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Early Findings in Controlled Studies of Herbal Cannabis: A Review

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Abstract

Despite the widespread public interest in the therapeutic potential of herbal cannabis, little rigorous data exist on its use for specific, chronic medical conditions. The Center for Medicinal Cannabis Research has funded research protocols which provide interesting results that may be useful in guiding future research programs. The data alone, however, fail to make the case that crude, smoked cannabis should be available to patients.

Introduction

Despite the widespread public interest in the therapeutic potential of the cannabis plant, little rigorous data exist reflecting on its safety and efficacy for the treatment of specific chronic medical conditions. Recently, the Center for Medicinal Cannabis Research (CMCR), based at the University of California San Diego, released a Report describing the results of research that it has funded since its inception ten years ago.(1) That report, as well as the published studies it describes, has garnered considerable media coverage.

CMCR was created in 2000 as the result of legislation (California State Senate Bill 847) enacted in 1999 for the purpose of conducting research into cannabinoids, including smoked cannabis. CMCR reports it focused on medical conditions identified by the Institute of Medicine (in its 1999 publication *Marijuana as Medicine: Assessing the Science Base*) as those for which cannabis might have therapeutic effects. In total, CMCR approved fifteen clinical studies, including seven clinical trials. As of February, 2010, five of those trials had been completed, and two were in progress. CMCR also approved four preclinical studies, which have all been completed. Three of the clinical studies examined the use of smoked cannabis as an adjunctive treatment in pain conditions associated with injury or disease.(2) Another examined the analgesic effect of smoked cannabis in experimental pain. Finally, an additional pilot study explored the use of vaporization as a cannabis delivery system. CMCR supported these studies with nine million dollars in funds appropriated by the California legislature. That funding source has not been renewed.

From the results of this research, CMCR concluded that there was “reasonable evidence” that cannabis is a “promising treatment” in certain pain syndromes and that the findings “provide a strong science-based context in which policy makers and the public can discuss the place of these compounds in medical care.” This article will explore a number of issues raised by this research and clarify the limits and significance of the clinical trial results.

The following discussion suggests that the CMCR funded studies provide interesting data that may be useful in guiding future research programs. Those data, however, are quite inadequate to provide evidence that smoked cannabis should be made available directly to patients. In light of the short duration of treatment, small patient size, potential failure of blinding, and other considerations elucidated below, these studies cannot support such a conclusion. Similarly, they do not resolve other important public policy questions, such as whether it is appropriate to commit additional scarce governmental funding resources to smoked/inhaled cannabis research or to reconsider the status of cannabis under Schedule I of the Controlled Substances Act. Indeed, these studies demonstrate that patients using inhaled THC-predominant cannabis experience a range of significant CNS side effects, including cognitive impairment and intoxication. This further underlines the need for all cannabis-based products to develop a robust body of risk-benefit data in specific medical conditions and for patients using such products to be under the supervision of their personal physicians.

The Stages of Modern Medication Development

Modern medication development takes place in discrete stages. Research begins with very small trials, often in healthy subjects, and proceeds into larger trials in patients with specific medical conditions, through which a product’s efficacy, side effects, optimal dosing, pharmacological activity, and toxicity are increasingly better defined. Late stage clinical trials are often followed by open label extension studies, where the persistence of treatment effects, as well as additional safety information, can be assessed:

PHASE I TRIALS: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

PHASE II TRIALS: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

PHASE III TRIALS: Expanded controlled and uncontrolled trials which follow preliminary evidence suggesting effectiveness of the drug; are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.

PHASE IV TRIALS: Post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.(3)

It is well-accepted in pharmaceutical development that only Phase III studies can normally establish “pivotal” evidence of an investigational product’s risks and benefits, defined as evidence sufficient to support a New Drug Application seeking approval for marketing from the Food and Drug Administration.(4) Many products, even those that may have shown considerable promise in Phase II, have failed at the more rigorous Phase III stage.(5) As the CMCR report acknowledges, all of its published clinical studies have produced data only at the Phase II stage.(6)

The CMCR studies can, therefore, be said to provide at best **preliminary** evidence of safety and efficacy—data that would justify further clinical research to explore potential cannabis-derived or cannabinoid formulations and alternative modes of delivery. Such data are not sufficient, however, to form the foundation of FDA marketing approval. For the reasons described in greater detail below, they are similarly inadequate to resolve other regulatory or policy issues.

Smoked Cannabis as a Treatment for Neuropathic Pain Syndromes

In its report, CMCR indicated that its intention was to study cannabis as a treatment option for individuals with intractable symptoms, i.e., who do not respond or respond inadequately to currently available therapies. Accordingly, the report averred, cannabis was studied as an add-on to the patient’s existing treatments. Each study was conducted in a small number of patients and was of very short duration—limited even by Phase II standards. The patients/subjects were almost exclusively cannabis-experienced. All clinical studies were approved by the FDA and registered (licensed) by the DEA. Cannabis was obtained in varying potencies from the National Institute on Drug Abuse (NIDA). The clinical studies used a standard, timed method of smoke inhalation. Patients were generally excluded for schizophrenia or bipolar depression, uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (including asthma), active substance abuse, and history of cannabis dependence. All protocols were approved by experts on CMCR’s Scientific Review Board and the relevant institutional review board.

All the studies examined in this article were randomized, double blind, placebo-controlled trials (RCTs) investigating the use of smoked cannabis in the treatment of neuropathic pain syndromes. Abrams et al. conducted a parallel-group study in 55 patients with painful HIV-associated sensory neuropathy (28 randomized to placebo and 27 to smoked cannabis) with an in-patient treatment phase of five days.(7) The THC content of the cannabis was 3.5%.

