Chapter 4

CANNABINOIDS AS ANTIEMETICS IN CANCER CHEMOTHERAPY

Martin Levitt

TABLE OF CONTENTS

I. INTRODUCTION

The evolution of cannabinoids as antiemetics in cancer chemotherapy required three preconditions: effective cancer chemotherapy; emetogenic and/or nauseating cancer chemotherapy, the relative antineoplastic effectiveness of which justified its clinical use; and the existence of antiemetic and/or antinauseant cannabinoid drugs with a favorable therapeutic index. The first two preconditions have existed since the 1960s and this chapter will address the third precondition.

The literature is replete with references to the use of marijuana under medical and pseudomedical circumstances for a variety of indications in many cultures for almost 5000 years. The appetite-stimulating and antiemetic effects of cannabinoids are well established but their mechanism is not well understood. Relatively early references to these medicinal properties can be found without difficulty in literature of the 19th century.[1-3]

Perhaps the earliest "modern" reference to the chemotherapy-antiemetic effects of marijuana was authored by a poet who was receiving chemotherapy for leukemia in 1972.[4] In 1975, Sallan et al. first demonstrated the antiemetic superiority of Δ^9-tetrahydrocannabinol (THC) over placebo in a double-blind randomized study of 22 patients, most of whom were "known to be refractory to conventional antiemetics."[5] This was based on the isolation and identification in 1964 of THC as the "major active psychotropic principle of marijuana."[6]

Pharmaceutically, pharmacologically, and aesthetically ingested THC is better than smoked marijuana. In efforts to improve further on pharmaceutical properties, pharmacologic properties, and for commerical reasons, the THC analogs nabilone[7]; and levonantradol[8] were synthesized by the pharmaceutical industry and have undergone extensive clinical trials which will be listed in the next section. Other advantages enjoyed by these synthetic analogs include lack of the social stigma attached to using marijuana and its natural components. At the time of writing, November 1984, nabilone is available by prescription in Canada and the U.K. It is reputedly soon to be prescribable in Australia as well, and it is possible that both THC and nabilone will soon be prescribable in the U.S.

II. CLINICAL TRIALS

Table 1[9-63] is a comprehensive listing of clinical trials involving THC, nabilone, and levonantradol, the three most commonly clinically tested cannabinoid antiemetics. General observations include the overwhelming confinement of these studies to English publications; the scarcity of studies exploring drug doses or schedules; the scarcity of studies comparing cannabinoids with each other; and the relative scarcity of studies where cannabinoids are combined with antiemetic drugs of other pharmacologic classes. The majority of studies involved patients described as previously refractory to conventional antiemetics; thus, anticipatory nausea and other factors related to previous experience were frequent confounding variables.

Notions have arisen from these studies, many of which have not been reproduced or precisely defined. Unfortunately, many of the studies have been uncontrolled, have included relatively few patients, and have been relatively heterogeneous with respect to variables such as chemotherapy, patient population, previous treatment, and study design. Nevertheless, there is undoubtedly validity to some of these "notions" which include (continued on page 75):

Table 1
CLINICAL TRIALS OF CANNABINOIDS AS ANTIEMETICS

Year published	Cannabinoid	Comments	Ref.
		Proceedings	
1984	THC	Abst; 136 patients; "prolonged" dosing with 2.5 mg/m²: better therapeutic index than 5 mg/m²	9
1984	THC	Abst; 20 patients RCDB crossover; ingested THC superior to smoked marijuana	10
1983	THC	Abst; 46 patients refractory to conventional antiemetics; partial RCDB crossover; THC enhances prochlorperazine antiemesis	11
1982	THC	Abst; 27 patients RCDB vs. metoclopramide; "metoclopramide superior"	12
1982	THC	Abst; 15 patients uncontrolled; "THC plus prochlorperazine" found ineffective	13
1981	THC	Abst; 36 patients RCDB crossover; "23/36 preferred THC, 1/36 prochlorperazine"	14
1981	THC	Abst; 120 patients RCDB; "15 mg THC best antiemetic, but prochlorperazine best antinauseant of 6 study treatments"	15
1979	THC	Abst; 15 patients RCDB; THC plus marijuana vs. placebo; THC superior	16
1979	THC	Abst; 111 patients (median age 61) RCDB vs. prochlorperazine; "THC antiemetic but significant dysphoria experienced"	17
1984	THC	31 patients RCDB crossover vs. metoclopramide (Cisplatin chemotherapy); "metoclopramide preferred"	18
1984	THC	7 patients RCDB vs. prochlorperazine in radiotherapy; "THC preferred"	19
1982	Marijuana	"Untreated street" marijuana cigarettes may contain pathogenic bacteria	20
1982	THC	214 patients RCDB crossover vs. prochlorperazine; "despite no measurable difference nausea or vomiting, more patients preferred THC"	21
1980	THC	55 patients RCDB crossover vs. prochlorperazine vs. placebo; THC "best"	22
1980	THC	25 patients RCDB crossover vs. prochlorperazine; "20 preferred THC"	23
1980	THC	35 patients RCDB vs. thiethylperazine vs. metoclopramide; "THC inferior"	24
1980	THC	52 patients RCDB crossover vs. haloperidol; "no preference"	25
1981	BRL-4664	23 patients phase 1: "an effective THC analog"	26
1981	THC	25 patients uncontrolled; "THC effective but toxic"	27
1981	THC	55 patients vs. prochlorperazine vs. placebo; THC "superior"	28
1981	THC	120 patients RCDB vs. prochlorperazine vs. placebo; "even 'low' (5-mg) doses of THC caused reduced intraocular pressure and distortions of perception"	29
1981	THC	22 patients RCDB vs. placebo (adriamycin + cyclophosphamide); "THC ineffective"	30
1979	THC	15 patients RCDB vs. placebo (high-dose methotrexate); "THC effective"	31
1979	THC	111 elderly patients RCDB vs. prochlorperazine; "THC more antiemetic but more dysphoric"	32
1981	THC	Admittedly anecdotal; "THC plus prochlorperazine studied, uncontrolled with apparently beneficial results"	33
1981	THC	Conclusion: "THC induces no apparent alterations of cyclophosphamide or adriamycin pharmacokinetics"	34
1983	THC	No data available	35

