the medical use of **marijuana** -

A progress report on Dr. Donald Abrams' pilot study comparing smoked marijuana and the oral THC capsule for the promotion of weight gain in patients suffering from the HIV-related wasting syndrome

RICK DOBLIN

TIME GOES BY, and the approval process for Dr. Donald Abrams' protocol seems to move from one political or scientific obstacle to another. As each obstacle is surmounted, the protocol gains momentum, yet additional obstacles have continually appeared on the horizon. The starting date for the protocol is still too difficult to predict. Fortunately, the approval process is inexorably moving forward. The study can be delayed but I don't think it can be prevented.

Widespread, bipartisan and powerful social forces are coming into play in support of MAPS' strategy of conducting FDA-approved research into the medical uses of marijuana. The image in my mind is of a slow-moving stream dammed at all outlets except for one (the FDA), forcing the flow of water to move in that direction. One example of popular support is a June, 1994 phone-in poll of the readers of Parade, a mainstream magazine with a circulation larger than any other magazine in America. The poll indicated that 89% of the callers favored the medical use of marijuana.

With respect to the AIDS study, the protocol design process is now complete. For the last two years, multiple drafts have bounced back and forth between the FDA, the Scientific Advisory Committee of the San Francisco Community Consortium (which helps coordinate all AIDS research in the San Francisco Bay area and whose research director is Dr. Abrams), the Institutional Review Board of UC San Francisco (where Dr. Abrams is on the faculty), and the California Research Advisory Panel. Finally, every agency with statutory responsibility to review the protocol design has approved the final draft of the study.

The last remaining obstacles involve obtaining DEA permissions for the study. Dr. Abrams has been waiting over four+ months for his DEA Schedule 1 license, and it is proving impossible at this time to obtain DEA permission to import high-potency marijuana from the Netherlands for the study. Before reporting on the unresolved aspects of MAPS' effort to conduct research into the medical use of marijuana and on the various strategies and options that are possible at this point, I'll first outline the agreements that have been reached concerning the protocol design.

Approved Protocol Design

The study will be a pilot project, rather than a full-scale clinical trial designed to get statistically significant results. With so many variables in this groundbreaking and very important project, it is wise to conduct a pilot study first. This will permit the research team to determine if the experimental procedures work as well in practice as they appear to on paper, and to decide if the experimental design needs any major modifications. In addition, the pilot study will gather statistical data that will enable a statistician to determine the number of subjects that will be required for the full-scale multi-site trial.

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The pilot study calls for 40 volunteers with a clinical diagnosis of the AIDS Wasting Syndrome. Subjects will be randomly assigned to one of four different experimental groups, each composed of ten people. The study will last for a period of three months, with the primary outcome variable being each subject's weight.

The subjects in three of the groups will receive smoked marijuana within the context of a double-blind methodology. One group will receive marijuana of high potency (10% THC), another group will receive marijuana of medium potency (4% THC), and the control group will receive marijuana of low-potency (1.5% THC). The subjects in each of the three marijuana groups will know that they are receiving smoked marijuana, but will be blind as to the potency of the marijuana they receive. The experimental team will also be blind as to which potency each subject is receiving. This range of potencies is intended to produce an effective double-blind. The range of potencies also permits the researchers to investigate whether high-potency marijuana significantly minimizes marijuana's potentially harmful effect on the lungs by virtue of the fact that less tar and particulate matter is inhaled per unit of THC.

Subjects in the fourth group will receive the oral THC capsules in what is considered an "open label" control group. This term is used because both the subjects in the group and the experimental team will be

told the identity of the test drug being administered.

A double-blind methodology for all four groups was not possible. To begin with, the Scientific Advisory Committee of the San Francisco Community Consortium rejected the use of any inactive placebo on the grounds that it would be unethical not to provide terminally ill patients with some form of treatment. Given that only active drugs could be used in the study, there is no known method of blinding people as to whether or not they are receiving an active THC capsule or are smoking active marijuana. Even if subjects were given both a pill and a cigarette, one of which was a placebo and the other was active, the patient would easily be able to tell which was the active drug. The clue would be the dramatically different times of onset of the subjective effects caused by the oral THC capsule and smoked marijuana. The subjective effects of the THC capsule generally take about 45 minutes to become noticeable. However, this time of onset varies considerably in the same person from day to day, depending on the contents of their digestive systems. Meanwhile, smoking marijuana produces virtually immediate effects.

