

Will the Obama Administration Stop Standing in the Way of Marijuana Research for Veterans?

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ON OCTOBER 24, 2013, THE Multidisciplinary Association for Psychedelic Studies (MAPS) and Principal Investigator Dr. Sue Sisley of the University of Arizona College of Medicine-Phoenix, resubmitted to the Public Health Service (PHS) our protocol to study the use of marijuana in treating 50 U.S. veterans with chronic, treatment-resistant posttraumatic stress disorder (PTSD).

A Guidance from the Department of Health and Human Services (HHS), issued May 1999, requires PHS protocol review and approval for privately funded studies seeking to obtain permission to purchase a supply of marijuana from the National Institute on Drug Abuse (NIDA). Unfortunately, NIDA holds a DEA-protected monopoly on marijuana legal for use in Food and Drug Administration (FDA)-regulated research.

MAPS began trying to conduct FDA-approved medical marijuana research in 1992, working with Dr. Donald Abrams to design a study of marijuana to promote appetite and weight gain in HIV-positive patients suffering from AIDS wasting syndrome. While we obtained approvals from the FDA, the University of California, San Francisco Institutional Review Board (IRB) and the Research Advisory Panel of California (RAP-C), NIDA refused to provide us with the marijuana.

In 1999, MAPS worked with Dr. Ethan Russo to obtain FDA and IRB permission for a study of marijuana in treating people suffering from migraines. Yet again, NIDA rejected the protocol and refused to sell MAPS the marijuana we needed, preventing the study from taking place. Between June 2003 and August 2009, MAPS unsuccessfully attempted to purchase 10 grams of marijuana from NIDA for research with vaporized marijuana. Due to excessive delays and frustration, in August 2009 the laboratory we were working with on the project withdrew its efforts.

MAPS and Dr. Sisley began working together in 2010 on our current protocol exploring marijuana for symptoms of PTSD in U.S. veterans. What follows is the initial portion of our October 24, 2013, resubmission to PHS of that protocol. We review the history of the protocol review process and request that HHS revise the 1999 Guidance and end the PHS protocol review, which exists only for studies with marijuana and is biased against studies designed to develop the marijuana plant into an FDA-approved prescription medicine.

In the letter, we request that privately funded medical marijuana protocols be reviewed the same way that protocols using MDMA, psilocybin, LSD, and any other Schedule I drug are reviewed, requiring approval from FDA, IRB, DEA, and state authorities, but not PHS review. We're currently in the early stages of seeking Congressional support for our request to HHS to eliminate the PHS protocol review process.

Our responses to the specific protocol critiques of the PHS reviewers can be found at maps.org/research/mmj/marijuana_for_ptsd_study. 🌿

October 23, 2013

Sarah A. Wattenberg MSW
Sr. Advisor on Substance Abuse Policy and Marijuana Research Review Committee Chairperson
Office of the Assistant Secretary of Health
U.S. Dept. of Health and Human Services

Ms. Sarah Wattenberg,

Hello again and best wishes from Rick Doblin, Ph.D., Executive Director of MAPS, a non-profit research and educational organization. I'm writing you now in a belated response to your September 21, 2011, letter reporting that all five Public Health Service (PHS) reviewers had recommended against approving the privately-funded, MAPS-sponsored, Food and Drug Administration (FDA)-approved drug development pilot study, "Placebo-Controlled, Triple-Blind, Randomized Crossover Pilot Study of the Safety and Efficacy of Five Different Potencies of Smoked or Vaporized Marijuana in 50 Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)". I had submitted the protocol to you for review four months and three weeks previously on April 28, 2011.

In your letter, you concluded, "If you plan to submit a revised protocol, please forward it to my office for review." Attached is our revised protocol and informed consent form for review. You also highlighted in your letter four specific issues regarding the protocol, to which I'll respond further below. I'll also respond to the critiques of the 5 PHS reviewers in a separate document that elaborates on the rationale for our protocol design decisions, as requested by the reviewers.

When I submitted our initial protocol to you, it had been approved by FDA but had not yet been submitted to an IRB. In July 2012, after all five PHS reviewers rejected the protocol, Dr. Sue Sisley, Principle Investigator, submitted the unchanged protocol to the University of Arizona Institutional Review Board (IRB). We also included in our IRB submission your cover letter, the comments of all five PHS reviewers, our document responding to the issues raised by the reviewers, an informed consent form and related documents. The IRB reviewed all the information and accepted all the core elements of our protocol design as originally approved by FDA, despite the critiques of the PHS reviewers.