Table 1 (continued)
CLINICAL TRIALS OF CANNABINOIDS AS ANTIEMETICS

Year published	Cannabinoid	Comments	Ref.
		Proceedings	
1984	Nabilone	Abst; RCDB crossover 22 pediatric patients; "nabilone superior to prochlorperazine"	36
1979	Nabilone	Abst; 35 patients RCDB crossover; "15 preferred nabilone, 4 prochlorperazine"	37
1984	Nabilone	Abst; 32 children RCDB vs. prochlorperazine; "nabilone preferred"	38
		Papers	
1983	Nabilone	20 patients RCDB crossover vs. chlorpromazine (Cisplatin chemo); "10 preferred nabilone, 5-chlorpromazine"	39
1983	Nabilone	34 patients RCDB crossover vs. prochlorperazine; "nabilone preferred but dysphoria noteworthy"	40
1982	Nabilone	38 patients RCDB vs. placebo; "nabilone effective; dysphoria"	41
1982	Nabilone	80 patients RCDB crossover vs. prochlorperazine; "60 preferred nabilone"	42
1979	Nabilone	113 patients RCDB crossover vs. prochlorperazine; "nabilone preferred"	43
1977	Nabilone	13 patients uncontrolled; "nabilone effective in 10"	44
1982	Nabilone	84 patients RCDB vs. placebo; "effective but dysphoria a problem"	45
1982	Nabilone	26 patients RCDB vs. prochlorperazine; "nabilone more effective but more dysphoria, hypotension"	46
1982	Nabilone	52 out-patients; uncontrolled; previous "phenothiazine-failures"; "two thirds of patients preferred nabilone to previous treatment"	47
1982	Nabilone	54 patients; RCDB vs. placebo; "67% preferred nabilone; 11 discontinued due to "side effects"	48
1982	Levo[a]	Abst; 36 patients uncontrolled; resistant to conventional antiemetics; "equivocal results"	49
1982	Levo	Abst; 42 patients RCDB vs. prochlorperazine; "levo more antiemetic also more dysphoric"	50
1982	Levo	50 patients "resistant to conventional antiemetics" vs. placebo; "levo effective"	51
1981	Levo	Abst; phase-I study; 31 patients, "levo effective"	52
1983	Levo	Abst; RCDB vs. THC; 46 entered/26 completed; "no difference"	53
1984	Levo	20 patients RCDB vs. prochlorperazine; "levo more side effects"	54
1982	Levo	36 patients phase-I study; "0.5 mg effective i.m."	55
1982	Levo	35 patients phase-1 study "drug effective"	56
1982	Levo	27 patients phase-1; "drug effective"	57
1982	Levo	12 patients uncontrolled; "high incidence of side effects"	58
1982	Levo	? patients uncontrolled; "high incidence of side effects"	59
1982	Levo	German; 87 patients; uncontrolled; "a good antiemetic effect with only mild side effects"	60
1982	Levo	43 outpatients receiving radiotherapy; levo, chlorpromazine equally effective	61
1982	Levo	21 patients were refractory to standard antiemetics; "toxicity was minimal, and efficacy not evaluable"	62
1983	Levo	23 patients "refractory to conventional antiemetics"; uncontrolled "Levonantradol is an effective antiemetic in approximately 50% of patients resistant to conventional antiemetics . . . side effects are common and frequently unpleasant."	63

Note: RCDB, randomized controlled double-blind; THC, delta-9-tetrahydrocannabinol; Abst, abstract; Levo, levonantradol.

1. "Pre-medication" and prolonged use of lower doses of cannabinoids[9] may have a better therapeutic index than the more acute use of higher doses. This principle seems to govern the "conventional" dosing schedule with nabilone, wherein the first dose generally precedes chemotherapy by approximately 12 hr.
2. Ingested THC has been found superior to smoked marijuana in a controlled study.[10] This observation is possibly related to the fixed-interval dosing and lower blood levels achieved with the inhaled marijuana.
3. A small number of preliminary studies[11,15,33] suggest that cannabinoids and phenothiazines may be therapeutically synergistic.
4. A small number of studies suggests that high-dose metoclopramide is superior to THC, especially in patients receiving cisplatin chemotherapy.[12,18]
5. Generally, but not universally, THC or nabilone have been found to be preferred over prochlorperazine by most patients in randomized controlled double-blind crossover studies. In most of these studies, however, the patients had exhibited prior "drug resistance" to the antiemetic effects of phenothiazines. In one study,[17,32] THC and prochlorperazine were equally effective in the antiemetic sense, but the conclusion was that prochlorperazine was preferred because of "the tendency toward dysphoric effects by THC in elderly patients."
6. One study[15,29] involving 120 patients demonstrated that while tetrahydrocannabinol was the best antiemetic, prochlorperazine was the best antinauseant. Another study indicated strong patient preference for one antiemetic regimen over another in spite of equivalent effectiveness of the two regimens for relief of nausea, or volume and frequency of emetic events.[66]
7. Marijuana cigarettes may contain pathogenic bacteria.[20] While the significance of this is unclear, it clearly supports the advantage of a defined oral pharmaceutical preparation.
8. The occurrence of reduced intraocular pressure and distortions of perception was independent of dose of THC in doses between 5 and 15 mg.[29]
9. The effectiveness of THC and, hence, other cannabinoids, may vary with the chemotherapeutic drug(s) involved.[30,31] Although the work cited describes therapeutic differences for drugs of approximately equal emetogenicity, it is generally felt that cannabinoids are less effective with cisplatin, which is generally recognized as the most emetogenic drug and that more clinical trials are necessary to elucidate the presumed enhancement of effect by combining cannabinoids with complementary antiemetics of other pharmacologic classes.
10. THC does not alter pharmacokinetics of cyclophosphamide or adriamycin.[34]
11. Nabilone is effective in pediatric patients and may be preferable to prochlorperazine.[36,38]
12. Nabilone may be preferable to chlorpromazine in patients receiving cisplatin chemotherapy.[39]

