☞ **09hr_SC-HHIPPTRR_sb0368_pt05**

(FORM UPDATED: 08/11/2010)

WISCONSIN STATE LEGISLATURE ...
PUBLIC HEARING - COMMITTEE RECORDS

2009-10
(session year)

Senate
(Assembly, Senate or Joint)

Committee on ... Health, Health Insurance, Privacy, Property Tax Relief, and Revenue (SC-HHIPPTRR)

COMMITTEE NOTICES ...

- Committee Reports ... **CR**
- Executive Sessions ... **ES**
- Public Hearings ... **PH**

INFORMATION COLLECTED BY COMMITTEE FOR AND AGAINST PROPOSAL

- Appointments ... **Appt** (w/Record of Comm. Proceedings)
- Clearinghouse Rules ... **CRule** (w/Record of Comm. Proceedings)
- Hearing Records ... bills and resolutions (w/Record of Comm. Proceedings)
  (**ab** = Assembly Bill) (**ar** = Assembly Resolution) (**ajr** = Assembly Joint Resolution)
  (**sb** = Senate Bill) (**sr** = Senate Resolution) (**sjr** = Senate Joint Resolution)
- Miscellaneous ... **Misc**

* Contents organized for archiving by: Stefanie Rose (LRB) (June 2012)

SB 368

Susanne's testimony-Jackie Rickert act

hello Everyone
Thank you for allowing me to share my story today, and listening to why I believe
we need to use Marijuana as a medicine here in Wisconsin. I am using using Marijuana
as my medicine, illegally,
I prefer not to do this and any thing that is un-lawful.. However this is one I am not
able to do due to several spinal fractures and fussion of my neck. My injury's are
30 yrs. old, so when I started to get athritis, my pain was indescribalble and off the
charts.
I had to make drastic life changes, give up my career and go on disability. I started
on pain medicine 3 yrs ago, It is not healthy for me and makes me sick. So I alternate
with Marijuana.It increases my appetite as well, Of course
I am not able to solely use it due to the nature of it being
illegal and the cost. I use it regualary mostly in the evenings, as it relaxes and
allows me to get out of constant pain. That in itself is quality in my life.
I don't feel I have to suffer 24/7, Marijuana relieves my pain in a way that
pain pills don't. Unless you suffer pain or have other issues you may not understand
this,but that is what compassion is, caring about others and their issues.
After two broken necks and a total of four spinal fractures. I am always in pain.
I need relief, Marijuana works, for me, without any side effects. I am afraid that pain
pills will kill me, likely they will. I have many side effects from the pill medicine.
If I could get by with just Marijuana, I feel like I could have a better quality of life and
live longer.
Many are facing the same dilema, if we use Marijuana we are criminals, If we buy it we
are criminals, yet we have no choice. It works. If it were prescribed to me here in
Wisconsin I could stop using pain pills, I would have to take many pills compared to how
much Marijuana I use.
Pills make me ill. Kill my appetite and make me nausea, where as Marijuana increases my
appetite. This is not a quality of life I am living, I know what that is,
pills are not the answer for me. Marijuana is. If it were available to medical patients,
I would no longer be doing anything illegal. That would help me sleep

Susanne's testimony-Jackie Rickert act

at night,
I have a lot to loose
Also if I have another drug test and THC comes up. I no longer will be prescribed pain pills,
where would that leave me. Medical patients need to be prescribed the proper amount and
do so legally. The taxes generated are one answer to our troubled economy. And
You know, I don't want to use Marijuana from Mexico tainted with chemical fertilzers,
this propagates the drug war there,
buying it from there makes me a part of the drug war there, we can limit our ties with them
and slow down border activity. Just because we don't live next to the border,
it still effects all of us.

I now would like to speak on be-half of my son who will be 18 yrs. old this month. and
is graduating from High School. He has had 9 in-patient mental health institutional
treatments. He has tried several medicines which either make him fat or just more
wacked out than he was at the time.
Today he uses Marijuana as his medicine, his choice. He claims it helps him with his
anxiety and P.T.S.D. I believe it does, he stopped using the prescribed pills at age 14,
it was the law here 4 yrs.ago, kids had the choice. He joined a gang, has a gang tatoo,
was on his way to prison. Today he is able to communicate in a non-violent way,
due to the nature of Marijuana and 100's of hours of therapy, therapy helped but did not cure
him. He smokes before tests and does remarkably well, he would not be finishing school with out
the help of Marijuana, he would be too anxious to even step into a classroom.
It's a small miracle he is graduating. And it is due to Marijuana Medicine.
The answer is to make Marijuana available to patients so we may have quality lifes,
so we are not criminals,and let us NOT be left with un-regulated Marijuana medicine.
We want to pay taxes and get out of the closet with it. Giving us more quality lives,
which is possible if you support this bill. Thank you for your support. Susanne Way


FORWARD
E PLURIBUS UNUM

Testimony on AB554/SB363

Good Morning:

By way of background, my name is Michael Wolkomir and I am a medical doctor from Barneveld,WI. I have been practicing medicine since 1971. I hold an MD degree from McMaster University and a doctorate in public health from the University of Toronto. I have served on the faculties of both Wisconsin medical schools, and am Board Certified in Family Medicine. I have practiced and taught in Wisconsin, Pennsylvania and the province of Ontario Canada.

I speak today in support of the Jacki Rickert Medical Marijuana Act. I want to thank my State Representative Steve Hilgenberg for his co-sponsorship of this important and eminently sensible proposal.

Both my reading of the scientific literature and history of this issue and my experience as a primary care physician lead me to the conclusion that marijuana is a useful adjutant medicine in the treatment of a variety of common medical ailments and actually among the safest agents available for these problems.