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A maximum of two grams of marijuana per day will be provided to the subjects in the three marijuana groups. This upper limit on the amount of marijuana each group can smoke will ensure that the members of the different groups do in fact receive different amounts of THC. If there were no quantity limits and the subjects were permitted to smoke as much as they wanted, it would be possible for the subjects receiving the low and medium potency marijuana to obtain the same dose of THC as the subjects in the high potency group. As a result, this could eliminate any differences in therapeutic levels of THC between the groups and leave the study without a marijuana control group. In any case, providing subjects with unlimited quantities of marijuana would be unacceptable to the DEA, and might increase the likelihood that some of the marijuana from the study would be diverted to other people (which could cause the entire project to be halted).

The Experimental Hypothesis

The study is designed to gather preliminary evidence about possible differences in weight gain between the subjects in the medium and high potency groups as compared to the control subjects receiving the low potency marijuana, and the control subjects receiving the oral THC capsule. If the hypothesis that smoked marijuana is effective in promoting weight gain is to be supported, the study will need to demonstrate that the subjects in the high and medium potency groups gained more weight than the subjects in the low potency group. The inclusion of the oral THC control group provides another point of comparison, though the lack of a double-blind for this group lessens its value. Due to the small number of subjects in each group, neither the FDA nor Dr. Abrams expects this pilot study to produce a statistically significant difference in weight gain between the subjects in the different groups. All this study is designed to determine is whether there are nonsignificant trends that suggest marijuana's efficacy, trends which might justify a larger scale multi-site study designed to be of sufficient size to generate statistically significant conclusions.

The DEA's Reservations

The current reason the protocol is delayed is DEA reluctance to issue Dr. Abrams' his DEA Schedule 1 license. Dr. Abrams needs the license in order legally to receive, store and distribute the marijuana that will be used in the study. Dr. Abrams submitted his application to DEA headquarters over four months ago, and at the time of this writing hasn't received any information as to its status.

The DEA official in charge of the department that reviews Schedule 1 licenses is Mr. Gene Haislip, Deputy Assistant Administrator, Office of Diversion Control, who has taken a personal interest in this study. Of the many people at the DEA with whom it is crucial to try to build bridges of understanding, Mr. Haislip is among the most important. Mr. Haislip recently wrote a letter to the FDA outlining his concerns about the protocol, both scientific and otherwise, concerns which he felt justified a delay in the approval of Dr. Abrams' Schedule 1 license. The matter is now in the hands of the FDA, which needs to respond to Mr. Haislip's concerns. Hopefully, the FDA's response will successfully address Mr. Haislip's concerns and convince him that the protocol should proceed. If not, the progress that has been made in moving from politics to protocols will be temporarily reversed, and the medical use of marijuana will once again become predominantly a political rather than scientific issue.

Governmental forces in support of the protocol

Fortunately, there are bureaucratic forces in motion that give rise to the hope that the DEA will issue Dr. Abrams his Schedule 1 license in the near future. Ironically, the support for FDA-approved research with marijuana has been strengthened by the total failure of all other efforts to secure legal prescription availability for marijuana. For example, 36 states have endorsed the medical use of marijuana. Nevertheless, since Federal law prevails, the medical use of marijuana in these states is still prohibited, and only FDA approval can change the situation.