A trial conducted by Ellis et al. in the same pain syndrome involved 34 randomized patients, of whom 28 completed the study.(8) After one 5-day treatment period and a 14-day washout period, the patients were crossed over to the other intervention for another 5-day treatment period. The THC content of the cannabis ranged from 1-8%. Patients were started at 4% THC and then titrated upwards or downwards in four smoking sessions depending on their symptom relief and tolerance of the dose.

Finally, a crossover study conducted by Wilsey et al. examined the use of smoked cannabis as a treatment for neuropathic pain of various origins.(9) Thirty eight patients were randomized, of whom 32 completed all the study sessions. Pain syndromes were diverse, rather than homogeneous: complex regional pain syndrome (22 patients), central neuropathic pain related to spinal cord injury or multiple sclerosis (10 patients), peripheral neuropathy related to diabetic neuropathy or nerve injury (6 patients). (10) The

treatment interventions comprised cannabis of 3.5% and 7% THC, and placebo. Patients engaged in a complex dosing scheme and were exposed to each treatment **only once**, in random order, with at least 3 day intervals between sessions. During each treatment session, patients were allowed a maximum of nine puffs over a six hour period and were assessed at hourly intervals.

These studies demonstrated a modest degree of efficacy; however, the extent of such efficacy was not fully consistent between the studies. In the Abrams study, the smoked cannabis group had a 34% reduction in daily pain versus a 17% reduction in the placebo group (net 17% reduction); in addition, 52% of the patients in the cannabis group reported a 30% reduction in pain scores over the 5 days versus a 24% reduction in the placebo group (net 28%). In the Ellis study, 46% of patients in the cannabis group achieved 30% pain relief compared with 18% of those in the placebo group (net 28%).

In the Wilsey study, by contrast, there was only a small--but statistically significant--difference in pain reduction from placebo (**net less than 10 points** on a 100-mm visual analogue scale of pain intensity). **Furthermore, this separation from placebo did not occur until a cumulative 9 puffs at 240 minutes (4 hours) had taken place.** This extended time to onset of analgesia, even longer than that in the Wallace study on experimental pain, infra, challenges the contentions of cannabis advocates that inhaling cannabis is necessary in order for patients to obtain rapid pain relief. No significant differences in analgesia were observed in the two different cannabis potency groups (3.5% and 7%).

The short duration of these studies, coupled with the small patient size and the variability of neuropathic pain syndromes (Wilsey), would afford them extremely limited significance in the FDA regulatory context. International regulatory standards call for randomized controlled clinical trials of 12 weeks duration in order to demonstrate the safety and efficacy of an investigational product in chronic pain conditions.(11) Such a duration is necessitated because short term efficacy may not be maintained in chronic use, and/or side effects may become cumulative or more apparent over time, thereby affecting the risk/benefit profile.

Furthermore, the significance of the Abrams results must be considered against the fact that almost 50% of the patients were **not** taking a concurrent analgesic. In the Ellis study, only 68% of the patients were taking concomitant opioids; the remaining patients used acetaminophen and NSAIDS; it is unclear whether the NSAIDS comprised only aspirin, ibuprofen, and naproxen, or also included COX-2 inhibitors. In the Wilsey study, patients were instructed to “take all other concurrent mediations,” but the prevalence and nature of such medications was not described. These discrepancies and omissions call into question the statement in the CMCR report that the trials were conducted in “treatment-refractory” patients, i.e., those who are not receiving adequate benefit from an optimized analgesic regimen.

Extent of Side Effects

All medications have side effects, and, in order to achieve marketing approval, an investigational product must have a favorable risk/benefit profile in a particular medical condition. In the studies described above, almost all patients were cannabis-experienced. (12) The side effect profile—particularly the incidence of adverse CNS events-- exhibited by patients in these studies cannot be extrapolated to a more representative patient population, which would include cannabis-naïve patients. Indeed, in the Wilsey study, the authors noted that only cannabis experienced patients were entered into the study in order “to reduce the risk of adverse psychoactive effects in naïve individuals.” For example, in the Ellis study, one cannabis-naïve patient was withdrawn due to an “acute cannabis-induced psychosis.”

Despite the fact that most patients were cannabis-experienced, the extent and range of side effects were notable in these studies. Although the Abrams study investigators opined that “An acceptable safety margin has been shown in the present study,” the adverse event data seem to reveal considerable CNS impact and, while intoxication scores were not collected, the complex of symptoms identified suggests that intoxication was prominent.

Table 1 (13)

In the Wilsey study, the authors concluded that “psychoactive effects were minimal and well-tolerated,” but conceded that “neuropsychological impairment was problematic, particularly with the higher concentration of study medication.” Patients using the 7% cannabis demonstrated neurocognitive impairment in attention, learning and memory, and psychomotor speed, whereas the 3.5% cannabis resulted in a decline in learning and memory only. This, the authors opined, suggested a possible therapeutic window. They further cautioned, however, that severe pain coupled with psychological distress is associated with lower scores on cognitive performance tests, which was true of the patients in this study. Therefore, “[i]n combination with the deficits in baseline neurocognitive performance….cannabis compounds this problem. This finding necessitates caution in the prescribing of medical marijuana for neuropathic pain, especially in instances in which learning and memory are integral to a patient’s work and lifestyle.” The authors speculated that, since the low and high doses were equally analgesic, it might be preferable to utilize a lower cannabis potency/dose, which would also reduce the diversion potential. This suggests that the high-potency cannabis available in dispensaries may seriously impact a patient’s neurocognitive functioning.