(Show prescription pad). This is a prescription pad. Any day, I am permitted under my medical license to write prescriptions for Oxycodone , Hydrocodone or Morphine. These are only a few of agents physicians can prescribe in every day practice. These drugs are effective in pain management, but like most medications for most conditions, carry the risk of serious complications. Pain medications in general have significant risks of overdose and even death. These and other opioid drugs are unquestionably addictive. They are subject to widespread abuse and are the most important drugs of abuse among young people in this state. There is a narrow distance (or "therapeutic index") separating useful does of these medications from overdose and death. I would certainly prefer not to use these agents if alternatives are available.

Now, marijuana is not a powerful enough agent to control very severe pain by itself. However, we use a huge amount of opioids for conditions in which mild pain medications like Tylenol or Advil are not enough. Combination of marijuana with milder pain medications has the potential of replacing a considerable amount of the opiate medications prescribed in this state with the safer combination of mild analgesics and cannabis. There are NO reported cases of a significant overdose of marijuana. There are NO creditable reports of death as a result of use of marijuana. It is effective and safer than most of pain medications available by prescription or over the counter. The pharmaceutical industry in fact has exploited this by producing an expensive and less complete agent called Marinol. The best evidence is that this agent is inferior to the natural product. I am sure that the Committee is aware that The American Medical Association, not known to be a bastion of wild-eyed liberalism, has called for the FDA to remove Marijuana from the list of Class 1 controlled substances.

I can now prescribe much more expensive and dangerous substances. I am frustrated that I am able to write prescriptions every day for dangerous substances, but cannot legally recommend the use of this naturally occurring, potentially cheap and effective substitute. Seventeen states including our neighbor Michigan have seen fit to enable doctors like myself to prescribe marijuana for conditions for which I now must prescribe less effective and more dangerous substances.

I am not an expert on canabinoid research, but I'd like to share just a little of the background which buttresses my clinical decision making on this issue. The Canadian government has sponsored a very comprehensive review of the use of cannabis in medical practice

called the Compass study. Four general conclusions come from that effort:

1. There is no lack of available research on this topic. The Canadians have been tracking scientifically valid peer reviewed studies on medical cannabis for the last 49 years! In 2008 alone there were more than 1600 published peer reviewed studies on the subject

2. Cannabis is effective. Often it is equally or more effective than standard therapies which are risker. One good example is t he use of cannabis for neuropathic or nerve function based,pain. Cannabis is consistently more effective than the frequently used Neruontin, which was recently made famous by the pharmaceutical company illegal advertising scandal.

3. Given the truism that all medical treatments are a balance between benefit and side effect or risk, cannabis is often the safest alternative.

4. Medical use is distinct from recreational use. Risks of significant side effects and habituation are substantially less in medical applications than recreational use. The recreational user seeks the euphoric and dissociative "side effects" of cannabis and doses him/herself to the level necessary to achieve that effect. The social setting of use is vastly different and the substance used, uncontrolled and sold illegally, is unpredictable and may contain anything from medical grade marijuana imported from another jurisdiction to totally unrelated vegetable matter. The Compass study places the risk of habituation to medical marijuana at approximately 9%, as compares to alcohol at 15% and tobacco at 32%.

   The suppression of breathing by Opiate medications kills people every day through overdose. The Canadian

review boldly states that " It is virtually impossible to die from the acute administration of Cannabis alone."

I will be happy to provide a copy of the Canadian Medical Association review to the committee.

I urge the Assembly and Senate to follow the lead of our 17 neighbor states and bring Wisconsin into the 21st Century on this issue.

Thank you for the opportunity to testify on this important issue. I am not an expert on the technical aspects of the research presented here today, but I have the insight of an experienced "old country doctor". I would be happy to try to answer any questions the committee may have.

Michael S. Wolkomir, MD, MA, DECH
Fellow of the American Academy of Family Physicians
Life Member Society of Teachers of Family Medicine
Barneveld, WI


FORWARD
E PLURIBUS UNUM

SB 368

ASAM

American Society of Addiction Medicine

Public Policy Statement on Marijuana

Marijuana is a mood-altering drug capable of producing dependency. Its chief active ingredient is delta-9-Tetrahydrocannabinol, but there are many other ingredients.

Marijuana has been shown to have adverse effects on memory and learning, on perception, behavior and functioning, and on pregnancy. Because of the widespread use of this drug, its effects on mind and body, and the increasing potency of available supplies,

ASAM strongly recommends:

1. **Education about drugs, beginning in the earliest grades of elementary school and continuing through university level. Drug education should contain scientifically accurate information on the dangers and harmful effects of marijuana, and on the disease of marijuana dependence.**

2. **Health and human service professionals should be educated about marijuana and marijuana dependence as a required part of their curriculum.**

3. **Persons suffering from alcoholism and other drug dependencies should be educated about the need for abstinence from marijuana and its role in precipitating relapse, even if their original drug of choice is other than marijuana. .Treatment programs providing addictions treatment for chemically dependent patients should include tests for cannabinoids with other drug test panels and consider test results when designing treatment plans.**

4. **Marijuana dependent persons, like other drug dependent people, should be offered treatment rather than punishment for their illness. Treatment of marijuana dependence should be part of the plan for rehabilitation of any person convicted of a drug-related offense, including driving under the influence of alcohol and/or drugs, who is found to be marijuana dependent.**

5. **Medical uses of pharmaceutical delta-9-Tetrahydrocannabinol (such as Marinol™) for the treatment of illnesses associated with wasting, such as AIDS, the treatment of emesis associated with chemotherapy, or for other indications should be carefully controlled. Smoking marijuana is dangerous to the health of any user, and produces health risks of passive smoke akin to risks of exposure to passive tobacco smoking. Inhaled smoke is a suboptimal delivery method for any agent**

intended to be health-promoting in any way. ASAM supports continued evidence-based research into alternative delivery systems of cannabinoid applications.

