



CENTER FOR MEDICINAL CANNABIS RESEARCH

*Report to the Legislature and Governor of the State of California
presenting findings pursuant to SB847 which created the CMCR and provided state funding*

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Objective

In 1999, the California legislature passed and Governor Gray Davis signed SB847, which commissioned the University of California to establish a scientific research program to expand the public scientific knowledge on purported therapeutic usages of marijuana.

We hereby submit this report of our scientific findings pursuant to this objective.

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“Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body.”

~ *Institute of Medicine, 1999*

“The question of whether marijuana has any legitimate medical purpose should be determined by sound science and medicine.”

~ *Asa Hutchinson, Former DEA Administrator, 2001*

“The scientific community, the medical community in particular, is divided on the real therapeutic effectiveness of marijuana. Some are quick to say that opening the door to medical marijuana would be a step toward outright legalization of the substance. But none of that should matter to physicians or scientists. It is not a question of defending general public policy on marijuana or even all illegal drugs. It is not a question of sending a symbolic message about “drugs”. It is not a question of being afraid that young people will use marijuana if it is approved as a medicine. The question, and the only question, for physicians as professionals is whether, to what extent and in what circumstances, marijuana serves a therapeutic purpose.”

~ *Canadian Senate Special Committee On Illegal Drugs. Cannabis: Summary Report, 2002.*

“Although the indications for some conditions (e.g., HIV wasting and chemotherapy-induced nausea and vomiting) have been well documented, less information is available about other potential medical uses. Additional research is needed to clarify marijuana’s therapeutic properties and determine standard and optimal doses and routes of delivery.”

~ *American College of Physicians, 2008*

“The Center for Medicinal Cannabis Research is currently conducting scientific studies to determine the efficacy of marijuana in treating various ailments. Until that research is concluded, however, most of what the public hears from marijuana activists is little more than a compilation of anecdotes.”

~ *John Walters, Former Director of the White House Office of National Drug Control Policy, 2002*

Executive Summary

The Center for Medicinal Cannabis Research (CMCR) at the University of California was created in 2000 to conduct clinical and pre-clinical studies of cannabinoids, including smoked marijuana, to provide evidence one way or the other to answer the question “Does marijuana have therapeutic value?” To accomplish this objective, the CMCR issued calls for applications from researchers at leading California institutions, developed a close working relationship with state and federal agencies to gain regulatory approvals, established panels of nationally-recognized experts to rigorously review the merit of applications, and funded carefully designed studies that have now been published in high impact scientific journals, making significant contributions to the available literature on cannabis and the cannabinoids.

Summary of Results to Date

In total, the CMCR has approved fifteen clinical studies, including seven clinical trials, of which five have completed and two are in progress. The CMCR has also approved four pre-clinical studies, all of which have completed.

By design CMCR clinical studies focused on conditions identified by the Institute of Medicine for which cannabis might have potential therapeutic effects, based on current scientific knowledge (Institute of Medicine, 1999). To date, four CMCR-funded studies have demonstrated that cannabis has analgesic effects in pain conditions secondary to injury (e.g. spinal cord injury) or disease (e.g. HIV disease, HIV drug therapy) of the nervous system. This result is particularly important because three of these CMCR studies utilized cannabis as an add-on treatment for patients who were not receiving adequate benefit from a wide range of standard pain-relieving medications. This suggests that cannabis may provide a treatment option for those individuals who do not respond or respond inadequately to currently available therapies. The efficacy of cannabis in treatment-refractory patients also may suggest a novel mechanism of action not fully exploited by current therapies. In addition to nerve pain, CMCR has also supported a study on muscle spasticity in Multiple Sclerosis (MS). Such spasticity can be painful and disabling, and some patients do not benefit optimally from existing treatments. The results of the CMCR study suggest that cannabis reduces MS spasticity, at least in the short term, beyond the benefit available from usual medical care.

Table 1. Clinical Studies Published or Submitted for Publication

Donald Abrams, M.D. UC San Francisco	Cannabis for Treatment of HIV-Related Peripheral Neuropathy
Donald Abrams, M.D. UC San Francisco	Vaporization as a Smokeless Cannabis Delivery System
Jody Corey-Bloom, M.D., Ph.D. UC San Diego	Short-Term Effects of Cannabis Therapy on Spasticity in MS
Ronald Ellis, M.D., Ph.D. UC San Diego	Placebo-controlled, Double Blind Trial of Medicinal Cannabis in Painful HIV Neuropathy
Mark Wallace, M.D. UC San Diego	Analgesic Efficacy of Smoked Cannabis
Barth Wilsey, M.D. UC Davis	Double Blind, Placebo Controlled Trial of Smoked Marijuana on Neuropathic Pain

To date, six of the studies have published (or are in the process of publishing) results in respected medical journals, garnering national and international attention from other researchers, media outlets, governmental agencies, and the general public (see Table 1). These results have helped to bring together accomplished international experts on cannabis and cannabinoids and foster scientific dialog on the possible utility of cannabis as a therapeutic agent.