Table 2 (14)

In the Ellis publication, little was described regarding safety issues. The authors stated only that “the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation and thirst.” However, they do warn that “Cannabis has potent psychotropic effects including ‘paradoxical’ effects (e.g., depersonalization, hallucination, suspiciousness) in an important minority of individuals.”

The CNS side effects reported in these controlled studies also suggest that many patients purchasing cannabis from cannabis dispensaries may be experiencing even more extreme reactions. Some of these patients are cannabis-naïve, and few receive proper evaluation and supervision from physicians. (13) Unlike the NIDA cannabis utilized in these studies, products from cannabis dispensaries vary wildly in THC content. Many types of sinsemilla—buds from unfertilized female cannabis plants, generally cultivated indoors—exhibit THC concentrations of well over 15%. (14) Cannabis-infused honeys, cannabis resin, and hash/cannabis oil can reach THC concentrations of 60%. Patients who are 1) debilitated by serious medical conditions and 2) lack adequate physician guidance concerning product composition and dosing, may experience more undesirable or even frightening effects. For example, in a media report, one patient with advanced cancer ingested 1/8 teaspoon of cannabis-infused honey that she had purchased at a dispensary: “After a few hours, she was hallucinating, too dizzy and confused to dress herself for a doctor's appointment. Then came vomiting far worse than her stomach upset before she took the drug.”(15) Such side effects may be quite unpredictable, since the cannabis products lack standardization. Patients also cannot be assured that they will experience the same effect from one cannabis purchase to the next.

The Concern with Blinding

Blinding is considered essential to the reliability and integrity of clinical trial results, particularly when the symptom being treated (such as pain) must be assessed by the patient, rather than by means of some objective measurement tool. As one expert stressed:

> If participants are not blinded, knowledge of group assignment can affect responses to the intervention received. Participants who know that they have been assigned to a group who will receive a new treatment might harbor favourable expectations or increased apprehension. Those assigned to standard treatment, however, might feel deprived or relieved….knowledge of the intervention received, and a perception of that treatment, can affect the psychological or physical responses of the participants. (16)

The fact that almost all of the patients in these studies were cannabis-experienced, coupled with the notable CNS side effects, calls into question the effectiveness of the blinding in these studies. In none of these studies did the researchers attempt to correlate the occurrences of side effects—particularly CNS side effects—with efficacy data. Therefore, it is impossible to know whether those patients on active medication who experienced notable CNS effects became unblinded and were influenced in their assessments of efficacy, i.e., whether those patients who believed they were on active medication were thereby influenced to think that they were obtaining greater pain relief. Furthermore, since almost all patients were cannabis-experienced, there was no way to attempt to correlate prior use of cannabis and efficacy, i.e., whether prior cannabis use was a predictive factor in determining clinical response. Since most of the patients were cannabis experienced, it is very probable that the blinding was not successful. Indeed, in the Ellis study, the authors specifically noted that, when asked, the majority of patients who had been exposed to cannabis (either initially or during the cross over) correctly guessed the treatment. This calls into question the validity of the efficacy results.

Effect of Smoked Cannabis on the Immune System

Although not funded by CMCR, another trial published by Abrams et al. in 2003 is of relevance to the current discussion. This study investigated the short-term effects of smoked cannabis on the viral load in HIV-infected patients receiving a stable antiretroviral treatment regimen of either indinavir or nelfinavir. Because the same systems metabolize cannabinoids and protease inhibitors, it was hypothesized that cannabinoids might alter viral loads in HIV-infected patients taking protease inhibitors. Patients were required to have a stable viral load for the previous 16 weeks and must have had previous smoked cannabis experience (6 or more times) in order “to ensure that they knew what neuropsychiatric effects to expect.”

The 62 study participants were randomized to cannabis cigarettes, a synthetic THC (dronabinol) capsule or placebo capsules three times daily for 21 days of in-patient treatment. NIDA provided the cannabis (3.95% THC). Patients randomized to smoked cannabis utilized a standardized puff procedure. Interestingly, the investigators noted that they had chosen not to include a smoked placebo group because they thought it "would be impossible to blind marijuana in study participants with previous marijuana experience." (17)

The investigators concluded that short-term use of cannabinoids, either smoked or oral, does not substantially elevate viral load in HIV-infected persons receiving specified antiretroviral regimens. The results also showed increased weight in both cannabinoid groups compared to placebo, although the weight gained was not in lean body mass but in fat. The investigators acknowledged that their conclusions were "limited by the short duration of the study" and that it would be desirable to produce additional safety information over longer exposure periods. They also noted that the effect of government-supplied cannabis of known potency and content cannot be extrapolated to the potential effects of cannabis available from other sources. Finally, the lack of a blinded control group for the smoked marijuana could bias the interpretation of some of the results, such as weight changes.