The overall impression is that dysphoria may be the major side effect with all three cannabinoids. The data seemed most precise for nabilone, suggesting an incidence of "intolerable" dysphoria of about 10% for this drug. The incidence seems higher for levonantradol, and possibly somewhat lower for THC.

All three drugs are effective antiemetics. Levonantradol has the advantage of availability, either orally or parenterally, but despite the absence of direct comparisons, it seems to be associated with a higher frequency of dysphoric effects, and at present it therefore seems unlikely to advance beyond the investigational stage. Nabilone and THC, on the other hand, appear to have a somewhat more promising present and future clinically.

III. MECHANISMS

A. Pharmacology and Physiology of Chemotherapy-Induced Emesis

Vomiting is the expulsion of contents of the gut, largely by forces generated by the respiratory muscles.[64] "Central" emetics of the apomorphine prototype effect their stimulus, primarily through the chemoreceptor trigger zone (CTZ), which is one of the sources of stimulation of the medullary vomiting center, the final central neurologic mediator of emesis. Since vomiting can also be induced by activation of other chemosensory inputs to the vomiting center, blockade of vomiting in cancer chemotherapy may require interruption of more than one type of chemosensory input; thus, for example, the pure blockade of dopamine-mediated vomiting may be relatively ineffective. Numerous hypotheses implicating a variety of neurotransmitters in the emetic effects of chemotherapeutic agents have been published, but their precise involvement in specific "chemotherapy situations" has not been conclusively demonstrated. Indeed, even when the neurotransmitter profile for each chemotherapeutic agent is defined, the challenge will remain to chemically interrupt emesis-related inputs selectively, while preserving respiratory homeostasis.[65]

Nausea, the sensation of discomfort associated with vomiting from most causes, is a cerebral function, as is "anticipatory emesis". Although the experiences of nausea and vomiting have been almost universally considered interchangeable by most authors and practitioners, there is some evidence that this may be unjustified. Anecdotally, patients frequently report feeling better when their nausea is "relieved by vomiting." Other evidence supporting the duality of nausea and vomiting is the finding in one study of THC as the best antiemetic and prochlorperazine the best antinauseant.[15] Another is the apparent lack of concordance between patient preference, antiemetic effect, and antinauseant effect of drugs in another study.[66]

Borison and McCarthy state that " . . . it is conceivable that nausea could persist even while the performance of vomiting was blocked.[64] As a case in point, rats are naturally unable to vomit, yet seem to experience the associated discomfort . . . the rat's failure to vomit is not simply a mechanical disability as is generally assumed; rather it is best explained as being a species-adaptive neurological deficit. Nevertheless, the rat is responsive to emetic stimuli, displays autonomic and behavioural signs corresponding to the presence of nausea." These authors also stress that normal paraemetic autonomic visceral responses yield widespread and profound physiological concomitants of nausea, but these are not essential for the performance of vomiting per se.

Borison and McCarthy go on to say that, "the crucial question for clinical purposes is whether nausea and vomiting might be separately vulnerable to pharmacological suppression . . . . It would appear from the evolutionary condition of emetic refractoriness in the rat, that the nausea-directed limb of the reflex arc originates in the emetic circuit before the signal passes to the vomiting-control mechanism, which is inoperative in this species. Theoretically, such arrangement of neural conditions should permit separate neurochemical access to the nausea control loop, as it bypasses the mechanical co-ordinating mechanism for emesis . . . . Hence in confronting the totality of nausea and vomiting in cancer chemotherapy, some credence should be given to the possibility that a drug may be found which could eliminate the suffering of nausea, while it leaves the vomiting unaffected. The successful application of hypnosis to overcome anticipatory emesis[67] offers encouragement for seeking a psychotropic drug capable of selectively allaying the mental distress of nausea."

A detailed description of the current state of knowledge of all aspects of the physiology and pharmacology of nausea and vomiting is beyond the scope of this chapter, and the reader is referred to the relevant reviews on the subject.[64,65,68]

B. Cannabinoids and Chemotherapy-Induced Emesis

The antiemetic effectiveness of nabilone was compared in unanesthetized cats, with that of prochlorperazine and no drug, against the emetic stimuli of the chemotherapeutic agents semustine (BCNU), mechlorethamine hydrochloride (nitrogen mustard), and cis-platinum (*cis*-diaminedichloro-platinum II).[69] Nabilone was found effective for all tested emetic stimuli, whereas prochlorperazine was ineffective in antagonizing the emetic response to mechlorethamine.