Adverse side effects experienced by participants included cough, nausea, dizziness, sedation and changes in cognition. However, these effects were typically mild and resolved rapidly after treatment. Currently approved analgesics are not without side effects, and the effects observed in CMCR studies tended to be no worse than would be expected with other potent analgesics. Following the conclusion of the two studies currently in progress, CMCR will have exhausted its available funding for clinical work, though the CMCR will continue to maintain a sample bank and to consult with researchers and policy-makers as needed.

The majority of CMCR studies that have been discontinued were cancer studies that experienced difficulty in recruiting participants. Many severely ill individuals were reluctant to volunteer for a rigorous research protocol where the experimental treatment addressed disease symptoms (i.e. nausea, pain) but did not affect tumor growth directly. Other factors, such as requirement that patients have stable pain scores over a period of time leading into the study, prohibition from driving for the duration of the study, and difficulty in providing cannabis for home administration may also have played a role in the lack of success in recruiting this population. A further impediment to participation in CMCR studies, particularly in cancer patients, was the inability of CMCR to continue to provide study drug beyond the study period to patients who find active treatment beneficial. Additionally, some individuals already were using cannabis to treat pain or other symptoms, and so had less incentive to participate in research.

The CMCR portfolio also included basic science studies in animals and in human cells (pre-clinical research). This research was supported because it had the potential to provide insights into therapeutic use of cannabinoids in human disease. One study provided evidence, by way of recordings of nerve cell activity and in awake animals, of analgesic effects of cannabis-like compounds on head and facial pain, suggesting that clinical trials of cannabis might be warranted in patients with headache or other facial pain. Another study reported that cannabis did not interfere with the function of blood cells involved with immunity, an important finding considering potential therapeutic use of cannabis compounds will be in persons with chronic illnesses.

Other CMCR Activities

In addition to the research, CMCR has also functioned as a catalyst for discussion and examination of the potential development of cannabis as medicine. In July, 2002, CMCR sponsored a workshop "Future Directions in Cannabinoid Therapeutics" featuring presentations by intellectual and scientific leaders in the field of cannabinoid science from around the world. CMCR hosted a second meeting in summer 2004 to address recent progress in science that would be likely to lead to clinical trials of new cannabinoid compounds. "Future Directions in Cannabinoid Therapeutics II: From the Bench to the Clinic" brought together the major stakeholders in the development of cannabinoid therapeutics in order to survey laboratory compounds that are most promising for testing in human trials and to confront potential stumbling blocks to testing and development of these compounds. A special issue of the journal *Neuropharmacology* (2005) was dedicated to publishing the research presented at this meeting.

Executive Summary (cont.)

CMCR researchers have also published two literature reviews on the neuropsychological effects of cannabis use in order to better understand the potential hazards of cannabis use in short and long-term treatment settings (Grant, et al., 2003 & Gonzalez, et. al, 2002 – see reference list).

Conclusion

As a result of the vision and foresight of the California State Legislature Medical Marijuana Research Act (SB847), the CMCR has successfully conducted the first clinical trials of smoked cannabis in the United States in more than 20 years. As a result of this program of systematic research, we now have reasonable evidence that cannabis is a promising treatment in selected pain syndromes caused by injury or diseases of the nervous system, and possibly for painful muscle spasticity due to multiple sclerosis. Obviously more research will be necessary to elucidate the mechanisms of action and the full therapeutic potential of cannabinoid compounds. Meanwhile, the knowledge and new findings from the CMCR provide a strong science-based context in which policy makers and the public can discuss the place of these compounds in medical care.

Mission Statement

“The Center for Medicinal Cannabis Research (CMCR) will conduct high quality scientific studies intended to ascertain the general medical safety and efficacy of cannabis products and examine alternative forms of cannabis administration. The Center will be seen as a model resource for health policy planning by virtue of its close collaboration with federal, state, and academic entities.”

Scientific and Legislative Precursors of the CMCR

Discovery of Cannabis Receptors in the Brain

During the late 1980's and early 1990's, a series of significant scientific breakthroughs revealed an in-built system of cannabinoid receptors and cannabinoid signaling molecules in the human brain. Cannabinoid receptors are located throughout the central nervous system and peripheral tissues and are implicated in nervous system excitability, movement, analgesia, neuroprotection, and feeding behaviors, including newborn suckling.

Scientific Reports

Following this period of scientific discovery and expanded understanding of the physiological basis of cannabinoid action, there was renewed interest in potential therapeutic applications of cannabinoid chemicals. The National Institutes of Health Ad Hoc Group of Experts and the Institute of Medicine, following thorough review of the existing scientific literature, identified medical conditions warranting further research regarding the possible therapeutic effects of marijuana. Medical evidence for likely therapeutic benefit was identified in the areas of appetite stimulation, neurological and movement disorders, analgesia, and nausea and vomiting.

