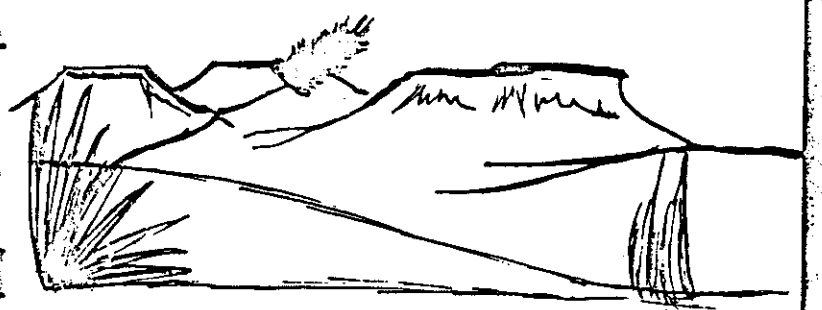
THE LYNN PIERSON THERAPEUTIC RESEARCH PROGRAM

A REPORT ON PROGRESS TO DATE



HEALTH & ENVIRONMENT

department

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Prepared by: Behavioral Health Services Division
Health and Environment Department

Robert P. McNeill
Secretary

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This report has been prepared and is submitted to the Thirty-sixth Legislature, First Session, pursuant to Section 26-2A-7, Report, of the Controlled Substances Therapeutic Research Act (26-2A-1 to 26-2A-7 NMSA 1978).

Introduction

The Lynn Pierson Therapeutic Research Program was established by State statute in 1978 and renamed in 1979 in honor of Mr. Lynn Pierson, a cancer patient whose efforts provided the impetus for the passage of the law and who died of his disease in the summer of 1978. The Lynn Pierson Therapeutic Research Program (LPTRP), administered by the Health and Environment Department[1], represented the first statewide research and treatment endeavor which provided marijuana and delta-9-THC to cancer chemotherapy patients suffering from the nausea and vomiting caused by their therapy. Although the Controlled Substances Act was amended to allow the possession of these drugs by patients who were participating in the LPTRP [see Section 30-31-7 A(1)e and f, NMSA 1978], the federal controlled substances laws superceded the State's, requiring an extensive and complicated process of gaining approval from the Food and Drug Administration, the Drug Enforcement Administration, and the National Institute on Drug Abuse for the LPTRP to begin. All necessary requirements were finally met in December 1978, the first shipment of the drugs arrived in January 1979, and the Program promptly began. This report to the Legislature synopsizes the activities of the LPTRP over the last four years and presents data regarding the efficacy of marijuana and delta-9-THC as anti-emetics to control the nausea and vomiting that result from chemotherapy in treating cancer patients.

To date, 180 patients have participated in the Program; another 51 individuals applied and were screened by the Patient Qualificaiton Board, but for one reason or another did not enter the Program. Virtually all

parts of New Mexico were represented by the residences of the patients, but, as would be expected from the population distribution in the State, most resided in the Albuquerque area. The kinds and locations of the cancer from which these individuals were suffering were varied, as were the types of chemotherapy which they were receiving. Since the Controlled Substances Therapeutic Research Act required that participants be restricted to patients "who are not responding to conventional controlled substances or where the conventional controlled substances administered have proven to be effective but where the patient has incurred severe side effects" (Section 26-2A-4 B NMSA 1978), all of the patients had already experienced at least one chemotherapeutic episode before entering the Program.

The Research Design

Briefly and simply stated, the research entailed administering half the patients marijuana and the other half delta-9-THC (thought to be the essential "active ingredient" in marijuana), with the former being inhaled by the patient and the latter ingested in the form of a capsule. Dosages were controlled to ensure that all patients received approximately the same amount, which was 15 mg. After having completed the application form and submitting it to the State, each patient was reviewed by the members of the Patient Qualificaiton Review Board and approved or disapproved for participation in the Program. Since the patient's physician had to complete part of the application form and, in essence, approve the patient's participation at the outset, there have been only two disapprovals since the Program began. Subsequent to his/her approval, the patient began the Program at the time of his/her next episode of chemotherapy. The marijuana or delta-9-THC capsule was administered in a physician's office (or, for many, at the Cancer Research and Treatment Center, University of New Mexico) at approximately the same time the chemotherapy began. All patients were monitored for the first four hours of taking the drug; the maximum length of time that any patient could receive the drug was five days. Blood samples were taken during this time, with analyses being conducted to determine the blood levels of delta-9-THC and two of its metabolites, in order to

determine the minimal level of the drug needed to produce the optimal anti-emetic effect. The results that are reported here emphasize the perceptions of the patients; the highly technical laboratory data will be reported in scientific journals. Of importance to the State and to the Legislature is the finding that these drugs have been determined to be effective in combatting and overcoming nausea and vomiting that are produced by chemotherapy. These results are briefly reviewed in the next section.