6. **Research on marijuana, including both basic science and applied clinical studies, should receive increased funding and appropriate access to marijuana for study. The mechanisms of action of marijuana, its effect on the human body, its addictive properties, and any appropriate medical applications should be investigated, and the results made known for clinical and policy applications. In addition, ASAM strongly encourages research related to the potential and actual effects of marijuana-related public policy.**

7. **Physicians should be free to discuss the risks and benefits of medical use of marijuana, as they are free to discuss any other health-related matters. Recognized scientific researchers following established research protocols should be free to conduct research on marijuana and pharmaceutical cannabinoids.**

Adopted by ASAM Board of Directors April 1987; revised April 1997, October 1997, July 1998, December 2000 and May 2006.

American Society of Addiction Medicine

4601 North Park Avenue • Upper Arcade Suite 101 • Chevy Chase, MD 20815-4520

TREAT ADDICTION • SAVE LIVES

PHONE: (301) 656-3920 • FACSIMILE: (301) 656-3815

E-MAIL: EMAIL@ASAM.ORG • WEBSITE: HTTP://WWW.ASAM.ORG


FORWARD
E PLURIBUS UNUM

Medical Marijuana
Senate Bill 368 and Assembly Bill 554

The Controlled Substances Board opposes Senate Bill 368 and Assembly Bill 554 for the following concerns and questions:

P8 50.65 (1) A compassion center may deliver or distribute THC or drug paraphernalia to a member of a treatment team if the compassion center ..... Shouldn't this read: "to a registered member of a treatment team" otherwise it seems to say that they can sell it to anyone who claims to be a member of a treatment team.

P9 59.54(25)(a) The board may enact ..... This is not clear to me and maybe I am missing something but what board are they talking about here?

P9 59.54(25)b1 This whole thing with ordinance is not clear to me. Is this saying that a city ordinance can not penalize someone for possession or use of medical marijuana? As a side light, I did not see anywhere in the law where a city could opt out to not allow any compassion centers or caretaker providers. Thus, if a city as a whole is opposed to the use of medical marijuana they have no way of stopping the establishment of a compassion center in their city (village, town, county, etc). This option is available in CA and they can at least say we don't want any of those allowed in our town, city, village, etc. Seems odd to me that before having the anti-smoking law in WI, cities did have that option for smoking cigarettes in bars and restaurants or other places but they will not have this option with medical marijuana.

P13 (4)2. The primary caregivers, if the ..... Both here and many other places where it talks about caregivers. Is caregivers here meant to be the possessive definition or a multiple definition? If multiple, then how many caregivers can a person have and must they all be registered and have a registration card? I do not see anywhere in the proposed law where it states a number of caregivers allowed if it is meant to allow more than one.

P13 (4)3.(c) A photograph of the registrant. Does this apply only to the person who is registering for the use of medical marijuana or to everyone who registers including the caregiver(s) and members of the patients medical team?

P15 Section 18 173.12 This deals with animals and I don't see how this applies to medical marijuana.

P18 961.01(5m)(c) Any other medical condition or any other treatment for a medical condition ..... This seems to be the medical loophole that allows almost any reasonable or unreasonable medical condition to allow the use of medical marijuana. I don't doubt that it wouldn't take long after this became law, for doctor shopping to start and info to spread around the state on which doctors to go to in order to get a prescription for medical marijuana.

P19 961.01(14c) "Maximum authorized amount" means 12 live marijuana plants and 3 ounces of usable marijuana. I find it ironic that the first cutoff of illegal manufacturing of marijuana is 4 plants but those growing it for medical use can have 12. It seems to me that the number of plants should be 4 or less not 12. As a sidelight here: if a caregiver is growing marijuana for someone for medical use (12 plants) what controls are there to guarantee that the caregiver isn't keeping and using the "medical marijuana" for their own use even if they have a registration card? Or another way of asking this, is the caregiver allowed to use the "medical marijuana" as long as they have a registration card? If so, are they then also exempt from any

charges or prosecution? What happens if they have more than 12 plants? A full grown marijuana plant will produce a pound (454 grams) or more of usable marijuana. That is almost five times the limit of 85 grams (3 ounces). If a caregiver can provide medical marijuana for five people can they have 12 plants or 60 plants? How many marijuana plants can a compassion center have? If the compassion center serves 50 medical marijuana patients can they then have 600 marijuana plants? If so, that would be 600 or more pounds of usable marijuana! Who monitors an individual, a caregiver or a compassion center to see if they are compliant with either the number of plants or weight of marijuana allowed? If they exceed the number of plants or weight what are the penalties? If they do exceed the limit are they liable for criminal charges?

P21 961.436(1)(a) The manufacture or possession of medical marijuana by the treatment team. Does this also imply that anyone on the medical team can manufacture, posses and "use" the medical marijuana? This is not clear to me here or am I totally reading this wrong?

P23 961.436 4.(b)1. The person drives or operates a motor vehicle while under the influence of THCS in violation of ..... Does this mean that the persons THC level must be zero or it implies (infers) driving under the influence? Unlike alcohol where there are set (blood alcohol) limits, we don't have anything like that for THC. Does this also apply to any caregiver(s) as well? Currently the hygiene lab is overloaded with cases involving driving under the influence of alcohol or controlled substances. What will happen to their backlog with the addition of those suspected of driving under the influence of marijuana? What are the cutoff levels for being charged with driving under the influence of THC? Any detectable amount? Even if a person is a registered medical marijuana user and violates the law by driving under the influence, what are the penalties for doing so?

P23 961.436 4(b)3 This list where medical marijuana can not be smoked. Therefore, does that mean it could be smoked in any other public place other than those specifically listed? Even though we will soon have an antismoking law for bars and restaurants does it also apply to smoking of "medical marijuana" in such places? Can it be smoked in a vehicle by a medical marijuana patient even if someone else is driving the vehicle?

P24 961.436(5) Not withstanding s.227,12(1) any person may petition the department of .... Does this create the loophole that a person could get medical marijuana for any reason as long as they find a "compassionate" doctor to write them a prescription for the use of medical marijuana? There certainly is some potential for abuse here.