1997: National Institutes of Health, Workshop on the Medical Utility of Marijuana

1999: Institute of Medicine Report, "Marijuana and Medicine: Assessing the Science Base"

(Available through the CMCR website at: <http://cmcr.ucsd.edu/geninfo/marijuana.htm>)

Legislative Origins

The triggering event which led to the creation of the CMCR was the passage by the people of California in 1996 of Proposition 215, the Compassionate Use Act, which approved the medical use of marijuana (although at that time the exact role the substance should play in patient care remained ambiguous). Following that, in 1999, the Legislature of California passed Senate Bill (SB) 847, authored by then Assemblyman, later Senator John Vasconcellos, after extensive negotiations with then Attorney General Dan Lungren, providing the bipartisan legitimacy that enabled this bill to obtain the required two-thirds vote in each house of the California legislature. SB847 proposed (subject to the approval of the Board of Regents of the University of California) to create a three-year program overseeing objective, high quality medical research that would "...enhance understanding of the efficacy and adverse effects of marijuana as a pharmacological agent," stressing that the project "should not be construed as encouraging or sanctioning the social or recreational use of marijuana." In August 2000, the Center for Medicinal Cannabis Research was established at the University of California to carry out this mission. In 2003, after CMCR had demonstrated its ability to carry out the proposed program of research, SB295 was approved to remove the 3-year program limitation included in the founding legislation.

1996: California voters pass the Compassionate Use Act of 1996.

1999: California State Legislature passes the Medical Marijuana Research Act of 1999 (SB847).

2000: Center for Medicinal Cannabis Research is established as a state-funded research center at the University of California to solicit, review, and support clinical and limited preclinical research

2000: CMCR issued its first call for proposals

2003: SB295 is passed, re-authorizing the CMCR to continue indefinitely

CMCR Review Process

In order to evaluate the scientific validity of the proposals submitted, the CMCR engaged senior scientists from around the nation to serve as a Scientific Review Board (SRB). Studies recommended for funding by the Scientific Review Board were then submitted for review to the Research Advisory Panel of California (RAP-C), the Office of Public Health and Science of the federal Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Institute on Drug Abuse (NIDA), and the Drug Enforcement Administration (DEA). Upon final approval from each of the above agencies, studies were authorized to order cannabis cigarettes from NIDA and to begin recruiting patients. This process is described in Figures 1 and 2.

Figure 1. CMCR Scientific Review

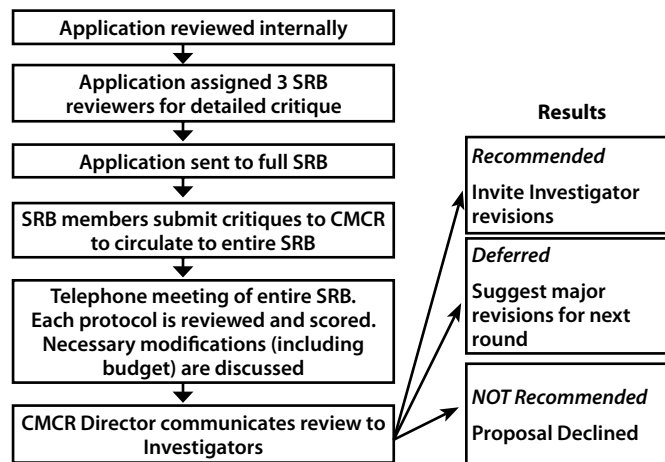
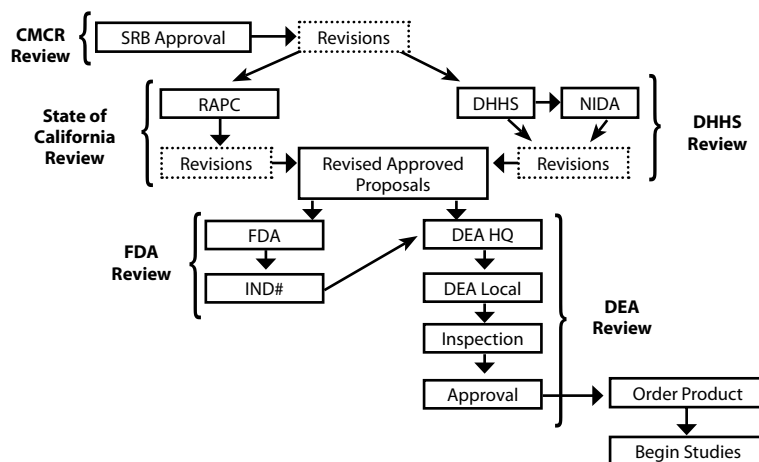


Figure 2. CMCR Regulatory Approval Process



CMCR Vision for Cannabis Therapeutics Research

CMCR envisions its role in the investigation of cannabis and cannabinoid compounds in three main research domains involving smoked cannabis, non-smoked preparations, and eventually new pharmaceutical drug candidates formulated to act directly on the endocannabinoid system.

Stage I: Smoked Cannabis

- Develop state and federal review process, and solicit proposals for initial studies.
- Conduct well-designed, rigorously controlled clinical trials of smoked cannabis. Until alternative delivery systems and new molecules are available, smoked cannabis offers the most efficient delivery of cannabinoids for clinical trials.
- Cannabis cigarettes are provided by the National Institute on Drug Abuse (NIDA).