Similarly, the main contribution of the 22-year long lawsuit against DEA by NORML, the Alliance for Cannabis Therapeutics, and the Drug Policy Foundation, has been to make FDA-approved research inevitable. The aim of the lawsuit was to force the DEA to reschedule marijuana into Schedule 2 to permit its medical use by prescription. After marijuana's proponents won an unbroken string of legal victories over the course of two decades, their hopes were crushed in February, 1994 when the United States Court of Appeals (D.C. Circuit) rejected their arguments and supported the position of the DEA. It is now clear to all the protagonists that the DEA has finally been able to craft a set of criteria that pass Court of Appeals scrutiny, criteria which permit the DEA to justify on solid legal grounds its refusal to reschedule marijuana. What this means is that short of congressional action (which even incurable optimists like myself think is out of the question for the foreseeable future), the only way to obtain the legal availability of medical marijuana is through FDA approval.

In an unusually helpful comment, even ex-DEA Administrator Mr. Robert Bonner, pointed the way to the FDA. In his ruling rejecting the rescheduling of marijuana, Mr. Bonner suggested that "Those who insist that marijuana has medical uses would serve society better by promoting or sponsoring more legitimate scientific research, rather than throwing their time, money and rhetoric into lobbying, public relations campaigns and perennial litigation." When research was not imminent, the DEA was more than willing to endorse that approach. Now, the DEA seems to need time to get used to the fact that MAPS actually took its advice and started working with Dr. Abrams to conduct FDA-approved research.

Two pronouncements this July by officials at the upper levels of the Department of Justice and the Department of Health and Human Resources further reinforce the lack of alternatives to conducting FDA-approved research. As you may recall, in 1992, the Assistant Secretary of Health in the Bush Administration, Dr. James Mason, shut down the FDA's Single Patient IND Program (Compassionate Access) for medical marijuana patients because it was growing too large, too visible, too expensive and too time-consuming for the FDA to administer. Over the course of the last year, the current Assistant Secretary of Health, Dr. Philip Lee, has been pressed by various congresspeople to review Dr. Mason's decision. In a letter sent in mid-July to Representative Barney Frank and the other congresspeople and senators who contacted him about this issue, Dr. Lee announced that he has finally reached a decision concerning his course of action. Sadly, but not unexpectedly, Dr. Lee indicated that he has decided not to reopen the Compassionate Access Program. According to Dr. Lee, the fatal flaw of that program was that it did not generate data that could be submitted to the FDA to either support or reject the hypothesis that smoked marijuana had a safe and efficacious medical use. Dr. Lee did not offer any government funds for research, yet indicated that only FDA-approved research could resolve this controversy.

Similarly, the Department of Justice announced in July that there would be no change in current policy. The old policy was affirmed in a letter from Jo Ann Harris, Assistant Attorney General, that was sent to medical marijuana advocates Valerie Corral and Elvy Musikka. The women had met with aides to Attorney General Janet Reno at the Justice Department earlier this year and had asked for a moratorium on prosecutions of medical marijuana patients. The letter indicated the Department of Justice was not willing or able to declare a moratorium on prosecutions of patients who use marijuana for its medicinal properties, nor would the Attorney General overrule the DEA Administrator and reschedule marijuana. According to the Attorney General's office, "this administration remains open to the possibility that sufficient medical and scientific evidence may be presented to permit a re-evaluation of the scheduling of marijuana." In other words, the only potential remedy for this situation is FDA-approved research leading to FDA approval of the prescription use of marijuana.

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The Clinton Administration seems to have adopted a uniform position that focuses on the lack of, and need for, FDA-approved clinical trials into the medical use of marijuana prior to any policy changes. Given the momentum forcing the issue into the hands of the FDA, I doubt the DEA can succeed in halting all research, even if it wished to do so. It's hard for me to imagine that the DEA doesn't realize that if marijuana moves into clinical trials, it will take years before the FDA may possibly have enough data to approve marijuana for prescription use, and during that time all the outside pressure for action shifts from the DEA to the FDA.