Findings of the Lynn Pierson Therapeutic Research Program

Of the 180 patients who participated in the Program, a complete set of data has been collected and analyzed from 140 individuals. The primary assessment questionnaire which has been utilized in the Program is the Target Problem Self-rating Scale, which was completed by the patients (a) as part of their application to the Program, (b) immediately prior to the administration of the drug and the chemotherapy, (c) four hours after the administration, and (d) 24 hours after administration. Copies of the Scale questionnaire are appended to this report.

The demographic characteristics of the 140 patients for whom complete data have been analyzed are presented below, along with the figures indicating the assignment of the patients to the experimental conditions (i.e., inhaled versus orally ingested routes of drug administration):

Sex: 76 females; 64 males

Age distribution by sex: Females: 12 years to 78 years
Males: 16 years to 76 years

Average age overall: 43.4 years

Assignment to experimental conditions:

	Female	Male
Inhaled	26.4%	19.3%
Oral	36.4%	17.9%

The findings that relate to the efficacy of the marijuana and delta-9-THC were compiled first by a composite score which simply

portrays the overall response of the patient, relative to his/her previous experiences. The possible outcomes are stated dichotomously; that is, a patient's response was either positive (e.g., with the use of marijuana or delta-9-THC there was a noticeable improvement relative to receiving chemotherapy with some other anti-emetic) or negative (e.g., there was no noticeable improvement). Overall, with both routes of administration combined, 74.83% of the patients showed a positive response, which is highly significant statistically (p .0001). A significant interaction was also found between positive/negative response and the route of administration (p .01). When the routes of administration were analyzed separately; it was found that inhalation was far superior to ingestion: 90.39% of the patients in the group that inhaled the marijuana showed improvement while only 59.65% of the patients in the group that orally ingested the delta-9-THC showed improvement. Statistically, the inhalation group improved significantly (p .0001), but the oral-ingestion group did not, when the results were tested against an hypothetical 50% chance improvement rate.[2] It should be noted that the route of administration is confounded, as a variable, with the administered drug; real marijuana is used by the smoking/inhalation group, whereas the capsules that are taken by the oral-ingested group contain synthetic delta-9-THC. Consequently, it is not possible to tell at this time if the difference in the effectiveness between the two groups is correctly to be attributed to the route <u>per se</u> or the drug that is being administered. Preliminary work is now underway to develop a means by which the synthetic delta-9-THC can be atomized and inhaled. If such a methodology is successfully tested and accepted by the Food and Drug Administration, it will be possible to separate the route variable from the drug variable, at least to the extent that the synthetic delta-9-THC can be used in the inhaled route of administration.

Assessing the different components of the Target Problem Self-rating Scale, it can be seen that the marijuana and delta-9-THC are more effective on certain symptoms than on others. Of the different feelings and conditions about which the patients were asked (see the Appendix for the items), statistically significant improvement was found for nausea, vomiting, pain, depression, and appetite. There was a small but

statistically significant change in the extent to which patients felt "high" after the drug's administration; the changes found on the item asking about sleep were ambiguous and equivocal.

On the basis of the results of the composite, overall effectiveness measure and on the separate subscales of the Target Problem Self-rating Scale, it can be concluded that the drug is effective as an anti-emetic in treating the effects chemotherapy (i.e., nausea and vomiting) and, additionally, other concomitant symptoms of both the disease and therapy (i.e., pain and depression), as reported above. Importantly, the finding that appetite was also improved significantly has bearing on the willingness and ability of the patients to eat, which can have further, positive effects on the nourishment of the patient and his/her prognosis for survival.

Although it is of interest to note that the marijuana cigarettes, when smoked, produce much greater overall positive effectiveness than does the delta-9-THC when orally ingested, the confounding of the route-of-administration variable and the type-of-drug variable prevents any conclusions to be drawn at this time. It is anticipated that during the next year the pilot work on the atomization methodology will be completed, and, if it is, the report submitted next year may provide answers to the questions regarding route and drug type.