However, the IRB did raise several new issues requiring additional safety measures and procedures. We then revised the protocol and, resubmitted it to the IRB on October 14, 2012. On October 23, 2012, the IRB issued its final approval of the protocol and informed consent form. Attached is a comprehensive eight page list of the changes from the initial protocol to the IRB-approved version we are now submitting. Below is a summary of the major changes.

New Safety Measures in Revised and IRB-Approved Protocol

The protocol now includes an assessment of anxiety as well as assessments of PTSD symptoms and depression. New safety procedures include increased monitoring for psychiatric symptoms through daily telephone contact by research staff with the subjects during the first week of marijuana self-administration and mid-week for the second, third and fourth weeks, and through research staff gathering information on a regular basis from a personal contact selected by each subject who will independently verify marijuana self-administration and report any signs of behavioral change.

A Plea for HHS to Defer Review of MAPS' Marijuana/PTSD protocol to FDA, IRB, DEA

Prior to our responding below to the specific protocol design issues you raised in your Sept. 21, 2011 letter, what follows first is the rationale for our request that HHS eliminate the PHS review process for privately-funded medical marijuana drug development studies. We request that HHS defer the review of MAPS' marijuana/PTSD protocol to FDA, IRB, and DEA, where Congress placed that responsibility and which is the review process for privately-funded research with all other Schedule 1 drugs.

The protocol that MAPS is now submitting to you is a much delayed and much needed attempt to gather pilot data in 50 US veterans with chronic, treatment-resistant PTSD at a time when about 22 veterans and 1 active duty soldier commit suicide every day.

Challenges to NIDA'S Monopoly on the Supply of Marijuana for Privately-Funded Research

Starting in 2001, MAPS began sponsoring the efforts of Prof. Lyle Craker, UMass Amherst, Medicinal Plant Program, Department of Plant, Soil and Insect Sciences, to obtain a DEA license to produce a supply of medical marijuana under contract to MAPS to be used exclusively in federally-regulated research. In February 2007, after extensive legal hearings before DEA Administrative Law Judge (ALJ) Mary Ellen Bittner, Prof. Craker won his lawsuit against the DEA for refusing to issue him a license. DEA ALJ Bittner recommended to the DEA Administrator that it would be in the public interest for DEA to license Prof. Craker to grow medical marijuana for MAPS' privately-funded, federally-regulated research.

After not responding to the ALJ recommendation for almost two years, DEA Administrator Michelle Leonhart finally rejected ALJ Bittner's recommendation on January 14, 2009, six days before the inauguration of President Barack Obama. Prof. Craker subsequently sued DEA in the US First Circuit Court of Appeals. On April 5, 2013, after more than four additional years, the US First Circuit Court of Appeals accepted DEA's rationale for rejecting the February 2007 recommendation of DEA ALJ Bittner, bringing to a conclusion our 12 years struggle. Out of necessity, MAPS and Dr. Sisley are now returning to the PHS to request approval to purchase NIDA marijuana at cost for our FDA and IRB-approved study.

PHS Review Biased Against Privately-Funded Medical Marijuana Drug Development Research

According to the May 21, 1999, Announcement of the Department of Health and Human Services' Guidance on Procedures for the Provision of Marijuana for Medical Research, PHS protocol approval is currently required by the Department of Health and Human Services (HHS) before sponsors of privately-funded medical marijuana research can purchase at cost any of NIDA's research grade marijuana, for which it has a Drug Enforcement Administration (DEA)-protected monopoly. Without PHS protocol approval, privately-funded medical marijuana drug development protocols cannot proceed.

In contrast, all other Schedule 1 drugs such as LSD, MDMA, psilocybin, mescaline, and DMT, are available from multiple DEA-licensed producers. Privately-funded drug development protocols studying the risks and benefits of all Schedule 1 drugs other than marijuana require approval from FDA, an Institutional Review Board (IRB), and DEA, but not the PHS. At present, PHS review and approval is required only for privately-funded medical marijuana drug development protocols, exists only because of NIDA's unique monopoly on DEA-licensed marijuana, protects no government funding, and asserts authority over drug development research that Congress created the FDA to review.

Fundamentally problematic, the current HHS Guidance explicitly rejects providing marijuana at cost to privately-funded medical marijuana drug development protocols seeking to obtain FDA approval for the prescription use of smoked marijuana in plant form. The protocol MAPS is submitting to you now for PHS review is seeking to conduct research with the exact aim that the HHS Guidance rejects as outside the boundaries of acceptable research, but which FDA and the UArizona IRB have approved.