Work Accomplished

CMCR has developed the scientific and administrative infrastructure to support application, review, selection, and implementation of studies, and has developed a rigorous process of peer review of scientific proposals by independent Scientific Review Board. CMCR has also established a relationship with state and federal agencies (RAPC, DEA, FDA, DHHS, NIDA) to facilitate regulatory approval.

The CMCR first solicited applications in fall 2000, and has funded fifteen clinical and four pre-clinical studies throughout California. The CMCR has issued five calls for proposals, most recently in summer 2006.

Stage II: Non-Smoked Preparations

- Explore the safety and effectiveness of non-smoked forms of medicinal cannabis.
- Expand trials to include alternative, non-smoked delivery of cannabis preparations.
- Alternative delivery may include vaporization, patches, suppositories, and alternative oral forms.

Work Accomplished

In the area of non-smoked routes of cannabis administration, Dr. Donald Abrams' study, "Vaporization as a 'Smokeless' Cannabis Delivery System," has been completed and the results published in the Journal of Clinical Pharmacology & Therapeutics. This study found that vaporization was a safe and effective mode of delivery. Two CMCR clinical trials are now in progress utilizing vaporization.

Stage III: Molecules To Target Endocannabinoid System

Stage III represents long-term goals for cannabinoid research. If the CMCR were to continue, the long-term research objectives would be to:

- Collaborate with laboratories around the world who are working on specific molecules (both natural and synthetic) to activate, modulate, or deactivate the body's in-built cannabinoid system.
- Perform Phase I, II, and III clinical trials on new molecules targeting the endocannabinoid system.

Overview of Research Program

Studies in Pain and Other Neurologic Conditions

Chronic pain—pain on a daily or almost daily basis for six months or longer—is one of the most prevalent and disabling conditions in California and in the US generally. Whereas many types of pain are caused by stimulation of specialized pain receptors on nerve endings, due to injury of tissues, neuropathic pain is produced either by direct damage to the central (brain, spinal cord) or peripheral nervous system itself, or by abnormal functioning of these systems. Infections, diabetes, physical trauma, strokes, and many other diseases can injure the nervous system, with resulting pain, which persists even though pain receptors themselves are not directly activated. It is therefore not surprising that neuropathic pain is widespread, affecting 5-10% of the US population. Only a few classes of medications are approved for use as analgesics in these conditions (opioids, anticonvulsants, antidepressants), and many patients obtain only partial relief, even when using combinations of all available therapies. Among the most difficult to treat neuropathic pain conditions are those secondary to HIV, diabetes, and to physical trauma to the nervous system. Because these neuropathic disorders are so prevalent, and treatment alternatives are so limited, the CMCR focused on these conditions.

A distinguishing scientific feature of this program of pain research, made possible only by the coordinating function of the CMCR, is the commonality of measures and methods across the research studies. This allows for the distinctive advantage of comparability of results across studies. Additionally, when possible we studied treatment of the same type of pain condition (e.g., HIV neuropathy) in more than one geographic site. Finding comparable results at two or more sites studying the same disease is scientifically important, since this suggests that the results are generally valid, rather than being due to chance or the specific characteristics of a single sample of patients, or of a particular team of researchers.

This research used the gold standard design for assessment of therapeutic effects, the randomized clinical trial. In this approach participants are assigned by chance, like flipping a coin, to an experimental treatment, in this case cannabis, or to a placebo (an inactive treatment). The placebo in all of our studies was a marijuana (cannabis) cigarette, made with cannabis from which the “active” ingredients, for example delta-9-tetrahydrocannabinol (THC), had been removed. The cigarette therefore had the appearance and the aroma of a marijuana cigarette, but without the crucial chemical ingredients hypothesized to be therapeutically active. Randomization ensures factors which might skew the results (like age, duration or intensity of pain) are equally present in both the experimental and placebo condition. Placebo is essential, since the expectation of pain relief from any treatment is a powerful analgesic itself. All of our protocols used measures of pain recommended by expert consensus as standard in the field. For studies of smoked cannabis, the researchers used a standard, timed method of inhalation; research using vaporized cannabis used similar, state-of-the-art technology. Researchers measured blood concentrations of the primary active ingredient of cannabis (THC), allowing estimates of relationships between dose, concentration, and magnitude of pain relief.

To date, the CMCR has completed four studies in the treatment of neuropathic pain. Two studies have focused on neuropathic pain resulting from HIV infection or the drugs used to treat HIV, one has focused on neuropathic pain of varying causes, and one has used an experi-

mental model of neuropathic pain tested in healthy volunteers. The results from these four studies have been convergent, with all four demonstrating a significant decrease in pain after cannabis administration. The magnitude of effect in these studies, expressed as the number of patients needed to treat to produce one positive outcome, was comparable to current therapies. Two additional studies involving neuropathic pain are underway.