As with later CMCR studies (and as acknowledged by the authors), this study provided at best short-term data about the effect of either oral or smoked cannabinoids on viral load in HIV infected persons. It took place in a controlled environment (in-hospital) with government-standardized cannabis. The results fail to establish that the chronic use of smoked cannabis will not impair immune function. Nor does it suggest that the many types of cannabis dispensary products—which may be contaminated with pesticides or dangerous microbes—will not cause injury to the immune system. A patient whose immune system has been compromised, either by disease process or by treatment (e.g., cancer chemotherapy), is likely to be particularly susceptible to harm from such contaminants. (18)

Smoked Cannabis and Experimental Pain

Using a human experimental pain model, Wallace et al. hypothesized that smoked cannabis would reduce the pain and hyperalgesia induced by intradermal capsaicin. (19) In an RCT with a crossover design, capsaicin was injected into opposite forearms of 15 active cannabis-using (20) healthy volunteers, 5 and 45 minutes after exposure to smoked cannabis. Subjects were exposed to placebo, low (2%), medium (4%), and high (8%) potency NIDA cannabis. They adhered to an observed, standardized smoking procedure, taking three inhalations at each dose, with 40 seconds between inhalations, followed by a one-week washout period. Pain, hyperalgesia, THC plasma levels, and side effects (including a "high") were assessed. (21)

The results demonstrated that 5 minutes after cannabis exposure, there was no effect on induced pain at any dose. Not until 45 minutes after cannabis exposure was there a significant decrease in capsaicin-induced pain with the medium dose. As with the Wilsey study, this undermines the claims of cannabis advocates that smoking or otherwise inhaling cannabis is necessary in order for patients to obtain rapid pain relief. Moreover, a significant **increase** in pain was seen with the high dose. There was no effect with the low dose, and there was no effect on hyperalgesia at any dose. There was also no effect on the pain quality.

Side effects were dose-dependent, with many more reported at the high potency, despite the fact that patients took only 3 inhalations. Tests of neuropsychological functioning showed no significant difference at any dose, although this may be inconsistent with the impairment in cognitive functioning displayed in the Wilsey study. (22) Subjective reports of a "high" were also dose-dependent. Five minutes after cannabis exposure, subjects rated a significant (7/10) "high" at the highest dose; although a prominent (5.4/10) "high" was still reported at the lowest dose. Intoxication scores were lower, but still notable, 40 minutes after exposure: 3/10 for the lowest dose, 4/10 for the medium, and 4/10 for the highest dose.

The biphasic effects (analgesia at a lower dose; hyperalgesia at a higher dose) reported in this study have been identified previously, (23) although they were apparently **not** consistent with the Wilsey study, where there was an equal analgesic response with both low and high dose cannabis. As the authors noted with concern, such an effect may suggest that there is a narrow therapeutic window of efficacy for inhaled cannabis and perhaps cannabinoids as a class. This indicates (particularly in light of the discrepant Wilsey results) that more research is needed to determine the therapeutic window for different cannabinoid formulations and modes of delivery. For example, a product containing both THC and CBD (cannabidiol) may have a different therapeutic window from a formulation that is almost exclusively THC. (24, 25) High-THC cannabis may be more likely to produce psychotic symptoms. (26, 27) Cannabis generally available in cannabis dispensaries is essentially devoid of CBD. (28) This is also true of the NIDA cannabis used in this and other CMCR studies.

The authors candidly acknowledge that the results of this study cannot be generalized to clinical research because of the small sample size and use of only healthy volunteers who were cannabis-experienced and able to tolerate the highest study dose of cannabis. They do conclude that more information is needed regarding abuse potential, tolerance, efficacy in neuropathic pain, and safety issues. Consequently, they "[could] not advocate a place for using cannabis in the treatment armamentarium at this time." Pointing to the health-related harms resulting from the long-term use of smoked cannabis, including respiratory symptoms "suggestive of obstructive lung disease," and the "paradoxical" psychotropic effects (e.g., dysphoria, dejection, depressed mood) often associated with cannabis use, they cautioned that: "[S]uch effects must be carefully considered in work addressing the future clinical application of cannabinoids."

Vaporization as an Alternate Delivery System

Cannabis is generally smoked. (29) Cannabis smoke contains many of the components of tobacco smoke. Smoking a cannabis cigarette can deposit as much as four times the amount of tar in the lungs, compared to smoking a tobacco cigarette. (30) This effect results from the fact that cannabis cigarettes lack filters, and cannabis smokers inhale more deeply and hold their breath longer than tobacco smokers hold theirs. (31) There is no doubt that chronic cannabis smoking is harmful to the lungs. (32, 33, 34)

Recognizing this concern, CMCR funded a study to examine vaporization as a potential cannabis delivery system. As the study investigators stated: "The Institute of Medicine sends a clear message suggesting that smoking is not a desirable delivery system for the potential therapeutic effects of cannabis." (35)

Abrams et al. conducted a 6-day in-patient pilot study involving 18 healthy subjects (not individuals with medical conditions), all of whom were active (rather than merely past) cannabis users. They were exposed to three separate cannabis concentrations (1.7%, 3.4%, and 6.8%), either by smoking or by vaporizing. Subjects were exposed to one type of intervention each day and were blinded to the THC concentration. The primary endpoint was the measurement of plasma concentrations of THC at specific time points for each strength of THC. The secondary outcome measure was the level of exhaled carbon monoxide (CO). Vaporization was accomplished by means of a device called the Volcano®. (36)

The study results demonstrated that the vaporizer actually resulted in **higher** concentrations of THC compared to smoked cannabis at 30 and 60 minutes, at both potencies. (37, 38) Subjects also reported their "high" on a 100-mm VAS scale; this "high" did not differ during vaporization compared to smoking, although it did increase in both instances with increasing strength of THC. Since these were active cannabis users, it is evident that vaporization, even at low levels of THC, produces intoxication. This would be even more pronounced in cannabis-naïve individuals, potentially more so in those afflicted with serious medical conditions. Surprisingly, the investigators stated that "no adverse events were reported," indicating that the subjects (and perhaps the investigators) did not consider such intoxication to be an adverse event. Seriously ill patients, however, generally consider intoxication to be an undesirable side effect of a medication.