Cannabinoids exercise a considerable influence on cerebral function,[68] above the level of the vomiting reflex arc. Cannabinoids could, therefore, interrupt vomiting through descending inhibitory connections to the lower brain stem centers. If it could be shown, on the other hand, that cannabinoids act specifically to interfere with emesis-related neurotransmission at the medullary level, these drugs could be much more rationally utilized, particularly in combination with drugs acting at complementary sites.

Other studies in animals suggest that THC has actions at the level of the reticular formation, thalamus, and cerebellum and exerts an anticholinergic effect.[70,71] Furthermore, there is evidence that cannabinoid antiemetic activity may be related to inhibition of the prostaglandin cyclic nucleotide system.[72,73] Finally, the interaction of opioids, endorphins, enkephalins, and cannabinoids may be relevant to this area. In a mouse model system[74] various cannabinoids inhibited the production of morphine abstinence by the opioid antagonist naloxone. There appeared to be a structure/response relationship in the effectiveness of the various cannabinoids in inhibiting this morphine abstinence syndrome. Subsequently, in a dog system[75] it has been demonstrated that pretreatment with intraventricular naloxone blocked the emetic responses induced by intraventricular endorphin (met-enkephalin) and morphine, but not apomorphine. It was concluded by the authors that "the selective protective action of the opiate antagonist (naloxone) against met-enkephalin and morphine supported the presence of enkephalin receptors in the emetic chemoreceptor trigger zone (CTZ)." It is tempting to contemplate a mechanism involving the interaction of endogenous (and possible exogenous) opioids with cannabinoids, and chemical and neurologic and psychologic aspects of chemotherapy and cannabinoids.

Thus, the precise mechanisms are unclear, but there are numerous clues.

IV. CONCLUSIONS

The use of cannabinoids as cancer chemotherapy antiemetics represents, in essence, the use of a drug with a relatively undefined mechanism of action to treat the side effects of other drugs, also with relatively undefined mechanisms of action, which are being used to treat cancer, a disease or series of diseases the precise nature of which remains enigmatic. In spite of these fundamental areas of ignorance, as well as the paucity of even specific empiric data (Table 1), the broad interest in and use of cannabinoids is at hand, partly as a result of its continuing "mythology", as well as the frequent absence of better alternatives. Indeed, the widespread, "unsupervised" use of cannabinoids as antiemetics is exemplified by the independent publication of a booklet in 1979[76] containing such information for "consumers" as the timing of marijuana use with chemotherapy and radiation therapy, acquiring marijuana, and preparation of marijuana in capsules, food, or suppositories. A variety of recipies includes marijuana brownies, honey slides, and chocolate chip cookies. Indeed, in the late 1970s and early 1980s many newspapers contained almost daily reports on this subject.

The level of public interest in this area in the U.S. at this time is further illustrated by the convocation of "Consensus Meetings" by the National Institutes of Health in 1978 and 1979[77,78] and a report to the U.S. Congress by Dr. Phillip Schein in 1980.[79]

The information and recommendations reported in these meetings are contained in Table 1. Perhaps the most explicit expression of legislative interest and intention was promulgated by the Research Advisory Panel of the State of California[80] in 1981. The panel stated that they had planned and were " . . . currently executing a large collaborative phase III trial of oral THC and smoked marijuana in patients receiving chemotherapy or radiation therapy for cancer." Four protocols were described. In the first, adults receiving "cyclic chemotherapy" were studied; in the second, adults receiving radiation therapy or "daily chemotherapy" (anticancer drugs on three or more consecutive days) were studied; the third protocol involved cyclic chemotherapy in pediatric patients (ages 5 through 14). Although these are alluded to as "phase-III studies", controls are not described; only THC regimens are described. Apparently doses were systematically raised with each succeeding chemotherapy treatment until either a satisfactory effect or prohibitive toxicity occurred. The fourth protocol provided marijuana cigarettes to hospitalized adult patients receiving cisplatin, dacarbazine, or 5-azacytadine, alone or in combination with other agents. This was intended only for "marijuana-experienced" individuals and a standardized smoking procedure was utilized.

It was expected that at least 3000 patients would be evaluated in this collaborative study. This reviewer has not encountered any publications or other information concerning results of this project, and it seems possible that the investigational objects may have paralleled the clinical objective of obtaining THC for what were thought to be appropriate patients.

Cannabinoids as "cancer chemotherapy antiemetics" have been extensively reviewed by others. The first such extensive review appeared in a 1981 monograph on the treatment of cancer-chemotherapy-induced nausea and vomiting generally.[81] This monograph was research oriented, and 102 of its 230 pages are devoted to cannabinoid studies. Other relatively new antiemetics less extensively described include high-dose metoclopramide, butyrophenones, and glucocorticoids. Other general reviews on antiemetic treatment of cancer chemotherapy antiemetics which prominently included discussions of cannabinoids, appeared in 1983.[82-84] Subjects such as anticipatory nausea and anticholinergics are addressed by Maule and Perry in their review.[83]

At this point "a distillation" of the material reviewed discloses the following information in hand. First, THC, nabilone, and levonantradol have some effectiveness as cancer chemotherapy antiemetics. It is virtually certain that smoked marijuana is similarly effective. Although hard data comparing the cannabinoids to each other or defining specific dose schedules seem not to exist, there seems to be a "general feeling" that levonantradol may have prohibitive psychological side effects and that nabilone may have unacceptable dysphoric effects in approximately 10% of patients, but on the other hand, may have less "abuse potential" than THC because of reduced euphoric effects.[85]