Multiple sclerosis (MS) is one of the most common chronic and disabling diseases of the nervous system. Caused by loss of the insulating sheath surrounding nerve fibers, the disease usually begins in young adulthood. Although it may initially wax and wane in intensity and be of mild severity, it often steadily progresses, causing fatigue, loss of balance, muscle weakness, and muscle spasticity. Affecting up to 70% of people with the disease, muscle spasms lead to pain, inability to walk, and difficulties with self-care, causing most of the everyday life disability from this disease. There is as yet no cure for MS. Treatments for muscle spasticity are only partially effective and have side effects which are not easily tolerated, making the search for new therapies of high importance. Given this background, the CMCR identified MS spasticity as an additional target for therapeutic research. As with all CMCR studies, the research used the most rigorous scientific approach to testing therapies, a randomized clinical trial, supplemented by modern measurement of muscle spasticity, everyday function, life quality, and side effects. Results to date have found a significant improvement in both an objective measure of spasticity and pain intensity in patients whose standard therapy had provided inadequate relief.

Synopsis of CMCR Published Clinical Study Results

“The Effect of Cannabis on Neuropathic Pain in HIV-Related Peripheral Neuropathy”

Donald I. Abrams, M.D., University of California, San Francisco

The primary objective of this study was to evaluate the efficacy of smoked cannabis when used as an analgesic in persons with neuropathic pain from HIV-associated distal sensory polyneuropathy (DSPN). In a double blind, randomized, five-day clinical trial patients received either smoked cannabis or placebo cannabis cigarettes. Patients continued on any concurrent analgesic medications (e.g., gabapentin, amitriptyline, narcotics, NSAIDs) which they were prescribed prior to the trial; the dose and amount of the medications were recorded daily.

The full results of this study appear in the journal *Neurology* (Abrams, et al., 2007– see reference list). In brief, 55 patients were randomized and 50 completed the entire trial. Smoked cannabis reduced daily pain by 34% compared to 17% with placebo. The study concluded that a significantly greater proportion of patients who smoked cannabis (52%) had a greater than 30% reduction in pain intensity compared to only 24% in the placebo group. This result is clinically important, since the threshold of a 30% reduction in pain intensity is associated with meaningful improvement in quality of life in other research on pain outcomes.

Cannabis appeared to be well-tolerated and there were no safety concerns raised. By design, all patients had smoking experience with cannabis. There were more side effects in those receiving cannabis than placebo, with the most frequent being sedation, anxiety, and dizziness, but these were all rated as “mild.”

“Placebo-Controlled, Double Blind Trial of Medicinal Cannabis in Painful HIV Neuropathy”

Ronald J. Ellis, M.D., Ph.D., University of California, San Diego

The primary objective of this study also was to evaluate the efficacy of smoked cannabis when used as an analgesic in persons with HIV-associated painful neuropathy. In a double-blind, randomized, clinical trial of the short-term adjunctive treatment of neuropathic pain in HIV-associated distal sensory polyneuropathy, participants received either smoked cannabis or placebo cannabis cigarettes. A structured dose escalation-titration protocol was used to find an individualized, effective, safe, and well-tolerated dose for each subject. Participants continued on their usual analgesic medications throughout the trial, with the dose and amount of these medications being recorded daily.

The full results of this study were published in the journal *Neuropsychopharmacology* (Ellis, et al., 2008 – see reference list). In brief, 34 eligible subjects enrolled and 28 completed both cannabis and placebo treatments. Among completers, pain relief was significantly greater with cannabis than placebo. The proportion of subjects achieving at least 30% pain relief was again significantly greater with cannabis (46%) compared to placebo (18%). It was concluded that smoked cannabis was generally well-tolerated and effective when added to concomitant analgesic therapy in patients with medically refractory pain due to HIV-associated neuropathy. Once again these results appeared to be relevant to everyday clinical practice, because the magnitude of pain relief is associated with that which improves life quality, and also because the benefit was above and beyond that conferred by the patients’ usual analgesics.

As in the study described above, side effects were more frequent with cannabis than with placebo, with the most common being sleepiness or sedation, fatigue, and difficulty with concentration. These were “mild” for the most part and did not raise safety concerns.

“A Double-Blind, Placebo-Controlled Crossover Trial of the Antinociceptive Effects of Smoked Marijuana on Subjects with Neuropathic Pain”

Barth Wilsey, M.D., University of California, Davis

This study’s objective was to examine the efficacy of two doses of smoked cannabis on pain in persons with neuropathic pain of different origins (e.g., physical trauma to nerve bundles, spinal cord injury, multiple sclerosis, diabetes). In a double-blind, randomized clinical trial participants received either low-dose, high-dose, or placebo cannabis cigarettes. As customary in CMCR trials, participants were allowed to continue their usual regimen of pain medications (e.g., codeine, morphine, and others).