Levels of exhaled CO, the secondary outcome, increased very little after vaporization, whereas there was a substantial increase after smoking. From this finding, Abrams et al. concluded that vaporization produced "little or no exposure to gaseous combustion toxins" and that the Volcano® device is an "effective and apparently safe vehicle for THC delivery." The lowered levels of exhaled CO, however, do not support this conclusion, since the study "did not measure other combustion products such as polycyclic aromatic hydrocarbons and oxidant gases."

Another recent non-CMCR study belies this conclusion. Noting that several previous vaporizer studies had examined only the presence of high molecular weight pyrolysis products, Bloor and colleagues analyzed the extent of low molecular weight toxic products, such as ammonia, resulting from vaporization versus smoking of both street cannabis and NIDA cannabis (3% THC). (39)

Two vaporizers, the Blue Meanie and the Volcano®, were examined. The Blue Meanie consists of an electrically heated metal cup which is enclosed in a glass container. The cup is temperature-controlled but not adjustable and reaches a temperature of about 250°C, which (according to the investigators) is below the temperature at which cannabis leaf combusts. The Volcano® consists of a ceramic heater with a heat vent; a removable chamber is positioned above the heat vent into which the cannabis sample is placed. Hot air is blown through the chamber to release vapors from the sample without combustion. The vapor inflates a disposable plastic balloon, which can be detached when filled; the vapor can then be inhaled. The device was set to its highest setting of 9, which equates to 218°C at the heater screen and 155°C at the sample surface.

Smoked cannabis from NIDA produced (in mainstream smoke) acetaldehyde at 45 ppm and ammonia at 10 ppm. Ammonia was the most abundant species in sidestream smoke, reaching the level of 250 ppm. The Blue Meanie produced ammonia (NH_3) at a mean of 205 ppm from street cannabis, compared with 4 ppm from NIDA cannabis; methanol at 212 ppm for street cannabis, compared to 73.8 for NIDA cannabis; acetaldehyde at 24.5 ppm for street cannabis, compared with 36.8 from NIDA cannabis. The

Volcano® produced ammonia at 60 ppm for street cannabis and 4.3 ppm for NIDA cannabis; methanol at 4.6 ppm for street cannabis and 13.8 ppm for NIDA cannabis.

The results demonstrated that, with street cannabis, the Volcano® produced levels of exposure to ammonia that are 1) greater than the maximum short-term occupational exposure limits of 35 ppm and 2) **higher than levels reported from tobacco smoke** (10-12 ppm). This is extremely concerning, since an industrial accident resulting in relatively low levels of ammonia resulted in significant neurocognitive impairment even after 22 months. (40) Furthermore, a recent study demonstrated that eye irritation, headache, dizziness and intoxication result from short-term exposure to only 5 ppm of NH3. (41)The Volcano® lowered the ammonia content of the vapor **only by 40-50% as compared to smoking NIDA cannabis**; it did not even approach total elimination.

It certainly cannot be said that vaporizers as a class, (42) fully or even adequately eliminate toxic products. In fact, Bloor et al. noted that closed system vaporizers **may actually expose the user to higher levels of ammonia than would be created by smoking tobacco**, since with smoking, most toxic combustion products are dispersed into the atmosphere through side stream smoke: "The use of closed systems to produce cannabis vapour results in the inhalation of most of the products of pyrolysis and thus exposure to higher levels of toxic products, such as ammonia, which may otherwise have been mainly lost in sidestream smoke." This would not be acceptable to regulatory agencies such as the FDA.

An earlier study with the Volcano® also demonstrated that at its highest setting of nine, it reduced, but did **not** fully eliminate poly aromatic hydrocarbons, as compared with smoking cannabis. Furthermore, the efficiency of THC delivery was poor. Using 200 mg. samples of 4.15% THC NIDA cannabis, an average of 1.95% of the sample weight was recovered as THC after vaporization (3.9 mg--47% of the maximum), compared to 3.24% with smoked cannabis (78% of the maximum, but without sidestream smoke loss or any residual butt). (43) In previous smoking machine tests, THC efficiencies of 30-60% had been demonstrated, with approximately 30% loss by heat destruction of THC and additional loss in sidestream smoke (44). Earlier vaporizer studies also demonstrated that vaporization can be a very inefficient way of delivering THC, (45) which is a significant concern in its own right, considering the high cost of much cannabis herbal material available in dispensaries. Moreover, vaporizers such as the Volcano® are not portable and cannot easily be used outside the patient's residence. Many non-smoking facilities, such as hospitals, will not permit the use of cannabis vaporizers, further limiting their usability by patients.

In addition, vaporizers cannot ensure a reliable and reproducible medication dose if the underlying cannabis material lacks standardization. Cannabis available in dispensaries varies significantly in THC and other cannabinoid content. Cannabis material may also be contaminated with pesticides (46) and/or dangerous microbes. (47, 48) These contaminants are not necessarily eliminated by vaporization, particularly at lower temperatures.

Current vaporization systems, therefore, do not mitigate many of the concerns and problems associated with cannabis smoking. Importantly, inhalation (whether vaporization or smoking) results in rapid delivery of a bolus of active substance to the lungs and consequently to the body and brain. As demonstrated by the Abrams pilot study, vaporized cannabis (even of low THC potency), produces significant intoxication and abuse liability.