P26 961.5755(1)(a) Except as provided in par (b), a member of a treatment team has a defense to prosecution under s.961573(1) if he or she uses or possesses with the primary intent to use, drug paraphernalia only for the medical use of THCs by the treatment team. Here is another example of where it is not clear to me if this means only the individual can use the medical marijuana or can anyone on the treatment team use it?

P27 961.5755(3) For the purposes of a defense raised under sub (1)(a) or (2), a valid registry identification card, a valid out-of-state registry identification card, or a written certification is..... How is law enforcement to check and verify an out-of-state registry card or a written certification? If an individual is charged with possession, delivery or manufacturing of marijuana can they claim it is only medical marijuana even if not registered? Can they apply for and receive a registration for medical marijuana after being charge? Would that then exempt them from the charges after the fact?

P28 968.072(2)(b) The person possesses a valid registry identification card, a valid out-of-state registry identification card, or **a copy of the qualifying patient's written certification**. Is this a loophole around the registration? Why is a copy good enough? Couldn't that be easily abused? If a person has a qualifying written certification do they have to register? If not, couldn't that be easily abused? If they only need a written certification would this be a way for a patient/doctor to get around the listed diseases for which medical marijuana could be used?

P29 968.072(3)1 The person uses, or possesses with the primary intent to use, drug paraphernalia only for ... This is another example where it seems to imply the use of marijuana or paraphernalia other than the registered individual using medical marijuana. Maybe I am just reading this incorrectly. Seems to me it should clarify which person is allowed to use the medical marijuana..

P30 (5) Penalty for False Statement. I would not be surprised that a lot of people, if stopped in possession of marijuana will use the defense or argument that is was/is medical marijuana. If they don't produce a registration card, have they then made a false statement? If so, they may be fined not more than $500. Does this now imply that for possession of marijuana (in any amount) as long as they said it was medical marijuana even if a false statement, that the penalty can not be more than $500? If so, then isn't that contrary to the current penalties for possession, delivery or manufacturing of marijuana based on the weights?

P32 968,20(3)(a) This deals with weapons. Not sure what this has to do with medical marijuana?

Here are some additional comments and questions about medical marijuana and its distribution. Since the compassion centers are to be nonprofit, I assume they must be compliant with all nonprofit rules and regulations and must apply and receive a nonprofit certification. Who will monitor that compassion centers are fulfilling all the requirements of a non-profit organization and are not in violation of any weight or plant number limits? How many patients can a compassion center service? How much can a compassion center or a caregiver charge for the medical marijuana? How must the medical marijuana be packaged and sold? What security must be provided by the caregiver or compassion center to protect against theft or robbery of the medical marijuana or cash? Must the medical marijuana be packaged in a certain fashion and must it include danger labels as a possible carcinogenic material? Who is liable should someone using medical marijuana become ill do to using the medical marijuana? What safeguards must a caregiver or compassion center do to prevent diversion of medical marijuana to someone who is not a registered medical marijuana recipient? Can compassion centers have "armed" guards in their lobbies as they do in California? Do we want that to happen?

These concerns and questions pertaining to the medical marijuana bill are the basis for the Controlled Substances Board's opposition to this bill.

Should you have any further questions after review of these concerns or questions, email or call me at the crime laboratory in Madison at 266-2031 or blockrh@doj.state.wi.us.

Robert Block
Controlled Substances Board (member and liaison)
Wisconsin Crime Laboratory
Madison, Wisconsin


FORWARD
E PLURIBUS UNUM

SB 368

REPORT 3 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (I-09)
Use of Cannabis for Medicinal Purposes
(Resolutions 910, I-08; 921, I-08; and 229, A-09)
(Reference Committee K)

EXECUTIVE SUMMARY

Objective. This report: (1) provides a brief historical perspective on the use of cannabis as medicine; (2) examines the current federal and state-based legal envelope relevant to the medical use of cannabis; (3) provides a brief overview of our current understanding of the pharmacology and physiology of the endocannabinoid system; (4) reviews clinical trials on the relative safety and efficacy of smoked cannabis and botanical-based products; and (5) places this information in perspective with respect to the current drug regulatory framework.

Data Sources. English-language reports on studies using human subjects were selected from a PubMed search of the literature from 2000 to August 2009 using the MeSH terms "marijuana'" "cannabis," and tetrahydrocannabinol," or "cannabinoids," in combination with "drug effects," "therapeutic use," "administration & dosage," "smoking," "metabolism," "physiology," "adverse effects," and "pharmacology." Additionally the terms "abuse/epidemiology," and "receptors, cannabinoid" in combination with "agonists," or "antagonists & inhibitors" as well as "endocannabinoids," in combination with "pharmacology," "physiology," or "metabolism" were used. Additional articles were identified by manual review of the references cited in these publications. Web sites of the Food and Drug Administration, Drug Enforcement Administration, National Institute on Drug Abuse, Marijuana Policy Project, ProCon.org, and the International Association for Cannabis as Medicine also were searched for relevant resources.

Results. The cannabis sativa plant contains more than 60 unique structurally related chemicals (phytocannabinoids). Thirteen states have enacted laws to remove state-level criminal penalties for possessing marijuana for qualifying patients, however the federal government refuses to recognize that the cannabis plant has an accepted medical benefit. Despite the public controversy, less than 20 small randomized controlled trials of short duration involving ~300 patients have been conducted over the last 35 years on smoked cannabis. Many others have been conducted on FDA-approved oral preparations of THC and synthetic analogues, and more recently on botanical extracts of cannabis. Federal court cases have upheld the privileges of doctor-patient discussions on the use of cannabis for medicinal purposes but also preserved the right of the federal government to prosecute patients using cannabis for medicinal purposes. Efforts to reschedule marijuana from Schedule I of the Controlled Substances Act have been unsuccessful to date. Disagreements persist about the long term consequences of marijuana use for medicinal purposes.