Professional organizations in support of the protocol

Several very prominent professional organizations, the American Medical Association and the Federation of American Scientists, are interested in seeing the controversy over the medical use of marijuana resolved through scientific research. In the June 1, 1994 issue of the Journal of the American Medical Association, an article reports on Dr. Abrams' protocol. Under the subheading, "Why Not Just Prove It?", the reporter quotes John Ambre, MD, Ph.D., the director of the

American Medical Association's Department of Toxicology and Drug Abuse. Ambre says, " It is important, in the subjects affected, to have control groups and use pure, well-defined material." The impression left with the reader is that a well-designed study that did have control groups and did use pure, well-defined material would receive the support of the AMA. Dr. Abrams' study seeks to do just that. As for the Federation of American Scientists, its enthusiastic support for Dr. Abrams' protocol has already been obtained. As important organizations within the medical and scientific establishment, as well as the FDA, express support for Dr. Abrams' study, the likelihood that the DEA will grant Dr. Abrams his Schedule 1 license is increased.

The search for high-potency imported marijuana

Not surprisingly, after Dr. Abrams receives his Schedule 1 license, there is still one more hurdle to surmount. We still need to find a legal source of high-potency marijuana for the study. Low-potency marijuana is available from NIDA (this is what will be used in the water pipe/ vaporizer study, page 19). NIDA also has just enough medium-potency marijuana to supply the needs of the 10 patients who will be randomized into the medium-potency group. Unfortunately, there is no legal domestic supplier of high-potency marijuana.

The third option, which I think is the best in the long-run, is to create a non-profit marijuana research and production company.

The only fully licensed grower of high-potency marijuana that MAPS is aware of is HortaPharm, a marijuana research firm in the Netherlands. HortaPharm has offered to donate all the marijuana needed for the study if the necessary import and export permits can be obtained. Four months ago, Mr. Larry Snyder, the DEA official in charge of overseeing the international importation and exportation of Schedule 1 drugs, rejected an application to import 250 grams of high-potency marijuana from HortaPharm for the water pipe/vaporizer study. Mr. Snyder's rationale was that he was obliged to reject the application for an import permit because the Dutch government does not currently have procedures in place that allow HortaPharm to export its marijuana. While this is formally true, the Dutch regulatory authorities have taken the position that they are bound by the International Convention on Psychotropic Substances which specifically states that an import permit must be issued before an export permit can be granted. The Dutch regulators are thus asking for the DEA to issue an import permit before they consider changing Dutch laws to permit HortaPharm to export marijuana.

Each government is asking the other to make the first move, which neither is willing to do at this time. Until the U.S. or the Dutch government changes its policies, I see little hope that an import permit will be obtained. There is a possibility that the Dutch government will change its policies before the U.S. government grants an import permit, but such a change will not occur for several months at the earliest, if at all.

The search for high-potency domestic marijuana

Several domestic sources of high-potency marijuana might be available, each with different sets of advantages and disadvantages. One option is for MAPS to attempt to contract privately for a supply of high-potency marijuana from the scientific team that currently grows marijuana for the National Institute on Drug Abuse. This team is fully licensed to grow marijuana and has the authority to produce marijuana legally for authorized uses such as an FDA-approved research protocol. A contract of this sort might cost MAPS in the neighborhood of $20,000 to $50,000, depending on whether the marijuana was to be grown indoors or outdoors. If a contract could be arranged, the earliest delivery date for the marijuana would be at least six months and probably a year away.

One problem with this option is that the cost of $20,000 to $50,000 is prohibitive. The second problem is the amount of time it would take. If AIDS were not a fatal disease, and if there were substantially effective medicines for the Wasting Syndrome, a delay of a year wouldn't matter so much. But time is of the essence for people with a fatal illness.

A second option is to seek permission to use seized supplies of high-potency marijuana for the pilot study. While seized marijuana might still comply with Dr. Ambre's requirement for "pure, well-defined study materials", the marijuana used in any subsequent studies would almost certainly be from a different seed stock with different genetic characteristics, resulting in marijuana with a somewhat different chemical profile. This would make it difficult to combine the data from the pilot study with that of any subsequent study. This isn't such an important limitation since Dr. Abrams' pilot study is not intended to form the basis of an application to the FDA to approve marijuana's medical use. Its purpose is rather to gather preliminary data that will guide researchers in deciding whether it is worth the effort to conduct a full-scale multi-site controlled study, and if so, how that study should be designed. Using seized supplies, assuming DEA permission for this could be granted, would be an acceptable solution to the supply problem. While Dr. Abrams' pilot study was underway, the search for a more permanent supply of high-potency marijuana could continue.