Discussion

As indicated above, the drug has been shown to be effective as an anti-emetic. But that finding should not be considered the only important result produced by the Lynn Pierson Therapeutic Research Program. It is, from some perspectives, equally important to note that a novel -- and at times controversial -- proposal to provide marijuana for medical use has been successfully implemented in New Mexico, no occasions have arisen regarding the misuse or abuse of the drug, no problems have been encountered (either by patients, doctors, or the administration) in approving patients for participation or getting the drug to them when they need it, and, of several programs that were federally approved (New

Mexico's being the first), the Lynn Pierson Therapeutic Research Program is the only one that remains.

It is hoped that the Program will be allowed to continue, even with the many changes that have occurred at the federal level, and that New Mexico's cancer patients will continue to be helped by this important and unique endeavor.

FOOTNOTES

1. The Lynn Pierson Therapeutic Research Program is administered by the New Mexico Health and Environment Department. The daily operation Program is carried out by the University of New Mexico School of Medicine, under a contract from the Health and Environment Department. This report was produced by Edward Deaux, Ph.D., Chief, Director's Office of Research, Evaluation, and Planning, Behavioral Health Services Division, Health and Environment Department, and Daniel A. Dansak, M.D., Chairman of the Patient Qualification Review Board and Director of the Program within the School of Medicine, with the assistance of Katy Brazis, R.N., research nurse for the Program.

2. A convincing argument can be made that the application of the hypothetical 50% chance improvement rate is unnecessarily strict. All of the patients have used other anti-emetic drugs before entry into the Program, and those drugs have failed. If it were assumed that marijuana/delta-9-THC would be only as effective as these other drugs, an expectation of zero improvement could be used, in which case both marijuana-inhaled and delta-9-THC-ingested groups would have statistically significant improvement with the improvement of the marijuana-inhaled group significantly greater than that of the other group.

APPENDIX

PATIENT NAME _____
PATIENT NO. _____
DATE _____

TARGET PROBLEM SELF RATING SCALE

INTRODUCTION

For each problem area, please indicate how strong you feel the problem has been during past chemotherapy treatments. Place the number corresponding to your answer in the box to the right of the question.

1 = Not a problem
2 = Slight
3 = Mild
4 = Moderate
5 = Severe

1. How much was nausea a problem with chemotherapy? ☐
2. How much was vomiting a problem with chemotherapy? ☐
3. How much was feeling "sleepy" a problem with chemotherapy? ☐
4. How "high" did you feel with chemotherapy? ☐
5. How "uncomfortable" did you feel with chemotherapy? ☐
6. How much was pain a problem with chemotherapy? ☐
7. How much was appetite a problem with chemotherapy? ☐
8. How much was depression a problem with chemotherapy? ☐

Target Problem Self-Rating Scale 2

,ent No. _____ Administration No. (circle): 1 2 3 4 Time 0+ 0 : _____

Please indicate by checking the appropriate column following each question below how much you feel the problem is at the present time - that is, right now while you are filling out the questionnaire.

	0 Not a Problem	1 Slight	2 Mild	3 Moderate	4 Severe
1. How much is nausea a problem at the present time?					
2. How much is vomiting a problem at the present time?					
3. How much is feeling "sleepy" a problem at the present time?					
4. How "high" do you feel at the present time?					
5. How "uncomfortable" do you feel at the present time?					
6. How much is pain a problem to you at the present time?					
7. How much is appetite a problem to you at the present time?					
8. How much is depression a problem at the present time?					
9. How much is no desire to live a problem at the present time?					

Target Problem Self-Rating Scale 3

Patient No. _____ Postchemotherapy Administration (circle): 3 days 6 days

Please indicate by checking the appropriate column following each question below how you feel today.

	0 Not a Problem	1 Slight	2 Mild	3 Moderate	4 Severe
1. How much is nausea a problem today?					
How much is vomiting a problem today?					
3. How much is feeling "sleepy" a problem today?					
4. How "high" do you feel today?					
5. How "uncomfortable" do you feel today?					
6. How much is pain a problem to you today?					
7. How much is appetite a problem to you today?					
8. How much is depression a problem at today?					
How much is no desire to live a problem today?					

THE LYNN PIERSON THERAPEUTIC RESEARCH PROGRAM

ANNUAL REPORT TO THE LEGISLATURE

1984

NEW MEXICO
HEALTH AND ENVIRONMENT
DEPARTMENT

This month, January 1984, marks the completion of the fifth year of operation or the Lynn Pierson Therapeutic Research Program, the nation's first statewide program for the provision of marijuana and synthetic delta-9-THC for use as a medicine, one of only four statewide programs remaining, and the only program in the country that offers both forms of the drug. As required by Section 26-2A-7, NMSA 1978, this Report has been prepared to document the activities of the Program since the last Legislative Session.

