a comprehensive clinical plan for the investigation of **marijuana's medical use** in the treatment of the hiv-related wasting syndrome

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THIS NEWSLETTER features two long articles about two marijuana research projects that MAPS is working to facilitate. One of the studies focuses on evaluating methods of reducing the health risks of smoking marijuana through the use of smoke filtration devices like water pipes and vaporizers (p. 19). The other study is focused on gathering pilot data about the possible benefits of smoked marijuana in promoting weight gain in patients suffering from the HIV-related wasting syndrome (p. 11). Both of these studies are designed to gather information that, in the long-run, may play a role in securing FDA approval for the prescription use of marijuana.

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As of yet, I have not fully explained how these studies can contribute to such a goal. Since donations from MAPS members are a critical element in enabling these studies to proceed, I feel a responsibility to provide a complete picture of the long-term strategy involved in MAPS' approach to medical marijuana research. I therefore offer the following outline of a sequence of studies designed to lead from here, where patients in need of the medical use of marijuana still risk arrest and jail, to there, where the medical needs of patients take priority over a self-destructive war against a humble weed and the people who value it.

Clinical Plan

This Clinical Plan outlines a program of scientific investigation designed to evaluate the safety and efficacy of smoked marijuana for the promotion of weight gain in patients with HIV-related wasting syndrome. The Clinical Plan has been submitted to the Food and Drug Administration (FDA) as part of Dr. Donald Abrams' Investigational New Drug (IND) application #43,542. Previous drafts of the Clinical Plan have been reviewed and critiqued by Dr. Dan Spyker, FDA Medical Review Officer. This Clinical Plan is a tentative outline of the studies that the FDA will require in order to produce sufficient data to enable a comprehensive analysis of marijuana's safety and efficacy for the wasting syndrome. This Clinical Plan is based on current data, and may be modified as additional data becomes available.

All data gathered during the course of this investigation will be submitted for review to the Pilot Drug Evaluation Staff of the FDA. If two "adequate and well controlled" trials demonstrate that smoked marijuana has a safe and efficacious medical use for the wasting syndrome, a New Drug Application (NDA) will be filed with the FDA.

The working assumption of this Clinical Plan is that it will take about two years of research to demonstrate whether marijuana is safe and effective for the Wasting Syndrome, and roughly $500,000. Marijuana will be evaluated through the combination of one pilot study (N=40), one large scale multi-site clinical trial (N=150), and a series of about 150 single-patient trials designed according to an appropriate N=1 methodology.

This Clinical Plan also includes an investigation of various drug delivery devices and marijuana extracts that may reduce health risks caused by the inhalation of marijuana smoke.

PROPOSED CLINICAL PLAN STUDY 1: THE HEALTH EFFECTS OF WATER PIPES, VAPORIZERS AND FILTERS – AUGUST '94 - JANUARY '95*

In August, 1994, scientists at a highly respected research center began a six-month study analyzing the constituents of marijuana smoke after filtration by various marijuana delivery devices. The primary aim of the study is to determine which of the devices, if any, are preferable to the use of an unfiltered marijuana cigarette. The study will quantifythe effectiveness of several different water pipes, filters, and a vaporizing device in selectively removing potentially harmful constituents of the smoke from marijuana. Once the most effective device has been identified, a subsequent smoke analysis will be conducted using a sample of pure THC (to establish a reference standard) and also a concentrated extract of marijuana (hash oil) which contains virtually no remaining vegetable matter.

If the data from any of the smoke analyses is encouraging, follow-up studies may be undertaken to develop further drug delivery devices and marijuana extracts that minimize non-therapeutic ingredients.

The first clinical trial will be a double-blind placebo controlled pilot study

STUDY 2: A PILOT STUDY INVESTIGATING SMOKED MARIJUANA V. ORAL THC IN THE TREATMENT OF HIV-RELATED WASTING SYNDROME – OCTOBER '94 - MARCH '95

The first clinical trial will be a double-blind placebo-controlled pilot study by Dr. Donald Abrams investigating weight gain in the HIV-related Wasting Syndrome. This will be a single-site study coordinated by the San Francisco Community Consortium, where Dr. Abrams serves as research director.

The study will investigate the use of high, medium and low THC-content smoked marijuana administered in a double-blind manner with an open label control group receiving the oral THC capsule (Marinol). The study will involve forty subjects, ten in each of the three smoked marijuana groups and ten in the Marinol comparison group.

The THC-content of the marijuana to be used in the study will range from approximately 10% in the high-THC group, 4% in the medium-THC group, and 1.5% in the low-THC group. The marijuana available for research purposes from the National Institute on Drug Abuse (NIDA) is primarily of low potency. Medium potency marijuana may possibly be available from NIDA but high potency marijuana definitely is not available. Therefore, we are seeking a procedural mechanism under the Single Convention to import marijuana from HortaPharm B.V. in the Netherlands, where it is grown legally for research purposes.