Patients with chronic conditions—the large majority of those using cannabis for medical purposes—do not require an immediate onset method of medication delivery. For example, patients with chronic pain are often prescribed an extended release opioid, such as OxyContin®. Oral transmucosal fentanyl (e.g.., Actiq®), by contrast, is reserved for patients with breakthrough (rather than persistent background) pain, which necessitates a medication with very rapid onset. Perhaps not surprisingly, the FDA has never approved a vaporizer for the home administration of a psychoactive substance for treatment of a chronic condition. (49) Indeed, because of the technological and regulatory obstacles, development by the pharmaceutical industry of vaporization systems is in its infancy. One company describes the challenges:

> Traditional dry powder and aerosolized inhalation delivery systems have been designed and used primarily for local delivery of the drugs to the respiratory airways, not to the deep lung for rapid systemic drug delivery. Certain recent variants of these systems, however, can provide systemic delivery of drugs, either for the purpose of rapid onset of action or to enable noninvasive delivery of drugs that are not orally bioavailable. Nevertheless, many of these systems have difficulty generating appropriate drug particle sizes and consistent emitted doses for deep lung delivery. To achieve appropriate drug particle sizes and consistent emitted doses, most traditional inhalation systems require the use of excipients and additives such as detergents, stabilizers and solvents, which may potentially cause toxicity or allergic reactions. Many traditional inhalation devices require patient coordination to deliver the correct drug dose, leading to potentially wide variations in the amount of drug delivered to a patient. (50)

These studies by Abrams and others demonstrate that vaporization technology is extremely challenging, particularly when it is used to deliver a potent psychoactive substance such as cannabis. Vaporizers differ significantly in the extent to which they reduce toxic substances and deliver THC and other cannabinoid components. This fact highlights the need for manufacturers of such products to seek FDA approval as medical devices through established regulatory channels. (51)

The Federal Government and Cannabis Research

Cannabis advocates often claim that the federal government is suppressing research into the therapeutic potential of the cannabis plant. The CMCR studies demonstrate that this contention is false. The CMCR report states that all protocols (15 clinical studies and 4 pre-clinical studies) were submitted to, and approved by, 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). In all instances, these studies involved collaboration with NIH as NIDA provided the research cannabis. Indeed, in the 2003 Abrams study, which was conducted outside of the CMCR "umbrella," NIDA provided the grant funding.

It is far from clear whether further funding- public or private- of smoked cannabis research is a wise use of resources. In 2001, Lyle E. Craker, a Professor in the Department of Plant, Soil and Insect Sciences at the University of Massachusetts Amherst , submitted an application to DEA to become registered as a bulk manufacturer/cultivator of cannabis for research purposes. The cannabis cultivation would be funded, not by the federal government, but through a grant from the Multidisciplinary Association for Psychedelic Studies (MAPS). (52) Dr. Craker, sponsored by MAPS, argued (53) that a second, privately-funded source of research cannabis was necessary in order for any cannabis-derived medications to achieve marketing approval from the FDA:

> No privately funded sponsor (such as MAPS, or alternatively, a for-profit pharmaceutical company) will invest significant sums in a realistic drug development research program aimed at obtaining FDA approval for the prescription use of marijuana without first obtaining its own independent source of supply of a drug whose quality, price and availability it determines. (54)

A number of factors undermine the credibility of this claim. First, it would be unprecedented for the FDA to approve herbal material for direct prescription, due to the difficulties in standardizing the dose. The FDA has provided a pathway for the marketing approval of prescription medication derived from botanical materials. (55) This Guidance permits some leniency at the very early stages of research and development. However, by the stage of advanced clinical trials and New Drug Application, the product must meet all the stringent requirements (e.g., specifications for product composition, clear dosing parameters, testing for carcinogenicity, reproductive toxicity, etc.) applicable to any new medication.

The FDA guidance document identifies three stages of development for a botanically derived medication: Botanical Raw Material (BRM), Botanical Drug Substance (BDS) and Botanical Drug Product (BDP). (56) Because of the difficulties in identifying a method of administration that provides a reproducible dose without producing carcinogens, it is unlikely that the FDA would approve cannabis herbal material itself. Rather, the agency would probably require that the plant components be extracted and formulated into an appropriate delivery system. As the American Medical Association recently recognized : "The future of cannabinoid-based medicine lies in the rapidly evolving field of **botanical drug substance development**, as well as the design of molecules that target various aspects of the endocannabinoid system." (57) Currently, Sativex®, an investigational product derived from cannabis extracts, is proceeding through the FDA process pursuant to the Guidance.

Second, herbal cannabis need not be cultivated in the United States in order for a specific cannabis-derived product to enter into the FDA approval process. For over 85 years, it has been the policy of the U.S. not to cultivate or produce narcotic raw material (NRM), such as opium or poppy straw. (58) By long-standing international practices, the U.S. is a country that imports and manufactures, rather than one that cultivates and supplies, NRM for the development of pharmaceutical products. (59) The U.S. relies on a specific list of countries authorized to import NRM into the U.S. in order to meet legitimate medical needs. This list is deliberately kept very short, in order to prevent a proliferation of NRM-producing countries. (60) The same approach could be taken to the cultivation of cannabis for the production of pharmaceutical products. Private foreign companies may, under circumstances permitted by their domestic laws, cultivate cannabis to provide the starting materials of a pharmaceutical development program. The resulting extracts or formulated finished products can then be imported into the U.S. for research (61) and, upon FDA approval, for marketing.

