vinciguerra V, T Moore, E Brennan. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *NY State J Med* 88:525-7.

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