The full results of this study have been published in the *Journal of Pain* (Wilsey, et al., 2008 – see reference list). Thirty-eight patients underwent a standardized procedure for smoking either high-dose (7%), low-dose (3.5%), or placebo cannabis; of these, 32 completed all three smoking sessions. The study demonstrated an analgesic response to smoking cannabis with no significant difference between the low and the high dose cigarettes. The study concluded that both low and high cannabis doses were efficacious in reducing neuropathic pain of diverse causes.

Disagreeable or unpleasant side effects were significantly more likely with high dose cigarettes compared to low dose or placebo, whereas there was no difference in these effects between low dose and placebo sessions. There was no indication of mood changes (e.g., sadness, anxiety, fearfulness).

“Analgesic Efficacy of Smoked Cannabis”

Mark Wallace, M.D., University of California, San Diego

This study used an experimental model of neuropathic pain to determine whether pain induced by the injection into the skin of capsaicin, a compound which is the “hot” ingredient in chili peppers, could be alleviated by smoked cannabis. Another aim of the study was to examine the effects of “dose” of cannabis, and the time course of pain relief. In a randomized double-blinded placebo controlled trial, volunteers smoked low, medium, and high dose cannabis (2%, 4%, 8% THC by weight) or placebo cigarettes.

The full results of this study were published in the journal *Anesthesiology* (Wallace, et al., 2007 – see reference list). Nineteen healthy volunteers were enrolled, and 15 completed all four smoking sessions. In brief, five minutes after cannabis exposure, there was no effect on capsaicin-induced pain at any dose. By 45 minutes after cannabis exposure there was a significant decrease in capsaicin-induced pain with the medium dose (4%) and a significant increase in pain with the high dose (8%). There was no significant effect seen with low dose (2%). There was a significant inverse relationship between pain perception and plasma THC. In summary, this study suggested that there may be a “therapeutic window” (or optimal dose) for smoked cannabis: low doses were not effective; medium doses decreased pain; and higher doses actually increased pain. These results suggest the mechanism(s) of cannabinoid analgesia are complex, in some ways like non-opioid pain relievers (e.g., aspirin, ibuprofen) and in others like opioids (e.g., morphine).

“Short-Term Effects of Cannabis Therapy on Spasticity in Multiple-Sclerosis”

Jody Corey-Bloom, M.D., University of California, San Diego

This objective of this study was to determine the potential for smoked cannabis to ameliorate marked muscle spasticity (chronic painful contraction of muscles), a severe and disabling symptom of multiple sclerosis. In a placebo-controlled, randomized clinical trial spasticity and global functioning was examined before and after treatment with smoked cannabis. Patients were allowed to continue their usual treatments for spasticity and pain while participating in the research.

The full results of this study are being submitted for publication. Initial results were presented at the meeting of the American College of Neuropsychopharmacology in 2007. Thirty patients with multiple sclerosis were enrolled. Compared to placebo cigarettes, cannabis was found to significantly reduce both an objective measure of spasticity, and pain intensity. This study concluded that smoked cannabis was superior to placebo in reducing spasticity and pain in patients with multiple sclerosis, and provided some benefit beyond currently prescribed treatments.

“Vaporization as a ‘Smokeless’ Cannabis Delivery System”

Donald Abrams, M.D., University of California, San Francisco

The aim of this study was to evaluate the use of a vaporization system (the Volcano; VAPORMED® Inhalatoren; Tüttlingen, Germany) as a “smokeless” delivery system for inhaled cannabis. Because of concerns regarding the practicality and palatability of using cannabis cigarettes as a standard treatment, there has been an interest in developing alternative delivery systems. Participants were randomly assigned to receive low, medium, or high dose (1.7, 3.4, or 6.8% tetrahydrocannabinol) cannabis cigarettes delivered by smoking or by the vaporization system on six study days.

The full results of this study have been published in the journal *Clinical Pharmacology & Therapeutics* (Abrams, et al., 2007 – see reference list). Eighteen healthy volunteers were recruited to participate in the research. The analysis indicated that the blood levels of vaporized cannabis are similar to those of smoked cannabis over a six hour period. However, blood concentrations of THC at 30 and 60 minutes after inhalation were significantly higher in vaporized cannabis as compared to smoked cannabis. In addition, carbon monoxide levels were significantly reduced with vaporization compared with smoked cannabis. Fourteen participants preferred vaporization, 2 preferred smoking, and 2 reported no preference. In summary, vaporization of cannabis was found to be a safe mode of delivery, and participants had a preference for vaporization over smoking as a delivery system in this trial.

Recently Completed And Ongoing Studies

“Sleep and Medicinal Cannabis”

Sean Drummond, Ph.D., University of California, San Diego

The primary objective of this study was to determine the effects of cannabis on insomnia and poor sleep quality, which are experienced by up to 90% of HIV-infected individuals. Participants in this study were individuals enrolled in the UCSD randomized trial comparing cannabis and placebo as an analgesic in painful HIV-associated neuropathy (see Dr. Ellis, above).

The results of this study suggest that cannabis administration during the day does not affect objective or subjective measures of sleep approximately 7-8 hours after the last use of cannabis.