Second, while adverse psychological effects and somnolence appear to be the most prominent side effects, a variety of potential side effects related to other pharmacologic effects and in vitro studies of the cannabinoids deserves inclusion.[86] Smoked marijuana may contain pathogenic microorganisms and its habitual use has been described as causing or contributing to bronchitis and emphysema. Furthermore, smoke from marijuana cigarettes accelerates malignant transformation of lung cells in tissue culture.[87] Arteriosclerotic heart disease has been considered a contraindication because of the pharmacologic tachycardia and reports that marijuana aggravates angina. The cannabinoids, particularly nabilone, have also been associated with orthostatic hypotension,[41] which, in general, is relatively mild. Other adverse effects include tremulousness, impairment of coordination, distortions of perception,[29] and hallucinations. There is no conclusive evidence on clinical effects relevant to pregnancy, but the drugs

are generally considered contraindicated in this setting with some in vitro justification.[88] The long-term physical and psychological consequences of using cannabinoids remain unclear.

Finally, it seems quite clear that cannabinoids are relatively effective cancer chemotherapy antiemetics, but their most advantageous application remains to be elucidated with further research, at least some of which should address the following questions:

1. The use of cannabinoids in optimum doses and schedules
2. The use of combinations of cannabinoids with other "established" antiemetics, or possibly complimentary drugs, such as tranquilizers
3. The possible development of new cannabinoids with better structure/function relationship[88a] and/or the possible alleviation of dysphoria induced by high dose cannabinoids using cannabidiol[89]
4. The possible more general application of cannabinoids in management of cancer-related symptoms, such as nausea/anorexia, and particularly pain[90,91]

Cannabinoids appear to be important drugs in the management of cancer. They may well have considerably broader implications than those currently under general consideration. Further basic and clinical research are required to address these important and interesting issues.

ACKNOWLEDGMENTS

The author is grateful for the contributions made by T. Reutcky, I. Steedman, and J. Powell.

REFERENCES

1. Wright, T. L., Some therapeutic effects of *Cannabis indica, The Cincinatti Lancet and Observer,* 7(2), 1863.
2. Aulde, J., Studies in therapeutics — *Cannabis indica, Ther. Gaz.,* 14, 523, 1890.
3. Adams, R., Marahuana, *Harvey Lect.,* 37, 168, 1942.
4. Rosenthal, T., *How Could I Not Be Among You?,* Avon Books, New York, 1973, 70.
5. Sallan, S., Zinberg, N., and Frei, E., III, Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy, *N. Engl. J. Med.,* 293, 795, 1975.
6. Gaoni, Y. and Mechoulam, R., Isolation, structure and partial synthesis of an active constituent of hashish, *J. Am. Chem. Soc.,* 86, 1646, 1964.
7. Lemberger, L. and Rowe, H., Clinical pharmacology of nabilone, a cannabinol derivative, *Clin. Pharmacol. Ther.,* 18, 720, 1975.
8. McCarthy, L. E. and Borison, H. L., Cis-platin emesis and cannabinoids in cats, *Pharmacologist,* 22, 448, 1980.
9. Meyers, F., Stanton, W., Dow, G. and Rocchio, G., Reduced adverse effects with optimal antiemetic dosage schedule of delta-9-tetrahydrocannabinol (THC), *ASCO Abstr.,* 3, 94, 1984.
10. Levitt, M., Faiman, C., Hawks, R., and Wilson, A., Randomized double blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics, *ASCO Abstr.,* 3, 94, 1984.
11. Artim, R. and DiBella, N., Tetrahydrocannabinol (THC) plus prochlorperazine (PCZ) for refractory nausea and vomiting (N/V), *ASCO Abstr.,* 2, 85, 1983.
12. Gralla, R. J., Tyson, L. B., Clark, R. A., Bordon, L. A., Kelsen, D. P., and Kalman, L. B., Antiemetic trials with high dose Metoclopramide: superiority over THC, and preservation of efficacy in subsequent chemotherapy courses, *ASCO Abstr.,* 1, 58, 1982.
13. Homesley, H. D., Gainey, J., Jobson, V. W., Spurr, C., Welander, C., Muss, H. B., and Kimball, J., Failure of delta-9-tetrahydrocannabinol and prochlorperazine to control chemotherapy induced nausea and vomiting, *ASCO Abstr.,* 1, 67, 1982.