Conclusions. Results of short term controlled trials indicate that smoked cannabis reduces neuropathic pain, improves appetite and caloric intake especially in patients with reduced muscle mass, and may relieve spasticity and pain in patients with multiple sclerosis. However, the patchwork of state-based systems that have been established for "medical marijuana" is woefully inadequate in establishing even rudimentary safeguards that normally would be applied to the appropriate clinical use of psychoactive substances. 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. To the extent that rescheduling marijuana out of Schedule I will benefit this effort, such a move can be supported.

Action of the AMA House of Delegates at the 2009 Interim Meeting: Council on Science and Public Health Report 3 Recommendations Adopted as Amended and Remainder of Report Filed.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 3-I-09

Subject: Use of Cannabis for Medicinal Purposes

Presented by: C. Alvin Head, MD, Chair

Referred to: Reference Committee K
(Peter C. Amadio, MD, Chair)

This report responds to three resolutions related to the use of marijuana for medicinal purposes.

Resolution 910 (I-08), submitted by the Medical Student Section and referred to the Board of Trustees (BOT), asked:

> That our American Medical Association (AMA) support reclassification of marijuana's status as a Schedule I controlled substance into a more appropriate schedule.

Resolution 921 (I-08), submitted by the Washington Delegation and referred to the BOT, asked:

> That our AMA support reclassification of marijuana's status from a Schedule I controlled substance to a more appropriate schedule; and
>
> That our AMA support efforts to cease criminal prosecution and other enforcement actions against physicians and patients acting in accordance with states' medical marijuana laws.

Resolution 229 (A-09), submitted by the New York Delegation and referred to the BOT, asked:

> That our AMA offer assistance in seeking clear, indisputable confirmation from the federal government that physicians who follow the proposed New York State legislation if passed and regulation when subsequently developed will not be prosecuted for allegedly failing to follow the Presidential order still in place making it illegal for a physician to prescribe or even advise a patient to use marijuana for medical purposes; and
>
> That our AMA seek a reversal of the Executive Order itself that makes it illegal for a physician to prescribe or advise medical marijuana.

The Council has issued two previous reports on "Medical Marijuana" in 1997 and 2001.[1,2] The first report is the basis for the current AMA policy on medical marijuana (Policy H-95.992, AMA Policy Database (Appendix A)) and was developed largely in response to emerging state initiatives designed to facilitate the medical use of marijuana. The second report in 2001 reviewed legal, regulatory, and scientific developments on this topic that had transpired since the first report. As of 2001, the Council had concluded that sufficient evidence existed to support further research on the potential use of marijuana:

Action of the AMA House of Delegates at the 2009 Interim Meeting: Council on Science and Public Health Report 3 Recommendations Adopted as Amended and Remainder of Report Filed.

- In HIV-infected patients with cachexia, neuropathy, or chronic pain, or who are suffering adverse effects from medication, such as nausea, vomiting, and peripheral neuropathy, that impede compliance with antiretroviral therapy;
- In patients undergoing chemotherapy, especially those being treated for mucositis, nausea, and anorexia, and those patients who do not obtain adequate relief from either acute or delayed emetic episodes from standard therapy;
- To potentiate the analgesic effects of opioids and to reduce their emetic effects in the treatment of postoperative, traumatic, or cancer pain;
- In patients suffering from spasticity or pain due to spinal cord injury, or neuropathic or central pain syndromes; and
- In patients with chronic pain and insomnia.

In 2001, the AMA House of Delegates reaffirmed that marijuana should be retained in Schedule I of the Controlled Substances Act pending the outcome of further controlled studies.

The Institute of Medicine (IOM) published a comprehensive report in 1999 commissioned by the Office of National Drug Control Policy, entitled "Marijuana and Medicine: Assessing the Science Base." [3] The findings in this report (see Appendix B) generally agreed with the Council's assessment of the evidence on the potential medical utility of synthetic and plant-derived cannabinoids. The IOM report also concurred with the Council that further research on the medical utility of marijuana and individual cannabinoids was warranted and that resources should be devoted to developing alternative, smoke-free delivery systems. The IOM further noted:

> "because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues. If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems."

Accordingly, the IOM report supported the availability of a compassionate-use protocol as an interim measure whereby the clinical use of medical cannabis would be allowed for symptom relief in seriously ill patients in limited and locally implemented peer-reviewed treatment trials. Recently the American College of Physicians (ACP) issued a policy statement on medical marijuana (Appendix C).[4] Like the AMA, the ACP supports approaches to conduct rigorous scientific evaluation of the potential therapeutic benefits of marijuana, and development of non-smoked forms. Additionally, ACP urged federal review of marijuana's status as a Schedule I substance to determine if it should be reclassified, and strongly supported exemption from federal criminal prosecutions, civil liability, or professional sanctions for physicians who issue recommendations for medical marijuana in accordance with state law, as well as protection from criminal or civil penalties for patients under such circumstances.

In light of the foregoing discussion, this report evaluates the merits of Resolutions 910 (I-08), 921 (I-08) and 229 (A-09). In so doing, the Council: (1) provides a brief historical perspective on the use of cannabis as medicine; (2) examines the current federal and state-based legal envelope relevant to the medical use of cannabis; (3) provides a brief overview of our current understanding of the pharmacology and physiology of endogenous cannabinoid receptors and substances (endocannabinoids); (4) reviews the more recent clinical trial evidence on the relative safety and

efficacy of smoked cannabis and other cannabis-based products; and (5) places this information in perspective with respect to the current drug regulatory framework, and the rights and responsibilities of physicians to provide optimal care for their patients. In many places the term "cannabis" is used. Marijuana is a slang term for the dried flowers and bracts of the cannabis plant. In cases where the term "marihuana" or "marijuana" is used in the statute, policy statement or other legal way, such terms are retained.