“Impact of Repeated Cannabis Treatments on Driving Abilities”

Thomas Marcotte, Ph.D., University of California, San Diego

The principal aim of this study was to examine whether routine administration of cannabis in the medical treatment of HIV-related neuropathy and spasticity associated with multiple sclerosis results in significant impairment in driving abilities. Participants in this study were individuals enrolled in the randomized clinical trials of cannabis for painful HIV neuropathy and for spasticity in multiple sclerosis conducted at UCSD (see Dr. Ellis and Dr. Corey-Bloom, above).

The results of this study are in preparation. Subjects were tested using a computerized driving simulator commonly used to demonstrate the effects of alcohol on driving ability. The driving simulator presents different driving conditions and circumstances and was done at four points: before cannabis, and at one, three, and 18 hours after the final dose in the therapeutic trials. These data will provide insights regarding the real life impact of using cannabis as medicine.

“Efficacy of Inhaled Cannabis in Diabetic Painful Peripheral Neuropathy”

Mark Wallace, M.D., University of California, San Diego

The primary objective of this ongoing study is to evaluate the efficacy of smoked cannabis when used as an analgesic in painful neuropathy due to diabetes. In a double-blind, randomized, placebo-controlled trial, participants will inhale low, medium, or high dose vaporized cannabis or placebo. Concurrent testing with experimentally-induced pain will help identify the potential mechanisms of therapeutic effects.

This study is actively recruiting its intended sample of 20 participants. No preliminary results are available at this time.

“The Analgesic Effect of Vaporized Cannabis on Neuropathic Pain”

Barth Wilsey, M.D., University of California, Davis

The primary aim of this study is to evaluate the analgesic effects of vaporized cannabis in patients with neuropathic pain of different origins. In a randomized clinical trial the effects of placebo and of low and medium (1.7 % and 3.5%) dose cannabis on clinical pain and on experimentally induced pain will be assessed. As noted above, use of experimentally-induced pain may help identify mechanism of actions.

This study is beginning to recruit participants. No preliminary results are available at this time.

Completed Pre-Clinical Studies

In addition to testing the possible benefits of medicinal cannabis, the CMCR supported a small number of laboratory and animal studies which might lead to either developing new treatments in humans, or better understanding the mechanisms of therapeutic actions.

“Mechanisms of Cannabinoid Analgesia”

Howard Fields, M.D., Ph.D., University of California, San Francisco

The aim of this study was to determine whether cannabinoids might be a useful class of medication for migraine and other headaches or facial pain conditions.

The full results of this study were published in the journal *Pain* (Papanastassiou et al., 2003 – see reference list). A cannabis-like drug (WIN 55.212-2) given to rats under anesthesia showed reduced activity of individual nerve cells transmitting pain, whereas giving another drug which blocked cannabis receptors on these nerve endings reversed this effect. Moreover, the analgesic effect of the cannabis-like drug was evident in tests of facial pain (heat) in awake rats. This study therefore provided direct scientific evidence, at the level of both individual nerve cells and in awake animals, of analgesic effects of cannabis-like compounds on head and facial pain. Randomized clinical trials in humans might be conducted to determine if cannabis could treat facial pain or headache.

“Cannabinoids in Fear Extinction”

Mark Barad, M.D., Ph.D., University of California, Los Angeles

The aim of this study was to determine if a cannabis-like agent could suppress fear-inducing memories or images that might be the basis for some psychiatric conditions such as Post-Traumatic Stress Disorder (PTSD) and other anxiety disorders. Therapeutic effects were thought possible because earlier research suggested that specialized in-built cannabinoid receptors in the brain are necessary for suppression of normal fears.

Tests using three different synthetic cannabis-like compounds showed no significant differences in behavior between mice treated with study drugs and untreated mice trained to fear specific locations. This study suggests that acutely enhancing the brain’s internal cannabinoid system does not extinguish specific fears (of place memory) in animals.

“Effects of Cannabis Therapy on Endogenous Cannabinoids”

Daniele Piomelli, Pharm.D., Ph.D., University of California, Irvine

The aim of this study was to determine the short-and longer-term effects of THC on the natural in-built system of nervous system chemical transmitters called endocannabinoids, which help regulate movement, cognition, pain and other physiological processes. Amplification or interference with activity of this system could influence outcomes of cannabinoid treatment.

These experiments contributed preliminary data to work that was later published in the journal *Neuropsychopharmacology* (Giuffrida et al., 2004 – see reference list). A synthetic cannabis-like compound had no effects on the levels of anandamide, an endocannabinoid, in blood or in brain tissue from regions involved in memory, motivation, movement, and wakefulness. Chronic, but not acute, treatment caused a marked increase in anandamide levels in the brain hippocampus, a region crucially involved in learning and memory. This study provides evidence indicating that exposure to cannabis-like drugs can alter endocannabinoid signaling in the brain. Alterations in this important signaling system might be involved in mediating the actions of cannabis in humans.