Impact of the CMCR Studies on Public Policy Questions

In its report, CMCR states that the results of its studies provide physicians and policy makers with "solid scientific data" to inform not only future medical research, but also "policy decisions." With regard to the direction of future medical research, CMCR acknowledges that the current Phase II published studies have generated only the early stages of data elucidating the therapeutic potential of cannabis. If funding were available, CMCR would advance its program into the next stages, which would involve larger (Phase III) RCTs to develop "definitive data" on therapeutic merit; head-to-head comparisons of cannabis with other therapies; studies evaluating whether cannabis, when added to other analgesics, can allow for a reduced dose of those analgesics without sacrificing pain relief (e.g., opioid-sparing effects); research exploring the safety and effectiveness of alternative (non-smoked) delivery forms of cannabis and cannabis preparations; models of take-home treatment; long-term studies to assess emerging toxicities, stability of treatment effects and possible development of tolerance to treatment over time; and research into synthetic agents that would affect/modulate the endocannabinoid receptor system. CMCR did **not** elaborate on its statement that its current studies could inform "policy decisions."

Certainly, the CMCR results could be used as promising data to encourage pharmaceutical companies and other sponsors of medication development to pursue the next stages of research outlined above. The results could also be used in a public policy discussion concerning the appropriateness *vel non* of allocating scarce governmental funding resources to such research. What other "public policy" questions, however, could the CMCR data inform?

Contrary to the report's statement, these studies, for the reasons stated above, do not constitute "reasonable evidence" that smoked cannabis is a "promising treatment" for certain painful conditions. In addition to the reasons outlined above, the studies obscure the fact that "cannabis" is not an identifiable, homogeneous material. Even in these studies, the cannabis potencies differed significantly. Outside the boundaries of government-approved studies utilizing NIDA cannabis - in cannabis dispensaries, for example - the quality and composition of cannabis and cannabis-based products vary enormously. Cannabis may differ significantly in THC and other cannabinoid constituents, depending on the cannabis strain, as well as the cultivation, harvesting, and storage practices. As mentioned above, cannabis products may be contaminated with pesticides or dangerous microbes. Therefore, the CMCR studies do not provide evidence that cannabis—in any and all iterations—should be made available directly to patients without meeting the requirements of the FDA process.

The studies also do not meaningfully inform the debate over whether cannabis should be moved from Schedule I to Schedule II of the Controlled Substances Act. Substances in Schedule I have:

> A high potential for abuse;
> No currently accepted medical use in treatment in the U.S.; and
> A lack of accepted safety for use under medical supervision. (62)

Substances in Schedule II have:

> A high potential for abuse;
> A currently accepted use in treatment in the US or a currently accepted medical use with severe restrictions; and
> Abuse of the substance may lead to severe psychological or physiological dependence. (63)

In order for a substance to have a "currently accepted medical use" in the U.S., the following criteria must be met:

> The drug's **chemistry must be known and reproducible;**
> There must be **adequate safety studies**;
> There must be **adequate and well-controlled studies proving efficacy**;
> The drug must be accepted by qualified experts; and
> The scientific evidence must be widely available. (64)

The preliminary safety and efficacy data from the CMCR studies do not satisfy these demanding requirements; in light of the short duration and small sample size, coupled with the serious blinding issues, they cannot be said to be the type of pivotal studies contemplated by these criteria. Furthermore, even if cannabis were rescheduled, that would not make it available directly to patients by prescription. Physicians may prescribe, and pharmacists may dispense, only those medications that have received FDA marketing approval. The FDA does not approve active ingredients or bulk botanical material for prescription and marketing. As one cannabinoid expert has stated: "In order for a Schedule II substance to be made available by prescription, it must be contained in one or more specific dosage forms, as is the case for opium. Each and every one of such dosage forms must pass FDA muster." (65) FDA approval of a specific cannabis Botanical Drug Product would constitute "currently accepted medical use in the US," thereby allowing that product to be rescheduled into Schedule II or below. (66) Cannabis itself need not be rescheduled in order for that to occur.

Conclusion

CMCR is to be commended for having contributed to the scientific discussion concerning the therapeutic potential of the cannabis plant. It is important, too, to emphasize that these studies would not have been possible without the sponsorship and support of the State of California and numerous federal governmental agencies, including NIDA, DEA, and FDA. This fact demonstrates the falsity of the argument of cannabis advocates that the federal government is actively suppressing cannabis-related research.

Despite being the first RCTs in smoked cannabis in 20 years, the Phase II CMCR studies do not offer data on quality, safety, and efficacy that are sufficiently robust either to have regulatory significance or to determine important public policy issues. With such short treatment duration, small patient numbers, and potential blinding failure, these studies should be characterized, at most, as preliminary guides for future research. The prevalence of CNS side effects, probable pulmonary damage with chronic use, and challenges of dose standardization, suggest that future research cannot focus productively on smoked cannabis. Vaporization of cannabis produces a sharp spike in THC blood levels and accompanying intoxication/abuse liability, as well as a still-unacceptable level of toxic byproducts. In sum, inhaled cannabis would seem to be a potential delivery system only for the small number of patients who suffer from intractable breakthrough pain and/or terminal disease, for whom a different risk/benefit calculus may be appropriate.

Further research into the direct use of inhaled cannabis herbal material, therefore, appears to be of limited usefulness. Government resources are scarce and precious. Accordingly, those resources should be devoted only to research likely to result in products that can achieve FDA approval and thereby become available to patients by prescription. Pharmaceutical companies, similarly, will sponsor only that research likely to produce definitive data on quality, safety, and efficacy and products with an acceptable risk/benefit profile in a broad patient population, which includes cannabis-naïve patients.