METHODS

English-language reports on studies using human subjects were selected from a PubMed search of the literature from 2000 to August 2009 using the MeSH terms "marijuana'" "cannabis," and tetrahydrocannabinol," or "cannabinoids," in combination with "drug effects," "therapeutic use," "administration & dosage," "smoking," "metabolism," "physiology," "adverse effects," and "pharmacology." Additionally the terms "abuse/epidemiology," and "receptors, cannabinoid" in combination with "agonists," or "antagonists & inhibitors" as well as "endocannabinoids," in combination with "pharmacology," "physiology," or "metabolism" were used. Additional articles were identified by manual review of the references cited in these publications. Web sites of the Food and Drug Administration, Drug Enforcement Administration, National Institute on Drug Abuse, Marijuana Policy Project, ProCon.org, and the International Association for Cannabis as Medicine also were searched for relevant resources.

BACKGROUND

Cannabis is one of the oldest psychotropic drugs in human history. Originating from central Asia, and then spreading to China and India, the first modern description of its pharmacological properties was provided by an Irish physician (William O'Shaughnessy) in 1839.[5] First listed in the United States Dispensary in 1854, cannabis was promoted for a variety of conditions based on its putative analgesic, sedative, anti-inflammatory, antispasmodic, anti-asthmatic, and anticonvulsant properties.[1,6,7] Many cannabis-containing oral extracts and tinctures were subsequently manufactured. Interest in the medical use of cannabis waned somewhat in the late nineteenth and early twentieth centuries with the advent of opiates, barbiturates, chloral hydrate, and aspirin and the widespread availability of hypodermic syringes for injection of water-soluble compounds. Nevertheless, cannabis remained available in the British Pharmacopoeia in extract and tincture form until 1971.

The U.S. government and popular media began condemning the use of smoked cannabis in the 1930s, linking its use to homicidal mania. The Marihuana Tax Act of 1937 introduced the first federal restrictions on marijuana. This federal law required industrial or medical users to register and pay a tax on marijuana of $1/ounce. Individuals using marijuana for recreational or other purposes were required to pay a tax of $100/ounce. A combination of the paperwork required of physicians who wished to use the drug in their practice, and regulations later imposed by the Federal Bureau of Narcotics designed to prevent diversion, quickly dampened enthusiasm for pursuing medical applications of cannabis.

At the time, the AMA was virtually alone in opposing passage of the Marihuana Tax Act. The AMA believed that objective data were lacking on the harmful effects of marijuana, and that passage of the Act would impede future investigations into its potential medical uses.[8] The AMA's Committee on Legislative Activities recommended that marijuana's status as a medicinal agent be maintained.[9] Nevertheless, secondary to governmental pressures, marijuana was removed from the U.S. Pharmacopoeia in 1942, thus losing its remaining mantle of therapeutic legitimacy.

In 1964, delta-9-tetrahydrocannabinol (hereafter referred to as THC) was identified as the primary psychoactive cannabinoid in *Cannabis sativa* (see below) and successfully synthesized.[10] The 1960s witnessed a resurgence in the recreational use of smoked cannabis, and the ability of cannabis to relieve certain disease symptoms was "rediscovered." Thereafter the recreational and "medical" forms of smoked cannabis became merged. This contrasts with the path of medicinal opioid development and the recreational use of smoked botanical opium, which became clearly distinct.

Receptors in the brain and periphery that bind THC (cannabinoid receptors) were discovered in the early 1990s, and the identification of endogenous compounds that act at cannabinoid receptors (endocannabinoids) soon followed. The last decade has seen an explosion in research about the "endocannabinoid system" (see below). Information gleaned from these investigations has shed light on the pharmacologic activity of phytocannabinoids, and created opportunities for the development of pharmaceuticals interacting with this system.

CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM

Cannabis Sativa. The plant contains over 400 chemical compounds.[11] The main psychoactive substance is generally believed to be THC, but more than 60 other cannabinoids (C_{21}-containing compounds) have been identified in the plant (phytocannabinoids) and pyrolysis products.[10-12] Cannabinoids are chemical compounds that are unique to the cannabis plant. Delta-8-THC is similar in potency to THC, but is present in only small concentrations.[13] Cannabinol and cannabidiol are the other major cannabinoids present. The former is slightly psychoactive, but not in the amounts delivered by smoking marijuana.[13] Cannabidiol is not psychoactive and has distinctive properties (see below). The average content of THC in cannabis plants is highly variable depending on the strain, climate, soil and growing conditions, and handling after harvest.[14] THC is a resinous weak acid, pKa = 10.6, with a very high lipid solubility and very low aqueous solubility.[15] It binds to glass, diffuses into plastic, and is photo labile and susceptible to heat, acid, and oxidation; these characteristics have served as barriers to the development of traditional pharmaceutical dosage forms. The (-) enantiomer is up to 100 times more potent than the (+) enantiomer depending on the pharmacological test.[16]

ENDOCANNABINOIDS

Cannabinoid Receptors

Two types of cannabinoid receptors (CB1 and CB2) have been clearly identified and both are members of the superfamily of G-protein-coupled receptors. The CB1 receptor, first cloned in 1990, is mainly expressed in the brain and spinal cord.[17] Distribution is heterogeneous with the highest densities present in the basal ganglia, hippocampus, and cerebellum, with comparatively fewer receptors in the brainstem.[18,19] CB1 receptors are among the most abundant G-protein coupled receptors in the brain.[20] By coupling predominately to inhibitory G proteins, CB1 receptors inhibit certain inwardly directed calcium channels, activate outwardly directed potassium channels, and activate various mitogen-activated protein (MAP) kinases.[21] The latter may play a role in the modulation of synaptic plasticity, cell migration, and neurite remodeling. CB1 receptors are located on the terminals of central and peripheral neurons. Generally, their activation inhibits the ongoing release of a number of different excitatory and inhibitory transmitters, or hyperpolarizes neurons, which also inhibits activity.[21]