14. McCabe, M., Smith, F. P., Goldberg, D., Macdonald, J., Wooley, P. V., Warren, R., Brodeur, R., and Schein, P. S., Comparative trial of oral 9-tetra-hydrocannabinol (THC) and prochlorperazine (PCZ) for cancer chemotherapy-related nausea and vomiting, *ASCO/AACR., Proc.*, 22, 416, 1981.
15. Levitt, M., Wilson, A., Bowman, D., Faiman, C., Kemel, S., Krepart, G., Schipper, H., Weinerman, B., and Weinerman, R., Dose vs. response of tetrahydrocannabinol (THC) vs. prochlorperazine (PCPZ) as chemotherapy antiemetics, *ASCO/AACR., Proc.*, 22, 422, 1981.
16. Chang, A. E., Shiling, D. J., Stillman, R. C., Goldberg, N. H., Seipp, C. A., Barofsky, I., and Rosenberg, S. A., A prospective randomized trial of delta-9-tetrahydrocannabinol (THC) as an antiemetic in patients receiving high dose methotrexate (MTX), *ASCO/AACR., Proc.*, 20, 377, 1979.
17. Frytak, S., Moertel, C. G., and O'Fallon, J. R., A comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as antiemetics for cancer chemotherapy, *ASCO/AACR., Proc.*, 20, 391, 1979.
18. Gralla, R., Tyson, L., Bordin, L., Clark, R., Kelsen, D., Kris, M., Kalman, L., and Groshen, S., Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol, *Cancer Treat. Rep.*, 68(1), 163, 1984.
19. Ungerleider, J., Andrysiak, T., Fairbanks, L., Tesler, A., and Parker, R., Tetrahydrocannabinol vs. prochlorperazine, the effects of two antiemetics on patients undergoing radiotherapy, *Radiology*, 150(2), 598, 1984.
20. Ungerleider, J., Andrysiak, T., Tashkin, D., and Gale, R., Contamination of marijuana cigarettes with pathogenic bacteria-possible source of infection in cancer patients, *Cancer Treat. Rep.*, 66(3), 1982.
21. Ungerleider, J., Andrysiak, T., Fairbanks, L., Goodnight, J., Sarna, G., and Jamison, K., Cannabis and cancer chemotherapy, a comparison of oral delta-9-THC and prochlorperazine, *Cancer*, 50(4), 636, 1982.
22. Orr, L., McKernan, J., and Bloome, B., Antiemetic effect of tetrahydrocannabinol compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis, *Arch. Int. Med.*, 140, 1431, 1980.
23. Sallan, S., Cronin, C., Zelen, M., and Zinberg, N., Antiemetics in patients receiving chemotherapy for cancer, *N. Engl. J. Med.*, 302, 135, 1980.
24. Colls, B., Ferry, D., Gray, A., and McQueen, E., The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy, *N.Z. Med. J.*, 662, 449, 1980.
25. Neidhart, J., Gagen, M., Wilson, H., and Young, D., Comparative trial of the antiemetic effects of THC and haloperidol, *J. Clin. Pharmacol.*, 21, 38S, 1981.
26. Staquet, M., Bron, D., Rozencweig, M., and Kenis, Y., Clinical studies with a THC analog (BRL-4664) in the prevention of cisplatin-induced vomiting, *J. Clin. Pharmacol.*, 21, 60S, 1981.
27. Sweet, D., Miller, N., Weddington, W., Senay, E., and Sushelsky, L., Δ-Tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy — a pilot study, *J. Clin. Pharmacol.*, 21, 70S, 1981.
28. Orr, L. and McKernan, J., Antiemetic effect of Δ^9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and Compazine, *J. Clin. Pharmacol.*, 21, 76S, 1981.
29. Levitt, M., Wilson, A., Bowman, D., Kemel, S., Krepart, G., Marks, V., Schipper, H., and Thomson, G., Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of Δ^9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications, *J. Clin. Pharmacol.*, 21, 103S, 1981.
30. Chang, A. E., Shiling, D. J., and Stillman, R. C., Goldberg, N. H., Seipp, C. A., Barofsky, I., and Rosenberg, S. A., A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy, *Cancer*, 47, 1746, 1981.
31. Chang, A. E., Shiling, D. J., and Stillman, R. C., Goldberg, N. H., Seipp, C. A., Barofsky, I., Simm, R. M., and Rosenberg, S. A., Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate: a prospective randomized evaluation, *Ann. Int. Med.*, 91, 819, 1979.
32. Frytak, S., Moertel, C., O'Fallon, J., Rubin, J., Creagan, E., O'Connell, M., Schutt, J., and Schwartau, N., Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy, a comparison with prochlorperazine and a placebo, *Ann. Int. Med.*, 91(6), 825, 1979.
33. Garb, S., Cannabinoids in the management of severe nausea and vomiting from cancer chemotherapy. Some additional considerations, *J. Clin. Pharmacol.*, 21 (Suppl. 8/9), 57S, 1981.
34. Riggs, C., Egorin, M., Fuks, J., Schnaper, N., Duffey, P., Colvin, O., Aisner, J., Wiernik, P., and Bachur, N., Initial observations on the effects of delta-9-tetrahydrocannabinol on the plasma pharmacokinetics of cyclophosphamide and doxorubicin, *J. Clin. Pharmacol.*, 21 (Suppl. 8/9), 1981.
35. Gez, E., Biran, S., Fuks, Z., Edelstein, E., Lander, N., and Mechoulam, R., A marihuana component for nausea and vomiting induced by chemo and radiotherapy, *Harefuah*, 105(10), 306, 1983.
36. Chang, H. S. L., MacLeod, S. M., and Correia, J. A., Nabilone vs. prochlorperazine for control of cancer chemotherapy-induced emesis in children, *ASCO Abstr.*, 3, 108, 1984.