“Effects of Medicinal Cannabis on CD4 Immunity in AIDS”

Rachel Schrier, Ph.D., University of California, San Diego

The aim of this study was to determine if cannabis might suppress the immune system in individuals with HIV. This is an important question since already fragile immunity is characteristic of AIDS and other serious illness where cannabis might be used.

Results of the study are being prepared for publication. Briefly, immune system cells (CD4+ white blood cells) obtained from 15 individuals with AIDS participating in another study were exposed to three concentrations of THC in tests of their functional “competence.” There was no evidence of acute impairment of immune function at concentrations achievable in living humans. These results parallel other research showing that short-term cannabis administration does not diminish the circulating number of this white blood cell essential for immunity.

Discontinued Studies

Five clinical studies were discontinued before completion, because they could not accrue a sufficient number of participants. The scientific and safety design of two studies, one studying the combination of cannabis and opioids (e.g., morphine) for cancer pain relief, and one on relief of muscle spasticity in multiple sclerosis, required either a nine day hospitalization or 16 weeks without driving an automobile. Understandably, chronically ill patients were reluctant to be re-hospitalized for research, or to surrender driving privileges for an extended period.

Two other cancer studies faced different “real life” obstacles to recruitment. One study on cannabis for severe nausea and vomiting due to chemotherapy could not identify a sufficient number of patients with sufficiently severe nausea. It appeared that current anti-nausea treatments are often highly effective. Alternative or adjunctive therapy may be required only by a minority of patients. Another project on cannabis for advanced cancer pain unresponsive to all other analgesics found that local hospice agencies were willing to refer potential participants. These patients, however, were often already smoking cannabis for pain control. One study of cannabis for use at home for neuropathic pain did not elicit sufficient interest, despite outreach to the community through advertisements and focus groups. Although the outcomes of these studies is disappointing, valuable lessons were learned in terms of design of future studies and selection of appropriate populations for study.

Summary And Future Directions

Results of CMCR studies support the likelihood that cannabis may represent a possible adjunctive avenue of treatment for certain difficult-to-treat conditions like neuropathic pain and spasticity. In establishing the University of California CMCR, the California Legislature enabled the creation of what is now arguably a world-class resource both for state-of-the-art clinical trials on medicinal cannabis and its derivatives, and for developing knowledge on the potential and limitations of cannabinoid therapeutics for selected indications. By facilitating high caliber clinical trials, whose results are published in leading peer-reviewed scientific journals, the CMCR is providing physicians and policy makers with solid scientific data to inform both medical research and policy decisions. As a seasoned and unique resource, the CMCR is well-positioned to inform public health and policy decision-makers.

Worldwide, the merit of new therapies is rigorously evaluated by a series of clinical trials, termed Phase I, Phase II, Phase III, and Phase IV. In Phase I, usually involving 20-50 participants, several possible doses of a drug are tested, safety is assessed, and hints of therapeutic value are revealed. Drug development then proceeds to Phase II trials (which may recruit up to several hundred individuals) to more accurately gauge the efficacy of treatment along with determining short term side effects and risks. Results from Phase II trials with smoked cannabis in neuropathic pain form the basis of the CMCR's efforts to date. In the next step, Phase III trials, involving hundreds to several thousand patients, are designed to provide definitive assessment of the efficacy of new treatment for specific conditions (usually by comparing the newer therapy to the best "standard" treatment available), while also adding to a better understanding of benefit-risk relationships. Finally Phase IV trials, conducted after a treatment is licensed or approved for general medical use, gather additional information on benefits, risks, and optimal use of the therapy. The expertise developed at CMCR is well-suited to contribute to each of these phases of cannabinoid research.

Were support for the CMCR to continue, research might focus on 1) larger placebo-controlled studies to generate definitive data on therapeutic merit (i.e., Phase III trials), 2) head-to-head comparisons with other current therapies (in Phase II or III studies), or 3) expanded studies evaluating cannabis as an adjunct to existing treatment with opioids and non-steroidal anti-inflammatory drugs (i.e. Phase II and III research determining if cannabinoids have an "opioid-sparing" effect, that is, if they might allow use of lower doses of opioids without sacrificing pain relief). Other Phase II and III studies might move from the question of efficacy to overall effectiveness, that is, evaluating 1) alternative delivery systems (e.g., vaporization) that reduce the harmful effects of smoking, 2) models of take-home treatment that more accurately mimic the way drugs are prescribed, and 3) long-term studies to assess emergent toxicities, stability of treatment effects, and possible development of tolerance to treatment over time. This research might extend into formal Phase IV trials.

Studies also might be conducted on newly-developed synthetic agents which enhance, antagonize, or otherwise modulate the cannabinoid system, comparing their efficacy to cannabis as a botanical product. In any event the "fundamental" nature of the endocannabinoid system—evident by its participation in essential functions like movement, pain, moods and other behaviors—suggests continuing clinical research on cannabis might yield important contributions to health care.

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CMCR Supported Publications

Results of CMCR Studies

Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 2007 68: 515-521.

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†Contents of CMCR special issue of the journal *Neuropharmacology*