This study will take about six months to conduct. At the conclusion of the pilot study, we hope to have gained valuable information for power analysis calculations concerning sample size for a full-scale controlled clinical trial. We also hope to have determined the best methodology for reducing experimenter and subject bias when both smoked marijuana and the oral THC pill are used in the same experiment.

STUDY 3: "N=1" STUDY OF THE HIV-RELATED WASTING SYNDROME – FROM COMPASSIONATE USE TO RESEARCH – OCTOBER '94 – JUNE '96

Beginning about October, 1994, numerous (150) single patient "N=1" studies will start to be initiated into the use of smoked marijuana in the treatment of the HIV-related Wasting Syndrome. Unlike the Single Patient IND program, this research design will provide the FDA with some of the scientific data it needs to evaluate the safety and efficacy of marijuana. In this study design, each subject acts as their own control. Subjects will be administered smoked marijuana of medium potency, oral THC and placebo in a double-dummy randomized sequence. As data from the pilot study becomes available concerning the potency of marijuana that is the most effective, the potency of marijuana used in this study may change. Experimental data will be gathered about the effects of the different medications on the weight of the subjects, the incidence of adverse effects,

*(all dates are tentative)

and quality of life. Those patients in the study who demonstrate a favorable risk/benefit from smoked marijuana would, upon the conclusion of their "N=1" trial, be allowed the option of continuing treatment to assess long-term safety and efficacy.

This study will be coordinated by a Principal Investigator (PI). The PI will develop the detailed design of the study in consultation with the FDA. After the study design is finalized, the PI will primarily interact with other physicians who want to enroll their patients in the study. The PI will assume the responsibility of reviewing each physician'sapplication for their patient to participate in the study. The physicians who serve as sub-investigators will need to obtain DEA licenses to administer marijuana. They will supervise patients' trials according to the approved protocol, administer outcome measures, and report their results to the PI.

After 150 reports are collected, the PI will collect the data and summarize the results for submission to the FDA along with the individual patient data. The data from all the separate "N=1" trials will be combined into one "adequate and well-controlled trial" of the use of smoked marijuana for the treatment of the Wasting Syndrome.

Additional studies, if any, will be considered after consultation with FDA

STUDY 4:

PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) JANUARY, '95 – JUNE '95

A series of pharmacokinetic/pharmacodynamic (PK/PD) investigations will be conducted. These PK/PD studies will be concluded before the start of the full-scale clinical trials, and may be used to guide their design. PK/PD studies will be conducted with about 10 subjects.

STUDY 5:

MULTI-SITE CLINICAL TRIAL FOR THE WASTING SYNDROME – JUNE '95 – JUNE '96

If Dr. Donald Abrams' pilot study generates encouraging data about the safety and efficacy of smoked marijuana in treating the wasting syndrome, a large scale multi-site study would then be conducted. This experiment will include about 150 patients located at five to fifteen different locations, each of which used the identical protocol. Results from the pilot study, the drug delivery device study, and the pharmacokinetic/pharmacodynamic study would all be used in the design of this clinical trial. This design will need to be determined by the FDA to be "adequate and well-controlled" since it is intended to be one of the two clinical studies required for NDA approval (the other being the combined N=1 trials).

POSSIBLE NEW DRUG APPLICATION (NDA) JUNE 1996 —

The series of studies listed above are designed to gather sufficient data to enable the FDA to determine whether or not smoked marijuana is safe and efficacious for the promotion of weight gain in patients suffering from the HIV-related Wasting Syndrome. If the data significantly demonstrates marijuana's safety and efficacy, an NDA will be filed with the FDA. If the data does not significantly demonstrate marijuana's safety and efficacy, an NDA will not be filed with the FDA. Additional studies, if any, will be considered after consultation with FDA. ■

2nd international congress for the study of modified states of consciousness: ethnocognition, shamanism, plants and cultural context, spain, october 1994

THIS CONFERENCE is being organized jointly by the Institut de Prospectiva and the Institut d'Estudis Ilerdencs. The conference will be held at the Institut d'Estudis Ilerdencs from October 3-7, 1994, in Lerida, Spain.

The first conference was entitled '1st International Congress on Plants, Shamanism and States of Consciousness', and was held in San Luis Potosi, Mexico during November of 1992. The objectives of the 2nd International Congress are to further transdisciplinary collaborations by sharing the results of our investigations into modified states of consciousness through the arts and sciences. We intend to increase the number of interested participants from the previous meeting, in order to enrich the perspectives initially opened by the conference in Mexico, however, we've planned to limit the number of participants to 150. ■

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Be sure to ask for the cool poster! I can answer some questions if needed. jace callaway: callaway@jolla.uku.fi