37. Steele, N., Braun, D., O'Hehir, M., and Young, C., Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis, *ASCO/AACR Proc.*, 20, 337, 1979.
38. MacLeod, S., Chan, H., and Correia, J., Nabilone (N) vs. prochlorperazine (P) for control of chemotherapy-induced emesis in children, *Can. Soc. Clin. Invest., 1984 Meeting*, 7 (Suppl. 2), 1984, 1.
39. George, M., Pejovic, M. Thuaire, M., Kramer, A., and Wolff, J., Essai comparatif randomise d'un novel ante-emetique: la nabilone, chez des malades cancereuses traitees part le cis-platinum, *Biomed. Pharmacother.*, 37, 24, 1983.
40. Ahmedzai, S., Carlyle, D., Calder, I., and Moran, F., Antiemetic efficacy and toxicity of nabilone, a synthetic cannabinoid in lung cancer chemotherapy, *Br. J. Cancer*, 48, 657, 1983.
41. Levitt, M., Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients, *Cancer Treat. Rev.*, 9, Suppl. B., 49, 1982.
42. Einhorn, L., Nagy, C., Furnas, B., and Williams, S., Nabilone: an effective antiemetic in patients receiving cancer chemotherapy, *J. Clin. Pharmacol.*, 21, 64S, 1981.
43. Herman, T., Einhorn, L., Jones, S., Nagy, C., Chester, A., Dean, J., Furnas, B., Williams, S., Leigh, S., Dorr, R., and Moon, T., Superiority of Nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy, *N. Engl. J. Med.*, 300(23), 1295, 1979.
44. Herman, T., Jones, S., Dean, J., Leigh, R., Dorr, R., and Moon, T., Nabilone: a potent antiemetic cannabinol with minimal euphoria, *Biomedicine*, 27, 331, 1977.
45. Wada, J., Bogdon, D., Gunnell, J., Hum, G., and Rieth, T., Double-blind randomized, crossover trail of nabilone vs. placebo in cancer chemotherapy, *Cancer Treat. Rev.*, 9 (Suppl. B), 39, 1982.
46. Johansson, R., Kilkku, P., and Groenroos, M., A double-blind controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy, *Cancer Treat. Rev.*, 9 (Suppl. B), 25, 1982.
47. Cone, L., Green, D., and Helm, N., Use of nabilone in the treatment of chemotherapy-induced vomiting in an outpatient setting, *Cancer Treat. Rev.*, 9 (Suppl. B), 63, 1982.
48. Jones, S., Durant, J., Greco, F., and Robertone, A., A multi-institutional phase-III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting, *Cancer Treat. Rev.*, 9 (Suppl. B), 45, 1982.
49. Tyson, L. B., Gralla, R. J., Bordin, L. A., Clark, R. A., Bosl, G. J., and Young, C. W., Levonantradol: dose-finding studies and antiemetic trials in patients treated with cisplatin, *ASCO Abstr.* 1, 56, 1982.
50. Long, A., Mioduszewski, J., and Natale, R., A randomized double-blind crossover comparison of the antiemetic activity of levonantradol and prochlorperazine, *ASCO Abstr.*, 1, 57, 1982.
51. Stambaugh, J., McAdams, J., and Vreeland, F., A phase-II randomized trial of the antiemetic activity of levonantradol (CP-50, 556) in cancer patients receiving chemotherapy, *ASCO Abstr.*, 1, 62, 1982.
52. Diasio, R. B., Ettinger, D. S., and Satterwhite, B. E., Levonantradol, synthetic cannabinoid with potential usefulness as an antiemetic in chemotherapy-induced emesis, *ASCO/AACR Proc.*, 22, 416, 1981.
53. Citron, M., Herman, T., Fossierck, B., Krasnow, S., Vreeland, F., Harwood, S., Ortega, L., and Cohen, M., Double blind randomized crossover study of the antiemetic effect of Levonantradol (LVN) vs. tetrahydrocannabinol (THC), *AACR Abstr.*, 24, 165, 1983.
54. Sheidler, V., Ettinger, D., Diasio, R., Enterline, J., and Brown, M., Double-blind multiple dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine, *J. Clin. Pharmacol.*, 24, 155, 1984.
55. Cronin, C., Sallan, S., Gelber, R., Lucas, V., and Laszlo, J., Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy, *J. Clin. Pharmacol.*, 21, 43S, 1981.
56. Laszlo, J., Lucas, V., Hanson, D., Cronin, C., and Sallan, S., Levonantradol for chemotherapy-induced emesis: phase I-II oral administration, *J. Clin. Pharmacol.*, 21, 51S, 1981.
57. Diasio, R., Ettinger, D., and Satterwhite, B., Oral levonantradol in the treatment of chemotherapy-induced emesis: preliminary observations, *J. Clin. Pharmacol.*, 21, 81S, 1981.
58. Joss, R., Galeazzi, R., Bischoff, A., Do, D., Goldhirsch, A., and Brunner, K., Levonantradol, a new antiemetic with a high rate of side effects for the prevention of nausea and vomiting in patients receiving cancer chemotherapy, *Br. J. Cancer*, 46(3), 492, 1982.
59. Stuart, J., Welsh, J., Sangster, G., Scullion, M., Cash, H., Kaye, S., and Calman, K., The antiemetic potential of oral levonantradol in patients receiving cancer chemotherapy, *Br. J. Cancer*, 46(3), 492, 1982.
60. Hisi, M., Niederle, N., Bremer, K., Schmitt, G., Schmidt, C., and Seeber, S., Levonantradol in the treatment of nausea and vomiting caused by cytostatic drugs, *Dtsch. Med. Wochenschr.*, 107(33), 1232, 1982.
61. Lucraft, H. and Palmer, M., Randomized clinical trial on levonantradol and chlorpromazine in the prevention of radiotherapy-induced vomiting, *Clin. Radiol.*, 33(6), 621, 1982.