The CB2 receptor, first cloned in 1993 is predominantly expressed in cells of the immune and hematopoietic systems but also is present in nonparenchymal cells of the liver, endocrine pancreas,

and bone.[22] Some CB2 receptors also are functionally expressed in the CNS, notably on microglial cells.[23,24] CB2 receptor activation alters the release of cytokines from immune cells and participates in the regulation immune function.[20] CB2 agonists generally suppress the functions of these cells. CB2 modulates immune cell migration both within and outside the central nervous system [25,26]

Endocannabinoids

In parallel with the discovery of cannabinoid receptors, endogenous substances that bind and activate these receptors were identified (endocannabinoids). The two best characterized are arachindonoyl ethanoamide (AEA or anandamide) and 2-arachidonoylglycerol (2-AG), although other putative endocannabinoids also have been identified. In contrast to conventional neurotransmitters, endocannabinoids are not stored in synaptic vesicles, but are produced on demand via cleavage of membrane lipid precursors and then released after *de novo* synthesis.[27,28] Once formed in response to presynaptic depolarization, endocannabinoids function as "retrograde" messengers, diffusing back across the synapse and signaling the presynaptic (upstream) neuron to decrease neurotransmitter release and/or activity. These effects have been implicated in the modulation of both short- and long term synaptic plasticity, events which are integral to the remodeling of synaptic networks in the CNS, as well as fundamental processes such as learning and memory.

Termination of the action of AEA and 2-AG is accomplished by re-uptake into the neuron and subsequent enzymatic degradation. These transport proteins and degradative enzymes represent other targets for manipulating the endocannabinoid system.

AEA primarily activates CB1 receptors, and also stimulates TRPV1 receptors.[29] The latter is an important component of pain signaling pathways. AEA is a partial or full agonist at CB1 receptors, depending on the species, tissue, and biological response being examined.[29] Partial agonists are capable of binding to a receptor, but do not cause maximal activation. Pharmacologically, they can function as agonists or antagonists, depending on the dose, and endogenous activity of the biological system they are interacting with. This fact complicates the interpretation of endocannabinoid effects that have been observed in animal models, as well as findings which may be relevant to phytocannabinoids such as THC. Although AEA binds to CB2 receptors, it has a low efficacy, and may act primarily as an antagonist.[29] 2-AG has approximately equivalent activity at CB1 and CB2 receptors, is much more abundant than AEA in the brain, and is believed to act primarily as an agonist at cannabinoid receptors.[30] Other putative endocannabinoids also tend to be considerably more active as CB1 receptor agonists.[31] Additionally, other receptor systems appear to respond to endocannabinoids.[31,32]

THC is also a partial agonist at the CB1 and CB2 receptors. Cannabidiol displays anti-oxidant activity, is a TRPV1 agonist like AEA, and inhibits the uptake and metabolism of AEA. It has low efficacy for CB1 and CB2 receptors.

Taken together, the endocannabinoid system is widely dispersed and it modulates the activity of several prominent neurotransmitters, immune regulating cells, and other tissue and organs. Accordingly, endocannabinoids likely play a role in the regulation of a wide variety of functions and disease states. Some of the most prominent include appetite regulation, peripheral energy metabolism, obesity and associated metabolic abnormalities, pain and inflammation, gastrointestinal motility and secretion, central nervous system disorders, neurotoxicity/neuroinflammation/neuroprotection, and certain mental disorders, including substance misuse.[32-38]

STATE MEDICAL CANNABIS LAWS

Thirteen states (Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, and Washington) have enacted laws since 1996 which remove state-level criminal penalties for qualifying patients (with physician recommendations or certifications) for cultivation, possession, and use of cannabis.[39] Most of these measures were adopted by ballot initiative, but some have been passed by state legislatures. Typically, these laws identify a number of "qualifying conditions." In California vagaries such as the presence of a "debilitating condition" or "chronic ailment" or any *other illness for which marijuana provides relief* are introduced. Most state laws provide a specific allowance for cannabis possession, and a few require/maintain registries or offer certification cards which may assist patients if they are confronted by police officers.

Two other state laws address medical marijuana to a lesser extent. Maryland's law does not create a medical marijuana program but protects patients from jail time for possession of marijuana if they can prove in court that their use of marijuana was a medical necessity; the maximum penalty is a $100 fine. Arizona allows physicians to prescribe marijuana, but such a system is not in place since federal law prohibits physicians from prescribing Schedule I substances. At least 13 other states have pending legislation or ballot measures to legalize medical marijuana.[40]

The number of patients who use cannabis in states that have removed state-level penalties and permit medical use is not clearly established. According to one compilation, approximately 7,000 physicians have authorized the use of cannabis for at least 400,000 patients.[41]

FEDERAL POLICIES

Controlled Substances Act

As recreational drug use proliferated during the 1960s, legislative concern led to passage of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (commonly referred to as the Controlled Substances Act). This Act classifies certain psychoactive drugs into 5 categories, or schedules that impose varying restrictions on access to the drugs under direction of the DEA.

A drug is placed in Schedule I if (1) it has a high potential for abuse; (2) it has no currently accepted medical use in treatment in the United States; and (3) there is a lack of accepted safety for use of the drug under medical supervision. In contrast, Schedule II criteria are that the drug (1) has a high potential for abuse; (2) has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions; and (3) abuse of the drug may lead to severe psychological or physical dependence.

Marijuana and tetrahydrocannabinols naturally contained in the cannabis plant (as well as synthetic equivalents and derivatives with similar activity) are assigned by statute to Schedule I, along with many other drugs such as heroin, lysergic acid diethylamide (LSD), mescaline and other hallucinogenic amphetamine derivatives, methaqualone, and illicit fentanyl derivatives. Certain other psychoactive botanical substances (e.g., peyote, psilocybin) also are in Schedule I. With regard to the placement of marijuana in Schedule I, the following definition is applied:

> The term "marihuana" means all parts of the plant *Cannabis sativa* , whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake

made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted there from), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination (21 U.S.C. 802).