A non-profit marijuana cultivation and research company

The third option, which I think is the best in the long-run, is to create a non-profit marijuana research and production company chartered and licensed specifically to develop the medical uses of marijuana and its constituents. Naturally, it would be very difficult to arrange. It would take a lot of time and careful planning to find the right people for the Board of Directors, administrative officers and staff. This project would probably require about $500,000 in start-up funds, and would require at least a year or more to obtain all the necessary governmental permissions. While the practical challenges are formidable, there are no theoretical obstacles to this concept. The idea is similar to the strategy of the Population Council, a non-profit organization which is undertaking the U.S. testing and development of the controversial abortion pill RU-486. I am proposing that a non-profit organization be created that will function like a traditional pharmaceutical company, but with marijuana and its constituents as its only products. With a drug as controversial as marijuana, it may be that a non-profit organization without private financial interests to protect may end up being more trusted by the public than a profit-making company, and permitted to operate more freely.

This approach gets the government out of the uncomfortable and untenable position of supplying ever larger amounts of marijuana for research, marijuana for which it is not supposed to charge. It also gives the DEA one centralized entity to regulate, which it should be able to handle without too much work. If ever the company were to obtain marketing approval for marijuana for any clinical indication, profits would be used to support further research, eliminating or reducing the need for constant fund-raising.

Of course, neither the money nor the start-up time that this project would require would be easy to come by. For the purposes of Dr. Abrams' protocol, this option would take too long to implement, even if the people and the funds for the project were available today.

Giving up on high-potency marijuana

The last option is simply to abandon the effort to use high-potency marijuana and ask the FDA if it would consider accepting a revised protocol with just medium- and low-potency marijuana. With all the recent media attention about the flood of highly potent marijuana sweeping the United States and making everything previously known about marijuana obsolete, it would be rather ironic if we couldn't obtain any for a government-approved study. However, if a legal source of high-potency marijuana could not be arranged, it may be best to give up that part of the study for the sake of moving forward.

In order to determine if high-potency marijuana is absolutely necessary, MAPS and California NORML are trying to have three samples of marijuana tested for potency. These samples would be gathered from the San Francisco Buyers Club, which distributes marijuana to AIDS patients who use it for treating the symptoms of their Wasting Syndrome.

Anecdotal evidence indicates that all the samples have some therapeutic properties. One of the samples would their least expensive variety and the other two would be their most expensive marijuana. Since marijuana from the Buyer's Club has never been analyzed for potency, no one knows what the THC-content of these samples is going to be. If their expensive samples test out to contain around 10% THC, then we would still need to find high-potency marijuana for Dr. Abrams' study.

If these samples turn out to be 5% THC or less (which we consider to be medium potency), then it doesn't seem essential to delay Dr. Abrams' study until the search for a legal supply of higher-potency marijuana is obtained. (This finding would put into question claims about the increased potency of today's marijuana.) While it would be a compromise to give up on the reduced risk profile of high-potency marijuana, it seems that a greater risk to the health of the AIDS patients in the study would be to wait and do nothing.

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Eliminating the high-potency group from the protocol might take some time to implement since the FDA and all the other regulatory agencies have approved a protocol design that specifically includes high-potency marijuana. Any modifications in the protocol would require additional reviews and approvals, which could take several months to obtain. Still, such a change would probably be approved, and the study would still be worth conducting.

Conclusion

After two years of effort, Dr. Donald Abrams' proposed pilot study comparing the safety and efficacy of smoked marijuana vs. the oral THC capsule is getting closer to actually beginning. It seems very likely that the study will start before the end of 1994. Whether the study will include high-potency marijuana is still to be resolved.

For a study that hasn't even taken place, this protocol has received an enormous amount of media attention. Stories about it have already appeared in Science, The New York Times, USA Today, and the Journal of the American Medical Association. Remember, you read about it here first, in the MAPS newsletter! ■