62. Kenny, J. and Wilkinson, P., Levonantradol effectiveness in cancer patients resistant to conventional antiemetics, *Clin. Oncol.*, 8(4), 335, 1982.
63. Stuart-Harris, R., Mooney, C., and Smith, I., Levonantradol: a synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and vomiting resistant to conventional antiemetic therapy, *Clin. Oncol.*, 9(2), 143, 1983.
64. Borison, H., and McCarthy, L., Neuropharmacology of chemotherapy-induced emesis, *Drugs*, 25 (Suppl. 1), 8, 1983.
65. Peroutka, S. J. and Snyder, S. H., Antiemetics: neurotransmitter receptor binding predicts therapeutic actions, *Lancet*, 1, 658, 1982.
66. Strum, S., McDermed, J., and Liponi, D., High-dose intravenous metoclopramide (MCP) vs. combination high-dose metoclopramide and intravenous dexamethasone (MCP + DXM) in preventing cisplatin-induced nausea and emesis, a single-blind crossover comparison of antiemetic efficacy, *J. Clin. Oncol.*, 3, 245, 1985.
67. Redd, W., Andresen, G. B., and Minagawa, R. Y., Hypnotic control of anticipatory emesis in patients receiving cancer chemotherapy, *J. Consul. Clin. Psychol.*, 50, 14, 1982.
68. Borison, H., Borison, R., and McCarthy, L., Phylogenic and neurologic aspects of the vomiting process, *J. Clin. Pharmacol.* 21, 23S, 1981.
69. Borison, H., McCarthy, L., and London, S., Cannabinoids and emesis, *N. Engl. J. Med.*, p. 1480, 1978.
70. Vincent, B. J., McQuiston, D., Einhorn, L., Nagy, C., and Brames, M., Review of cannabinoids and their antiemetic effectiveness, *Drugs*, 25(Suppl. 1), 52, 1983.
71. Mechoulam, R., *Marihuana: Chemistry, Pharmacology and Metabolism*, Academic Press, New York, 1973.
72. Burstein, S. H., *Prostaglandins and Cannabis. IV. A Biochemical Basis for Therapeutic Applications, The Therapeutic Potential of Marijuana*, Cohen and Stillman, Plenum Medical Book Company, New York, 1976, 19.
73. Krupp, P. and Wesp, M., Inhibition of prostaglandin synthetase by psychotropic drugs, *Experientia*, 31, 330, 1975.
74. Bhargava, H., Effect of some cannabinoids on naloxone-precipitated abstinence in morphine-dependent mice, *Psychopharmacology*, 49, 267, 1976.
75. Bhargava, K., Dixit, K., and Gupta, Y., Enkephalin receptors in the emetic chemoreceptor trigger zone of the dog, *Br. J. Pharmacol.*, 72, 471, 1981.
76. Hoffman, R., *Using Marijuana in the Reduction of Nausea Associated with Chemotherapy*, Murray Publishing, Seattle, Wash., 1979.
77. Minutes of Meeting on the Current Status of Research with Tetrahydrocannabinol and Nabilone for the Control of Cancer Chemotherapy-Induced Vomiting, Department of Health Education and Welfare, Washington, D.C., 1978.
78. Meeting: National Institute of Health Consensus Meeting, Control of Cancer Chemotherapy-Induced Vomiting, Current Status of Anti-emetic Research, Bethesda, Maryland, 1979.
79. Schein, P., Delta-9Tetrahydrocannabinol (THC) for the Prevention of Nausea and Vomiting Associated with Cancer Chemotherapy, Report to the U.S. Congress, Washington, D.C., 1980.
80. Dow, G. and Meyers, F., The California program for the investigational use of THC and marijuana in heterogeneous populations experiencing nausea and vomiting from anticancer therapy, *J. Clin. Pharmacol.*, 21 (Suppl. 8/8), 128S, 1981.
81. Poster, D. S., Penta, J. S., and Bruno, S., *Treatment of Cancer Chemotherapy-Induced Nausea and Vomiting*, Masson Publishing U.S.A., New York, 1981.
82. Brigden, M., Wilson, K., and Barnett, J., Rational choice of antiemetic agents during cancer chemotherapy, *Can. Fam. Phys.*, 29, 1682, 1983.
83. Maule, W. and Perry, M., Management of chemotherapy-induced nausea and emesis, *Pract. Ther.*, 27(1), 226, 1983.
84. Kaminski, M. and Erlichman, C., Current management of chemotherapy-induced nausea and vomiting, *Ther. Rev.*, 38(1), 53, 1983.
85. Lemberger, L., Rubin, A., Wolen, R., DeSante, K., Rowe, H., Forney, R., and Pence, P., Pharmacokinetics, metabolism and drug-abuse potential of nabilone, *Cancer Treat. Rev.*, 9(Suppl. B), 17, 1982.
86. *The Medical Letter*, Medical Letter, Inc., New York, 1976, 69.
87. Leuchtenberger, C. and Leuchtenberger, R., *Pharmacology of Marijuana*, Raven Press, New York, 1976, 595.
88. Nahas, G., et al., *Marijuana: Chemistry, Biochemistry and Cellular Effects*, Springer-Verlag, New York, 1976, 299.
88a. Dewey, W. L., *The Cannabinoids: Chemical, Pharmacologic, and Therapeutic Aspects*, Academic Press, Orlando, Fla., 1984.

89. Zuardi, A., Shirakawa, I., Finklefarb, E., and Karniol, I., Action of cannabidiol on the anxiety and other effects produced by Δ^9-THC in normal subjects, *Psychopharmacology*, 76, 245, 1982.
90. Ghosh, P. and Bhattacharya, S. K., Cannabis-induced potentiation of morphine analgesia in rat-role of brain monoamines, *Indian J. Med. Res.*, 70, 275, 1979.
91. Noyes, R., Brunk, S., Avery, D., and Canter, A., The analgesic properties of delta-9-tetrahydrocannabinol and codeine, *Clin. Pharamcol. Ther.*, 18(1), 84, 1975.