A look at modern history reveals that smoking cannabis for therapeutic purposes is largely an anachronism arising out of the general increase in the use of smoked cannabis in the 1960s. In 1839, William B. O'Shaughnessy introduced the Western world to the therapeutic properties of cannabis. In his studies, however, cannabis was formulated into tinctures and extracts; it was not smoked or inhaled. Unfortunately, the technology available throughout the 1800s and most of the 1900s was not adequate to permit these and other formulations to be developed in accordance with modern medical standards, and they gradually fell out of favor with the medical profession. That technology has now emerged, and many cannabis-derived and cannabinoid products are currently in various stages of development. These products will be comprised of various cannabinoids/ratios (rather than solely THC), may target CB2 rather than CB1 receptors (thereby minimizing psychoactivity), or modulate the endocannabinoid receptor system. Funding further studies into smoked cannabis would be retrogressive.

Author Information

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Andrea Grubb Barthwell, M.D., F.A.S.A.M., is the founder and Chief Executive Officer of the global health care and policy-consulting firm EMGlobal LLC and Director at Two Dreams Outer Banks Treatment Center. President George W. Bush nominated Dr. Barthwell in December 2001 to serve as Deputy Director for Demand Reduction in the Office of National Drug Control Policy (ONDCP). The United States Senate confirmed her nomination on January 28, 2002. As a member of the President's sub-cabinet, Dr. Barthwell was a principal advisor in the Executive Office of the President (EOP) on policies aimed at reducing the demand for illicit drugs.

During Dr. Barthwell's tenure, the Bush Administration widely publicized the science-based facts about the dangers of marijuana use and the harms of drug legalization. The Administration encouraged student drug testing as a deterrent to the initiation of drug use and as an early identification tool, and it promoted the expansion and improvement of drug courts. The ONDCP 25-Cities Initiative fostered local coordination of drug control efforts.

While serving in the EOP, Dr. Barthwell was an active member of the White House Task Force on Disadvantaged Youth and the White House Domestic Violence Working Group. She worked closely with the National Institute on Drug Abuse (NIDA) to define the scope of its Health Services Research portfolio.

Dr. Barthwell received a Bachelor of Arts degree in Psychology from Wesleyan University, where she serves on the Board of Trustees, and a Doctor of Medicine from the University of Michigan Medical School. Following post-graduate training at the University of Chicago and Northwestern University Medical Center, she began her practice in the Chicago area. Dr. Barthwell served as President of the Encounter Medical Group (EMG, an affiliate of EMGlobal), was a founding member of the Chicago Area AIDS Task Force, hosted a weekly local cable show on AIDS, and is a past president of the American Society of Addiction Medicine.

In 2003, Dr. Barthwell received the Betty Ford Award, given by the Association for Medical Education and Research in Substance Abuse. In 1997, Dr. Barthwell's peers named her one of the "Best Doctors in America" in addiction medicine.

Conflict of Interest Statement

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled Early Findings in Controlled Studies of Herbal Cannabis: A Review except for the following:

GW Pharma, consultant, stock

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After demonstrating positive results in a Phase II study, dexanabinol (a synthetic cannabinoid) failed in Phase III, in which it was tested on 861 patients with head trauma in 86 trauma centers in 15 countries.

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15. Many physicians blatantly fail to adhere to the standard of care in recommending cannabis to their patients. In California, despite the existence of strict guidelines promulgated by the state medical board, a substantial number of physicians advertise on the internet, accept cash only, and offer recommendations without following the basic professional requirements of good patient care: a physical examination, medical history, review of past medical treatments, development of a treatment plan, follow up and continuing oversight. Lopez S. A visit to the medical marijuana doctor. Los Angeles Times (Oct. 28, 2009).

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22. The subjects must have used cannabis within the last six months. Furthermore, all subjects were exposed to a preliminary high-dose training session. Those who were unable to tolerate the highest dose of THC were excluded from the study.

23. As with the other CMCR analgesic studies, blinding was questionable. It is likely that cannabis experienced subjects could identify accurately when they were receiving placebo.

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39. Interestingly, the plasma THC AUC was progressively lower at higher THC concentrations, and the investigators were uncertain whether this suggested higher bioavailablity and/or more intensive puffing at lower THC potency. Despite the use of the standardized puff procedure, the investigators could not resolve this issue, since the number of puffs taken using vaporized cannabis tended to decrease with increasing THC potency, but this trend was not significant.

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52. Alexza Pharmaceuticals http://www.alexza.com/. Utilizing its Staccato® system, Alexza has six development programs focused on five acute and intermittent conditions.

53. The FDA permitted the Volcano® to be used in the Abrams pilot study. This, however, was an investigator-led study, not a study sponsored by a pharmaceutical company that is intended to result in the marketing approval of a device and/or investigational medication.

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55. Dr. Cracker also argued that NIDA cannabis was both qualitatively and quantitatively inadequate.

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58. BRM is fresh or processed (e.g., cleaned, frozen, dried, or sliced) part of a single species of plant or a fresh or processed alga or macroscopic fungus. BDS is prepared from botanical raw materials by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. It may be available in a variety of physical forms, such as powder, paste, concentrated liquid, juice, gum, syrup, or oil. BDP is a botanical product that is intended for use as a drug, i.e., a finished drug product that is prepared from a botanical drug substance. Botanical drug products are available in a variety of dosage forms, such as solutions (e.g., teas), powders, tablets, capsules, elixirs, and topicals.

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61. 44 Fed. Reg. 33696 (June 12, 1979).

62. See DEA, "Authorized Sources of Narcotic Raw Materials," 73 Fed. Reg. 6843 (Feb. 6, 2008).

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65. 21 USC sec. 812(c) (Schedule II (a)). Substances in Schedules III-V have decreasing levels of abuse potential and are subject to lesser degrees of control.

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