During calendar year 1983, 33 cancer patients received marijuana and/or synthetic delta-9-THC to counter the nausea and vomiting caused by their chemotherapy and/or radiation therapy. The use of the drugs, whether administered orally or through inhalation, strictly follows the research protocol submitted to and approved by the Food and Drug Administration, Drug Enforcement Administration, National Institute on Drug Abuse, and the National Cancer Institute, all of which continue to monitor the Program. Participation continues to be limited to patients who have been carefully screened and approved by the Patient Qualification Review Board, of which Daniel Dansak, M.D., is Chairman. Although the Program is technically and legally defined as a research project and detailed data are gathered from participants before, during, and after the use of the drug, the Program is more generally a therapeutic endeavor designed to ease the pain and suffering of cancer victims. That statement is, importantly, not an assertion but rather a conclusion based on the results that have accumulated over the last five years.

To review the background of the Lynn Pierson Program briefly, the impetus for the Controlled Substances Therapeutic Research Act (Sections 26-2A-1 to 26-2A-7 NMSA 1978) was the need, emphatically expressed by Mr. Lynn Pierson, for the State of New Mexico to sanction, in some way, controlled and limited use of marijuana by cancer patients undergoing chemotherapy. At the time that the request was made by Mr. Pierson, during the 1978 Session, there was anecdotal evidence that marijuana was effective in some cases as a means of countering the nausea and vomiting caused by chemotherapy, and, as Mr. Pierson's testimony revealed, numbers of patients were using the drug, albeit illegally. As a compassionate response to Mr. Pierson's request, the Controlled Substances Therapeutic Research Act passed (with almost unanimously "yes" votes in both the House and the Senate), with the clear intent being that a program be established that would enable cancer patients undergoing chemotherapy and some glaucoma patients to obtain marijuana and/or delta-9-THC for limited and controlled medical usage. Due to the superseding Federal controlled

substance laws, the only way in which the Program could be implemented was through the development and approval of a detailed, lengthy, and highly complex research protocol. The process of gaining the necessary approval of the Federal agencies was further complicated by the fact that New Mexico's Program was the first of its kind in many respects, not the least of which were its statewide implementation and the need of the Health and Environment Department to avoid research/experimental approaches that were designed to "fool" patients into thinking that they were being administered the drug when in fact they were receiving a non-active placebo of some type (which would clearly have been counter to the Legislature's intent). In brief, almost a year was taken in gaining the required Federal approvals, the first shipment of the drug was received in January 1979, and the Program has been operational ever since. Mr. Pierson died before all the approvals necessary to implement the Program were obtained, but the Program was renamed in his honor through an amendment to the Act that passed during the 1979 Session. Throughout the history of the Program -- and most definitely in the perceptions of all those who have benefited from it -- the word "therapeutic" is the key descriptor for the Program, with the "research" component being viewed as secondary in some respects. The experimental activities are certainly important, in that they are required by both State and Federal law, have been carefully and rigorously conducted, reported, and monitored, and have led to accepted, documented results that substantiate the medical efficacy of the drug as an antiemetic. But the Program has also fulfilled the compassionate intent of the legislature by easing the pain and suffering of cancer patients who have had to face the awful consequences of chemotherapy. That New Mexico's Program is one of very few that remain from the surge of "duplicate bills" that were passed by other states in the years that followed New Mexico's pioneering effort is testimony to its successes, in terms of both "therapy" and "research."

Turning to the data that have been collected during the preceding year, the demographic characteristics of the participants are as follows.

Of the patients participating in the Program during the year, 42.4% were male, ranging in age from 18 to 73 years old (mean age = 39.8 years); 57.6% were female, ranging from 17 to 76 years of age (mean age = 49.4 years). Those who received only one course of treatment, defined as one chemotherapy session in which marijuana and/or delta-9-THC were used, represented 18.2% of the patients; the remaining 81.8% engaged in treatment during more than one course of chemotherapy during the year. These patients completed a course of treatment six times, on the average.

The number of treatment courses or episodes provided totalled 170. Patients residing in many parts of the State participated in the Program, as can be seen in the following Table.