Section II of the Guidance, "Availability of Marijuana For Research Purposes", states, "The goal of this program must be to determine whether cannabinoid components of marijuana administered through an alternative delivery system can meet the standards enumerated under the Federal Food, Drug, and Cosmetic Act for commercial marketing of a medical product (see e.g., 21 U.S.C. 355). As the IOM report stated, "Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but such trials could be a first step towards the development of rapid-onset, nonsmoked cannabinoid delivery systems."

As long as HHS's May 21, 1999, Guidance on Procedures for the Provision of Marijuana for Medical Research remains in force and are followed by PHS reviewers, the rejection of MAPS' revised protocol, now approved by both FDA and the UArizona IRB, seems inevitable. When the DEA-protected NIDA monopoly and the PHS review process operating under the HHS Guidance combine to block all efforts to develop the marijuana plant itself into an FDA-approved prescription medicine, science is preempted by politics. It's therefore only to be expected that when the science is blocked, advocates of the medical uses of marijuana will turn to politics to provide access for physicians and their patients to medical marijuana.

There are currently 20 medical marijuana states and the District of Columbia. Of these states, PTSD is an explicit qualifying condition for a medical marijuana recommendation in 5: New Mexico, Maine, Oregon, Connecticut, Delaware,

and its use for PTSD is permitted in California., all without a single controlled study of the use of marijuana for PTSD. It's long past time to facilitate privately-funded, federally-regulated research into the use of marijuana in veterans with chronic, treatment-resistant PTSD, for which there are many positive anecdotal reports.

PHS Review is Inappropriate for Privately-Funded, FDA-regulated Research

Even if the HHS Guidance didn't explicitly reject providing NIDA marijuana at cost to privately-funded protocols seeking to develop the marijuana plant into an FDA-approved prescription medicine in smoked form, there is a fundamental mismatch when PHS reviewers evaluate a privately-funded drug development protocol design through the lens of basic science grant application standards.

PHS protocol reviewers have extensive and valuable experience reviewing grant applications submitted by academic researchers seeking National Institutes of Health (NIH) funding for basic science studies. NIH-funded basic science research is primarily about understanding mechanisms of action to gain insight into the processes and building blocks of life. In contrast, privately-funded drug development protocols are focused on proving safety and efficacy to FDA standards. FDA does not require an understanding of mechanisms of action for approval for prescription use.

PHS reviewers of grant applications are stewards of public funds while privately-funded drug development studies are investing and risking private money, not public money. PHS reviewers of grant applications can appropriately require additional measures and tests to better understand mechanisms, or can require larger studies to reduce uncertainty, the cost of which will be paid by the NIH grant should the application be accepted. Such protocol critiques are justified for basic science purposes but are not required by FDA or IRB and are inappropriate for privately-funded studies. Costs from additional research into mechanisms required by PHS reviewers must be paid by the private sponsors of the research, imposing in essence an arbitrary tax on privately-funded research into marijuana's potential medical uses.

Request to Waive PHS Review and Accept Approval by FDA, IRB, DEA, State Authorities

Fortunately, there is a way forward. The HHS Guidance states that "HHS will re-evaluate these procedures periodically..." As far as I can tell, the HHS Guidance document has not been reevaluated since it was written more than 14 years ago. The current NIH grant review process does a good job providing marijuana from NIDA's monopoly for NIH-funded basic science studies while ensuring that taxpayer funds are expended wisely. In contrast, the PHS review process is a success only at obstructing privately-funded medical marijuana drug development studies, an outcome contrary to the public interest. Approval from FDA, IRB, DEA and state authorities without the marijuana-only PHS review should be sufficient for NIDA to accept a request from privately-funded sponsors to purchase its marijuana at cost, especially since that process is sufficient for privately-funded research with MDMA, psilocybin, LSD, DMT, etc.

I'm writing to request that you consider the approvals of this protocol from FDA and the University of Arizona IRB, subject to licensing by DEA and state authorities, as sufficient for this study to proceed, as they would be for research with any other Schedule 1 drug. After licensing by DEA and state authorities, NIDA could then provide the required marijuana at cost.

New Promising but Uncontrolled Research into the Use of Marijuana for PTSD

In addition to our protocol, I am submitting two papers that report on uncontrolled studies of the use of marijuana in subjects with PTSD. The paper discussing the results of a study conducted by New Mexico psychiatrist Dr. George Greer in 80 PTSD patients applying for enrollment in the New Mexico Medical Cannabis Program has recently been accepted for publication in a peer-reviewed journal indexed on Medline. The other paper, reporting on a study conducted by the Israeli Ministry of Health in 29 Israeli Defense Force soldiers, is currently under review by a peer-reviewed journal indexed on Medline. Both report promising findings and call for controlled studies, none of which have yet been conducted.

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