Residence of Program Participants for 1983

Albuquerque	20
Las Cruces	2
Santa Fe	2
Belen	1
Carlsbad	1
Clovis	1
Dexter	1
Los Lunas	1
Los Alamos	1
Mesilla	1
Roswell	1
Sunland Park	1

The data relating to the efficacy of the drug in countering the nausea and vomiting caused by chemotherapy include measures taken before, during, and after all 170 treatment episodes completed during the year. In brief, several assessments were made of the patients regarding the severity of the side effects that they had suffered during previous chemotherapy sessions, which constituted the "baseline data" against which were compared the side effects that they experienced while using the marijuana and/or delta-9-THC. The research protocol calls for the random assignment of patients to one of two groups, Group A receiving the synthetic delta-9-THC in capsule form and Group B receiving marijuana in cigarette form. However, the protocol also allows for (1) patients to refuse their assignment and therefore be reassigned to the group of their choice (a safeguard built in to avoid "forcing" someone to smoke), (2) patients to begin the Program using one route of administration and to switch to the other route during the course of treatment, and (3) in some clinically indicated cases for a patient to use both routes. Since, if vomiting does begin, the THC capsule may be regurgitated before the drug can be absorbed, it can be seen that the use of the inhaled drug is medically prudent at times. To compare the relative effectiveness of the two routes

of administration (and simultaneously the two types of the drug), statistical analyses are applied to Group A versus Group B. However, in assessing the overall effectiveness of marijuana alone, synthetic THC alone, and the combination or sequential use of both during treatment, all three groups are considered, the "combined use" being designated Group C. Treatment courses in which patients showed significantly decreased side effects (i.e., specifically nausea and vomiting) while using the drug as compared to previous chemotherapy sessions during which neither marijuana nor synthetic THC was used are presented in the "Success" rows of the table below. If there was no reduction in nausea or vomiting while using the drug relative to previous chemotherapy sessions, the treatment course is shown in the "Failure" row. The results are presented for males and females separately; however, there is no statistically significant difference between the sexes with regard to the percentage of treatment courses that were found to be successes or failures.

		Group A	Group B	Group C	
Males	Success	2	37	61	Total male successes = 100
	Failure	0	2	0	Total male failures = 2
Females	Success	4	42	18	Total female successes = 64
	Failure	1	2	1	Total female failure = 4
Group Totals		A = 7	B = 83	C = 80	

Overall, the treatment courses that were "Successes" represented 96.5% of the total number administered. It is obvious that very few patients remained in the oral administration group (i.e., Group A), and there was a disproportionately low number of treatment courses in the capsule-only category as a result. Given the small number of cases in that category, it is unsafe to infer from the 1983 data whether there is any difference between the effectiveness of marijuana administered through inhalation and synthetic THC taken in capsule form. However, the data accumulated over all five years of the Program's operation do show that marijuana smoked results in a higher percentage of success than does the THC ingested; earlier reports have discussed the inability of the research design to separate the relative efficacy of the route of administration (i.e., inhaled versus ingested) from that of the form of the drug (i.e., real marijuana versus synthetic THC, respectively), since it is impossible to inhale the capsules or ingest the marijuana (note that raw marijuana is inactive if ingested).

Of greatest importance in this brief summary, which has been prepared in such a way that the general findings are stated simply and the complications and technicalities of the "research" activities and jargon are avoided, is the overall finding (again) that in 96.5% of the treatment courses with either or both forms of the drug significantly fewer symptoms of nausea and vomiting were experienced by the patients undergoing chemotherapy, compared with previous chemotherapy sessions in which these drugs were not used. It is also important to note that the previous chemotherapy sessions did involve the use of other antiemetic drugs, including Compazine, Reglan, Tigan, and Torecan.

In conclusion, the results from the Lynn Pierson Therapeutic Research Program duing 1983 have continued to demonstrate the effectiveness of marijuana and synthetic delta-9-THC as antiemetics to be used in controlling the nausea and vomiting caused by chemotherapy. These results should not be viewed only as "cold" numbers and "hard" facts (although, in a statistical sense, they are). Rather, each "Success" in the table should be seen empathically as a course of chemotherapy in which a New Mexican suffered less severely than he or she would have if the "experimental" drug had not been administered. In this more humane view of the data, the reader can more closely sense the needs which brought about the Controlled Substances Therapeutic Research Act of 1978 and may (hopefully) gain some satisfaction as a member of the Legislature in being a part of the Program, its successes, and the reduction in human suffering that it has directly brought about.