Some botanical products that serve as raw materials (i.e., coca leaves; raw opium, opium poppy and poppy straw) for controlled substances are themselves placed in Schedule II. These raw materials are imported into the U.S. from other countries under international treaty and convention. FDA-approved pharmaceutical preparations containing THC are in Schedule III, whereas a synthetic analogue (nabilone) is in Schedule II. Schedule III criteria are that the drug (1) has less potential for abuse than drugs or other substances in schedules I and II; (2) has a currently accepted medical use in treatment in the United States; and (3) abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Federal Court Cases Relevant to Medical Marijuana

Three prominent federal court cases evolved out of California's 1996 passage of its medical marijuana ballot initiative (Proposition 215).

Conant v. Walters (2002). After California passed its medical marijuana regulation in 1996, Barry R. McCaffrey, Director of the Office of National Drug Control Policy (ONDCP) issued a statement entitled "The Administration's Response to the Passage of California Proposition 215 and Arizona Proposition 200." This statement threatened physicians who recommended marijuana with the loss of their license to prescribe controlled substances and the ability to participate in Medicaid and Medicare. Physicians and patients filed a class action lawsuit, claiming a constitutional free-speech right, in the context of a doctor-patient relationship. In *Conant v. Walters* the United States Court of Appeals in a permanent injunction recognized that physicians have a constitutionally-protected right to discuss the use of marijuana as a treatment option with their patients and to make oral or written recommendations for medical marijuana (the AMA had already endorsed this view).[42] However, the court cautioned that physicians could exceed the scope of this constitutional protection if they conspire with, or aid and abet, their patients in obtaining medical marijuana. The U.S. Supreme Court denied the appeal.

USA v. Oakland Cannabis Buyer's Cooperative (OCBC) and Jeffrey Jones (2001). A medical cannabis buyer's cooperative was established in Oakland (Oakland Cannabis Buyer's Cooperative). Its proprietor (Jeffrey Jones) distributed marijuana based on the theory that the cooperative could operate as each patient's "caregiver" and use a medical necessity defense. The U.S. government disagreed and the Department of Justice filed a civil suit in January 1998 to close six medical marijuana distribution centers in northern California. Ultimately, the case went to the U.S. Supreme Court which ruled unanimously that a medical necessity exception for marijuana was at odds with the terms of the Controlled Substances Act (i.e., the CSA classified marijuana as lacking a recognized medical benefit).[43]

Gonzales v. Raich (2005). In response to DEA agents' destruction of their cannabis plants, two patients and caregivers in California brought suit. They argued that applying the CSA to a situation in which cannabis was being grown and used locally for medicinal purposes (and not being sold) exceeded the federal government's constitutional authority under the Commerce Clause, which allows federal regulation of interstate commerce. The U.S. Supreme Court eventually ruled that Congress's power to regulate commerce "extends to purely local activities" that are "part of an economic class of activities that have a substantial effect on interstate commerce."[44] While not invalidating state medical marijuana laws, this ruling preserved the ability of the DEA to enforce the CSA against medical marijuana patients and their caregivers.

Another relevant case is the *County of San Diego v. State of California* (2009) in which the U.S. Supreme Court denied an appeal by the County of San Diego allowing a lower court's ruling to stand which held that federal law does not preempt California's medical marijuana law. The County had argued that it did not have to comply with the state-mandate to implement an identification card program for patients based on federal preemption.

Accordingly, states can create medical marijuana laws protecting patients and caregivers from prosecution under their own state-level controlled substance laws, but federal agents can still investigate, arrest, and prosecute medical marijuana patients, caregivers, and physicians (if they willfully aid and abet) in such states.

RESCHEDULING

Efforts to Remove Marijuana from Schedule I

Advocates of decriminalizing marijuana have attempted to have it removed from Schedule I ever since its original placement. A petition was first filed in 1972 by the National Organization for the Reform of Marijuana Laws (NORML) to the Bureau of Narcotics and Dangerous Drugs seeking to reschedule marijuana to Schedule II. After this petition was denied and public hearings were not conducted, NORML filed suit in 1974 against the Bureau and in 1975 against its successor, the DEA. After further legal maneuvering, the petition was eventually sent back to the DEA for consideration in 1980 by the U.S. Court of Appeals for the District of Columbia. Eventually, public hearings were held over a 2-year period from 1986 to 1988, at which time the DEA Administrator once again rejected the position of NORML (now joined by the Alliance for Cannabis Therapeutics [ACT], the Drug Policy Foundation, and the Physicians Association for AIDS Care, among others) despite recommendations to the contrary by the DEA administrative law judge in the case which called for reclassification of marijuana to Schedule II. The latter parties petitioned the District Court for review of this order; after once again remanding the case in 1991, the District Court denied the petition for review on February 18, 1994. Subsequent rescheduling petitions also have been rejected.

Although the petition for review was denied, it led to a revised formulation by the DEA for determining whether a drug has a "currently accepted medical use." The 5-part test for fulfilling the accepted medical use criteria of Schedule II is now comprised of the following:

- 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.

A drug must meet all 5 criteria to be considered for rescheduling by the DEA.

Even if marijuana were rescheduled under current law it could not be marketed or medically available for general prescription use unless it was reviewed and approved by FDA under the Federal Food, Drug, and Cosmetic Act (FFDCA) (see below). Conceivably, a physician may be able to write a prescription for an individual patient with the cooperation of a compounding pharmacist with a schedule II license. However, the FDA treats compounded products as "new drugs" subject to all the requirements of the FFDCA if pharmacists attempt to compound large quantities of medication.

Congress or the Executive branch (through regulatory procedures authorized by the CSA) could reschedule marijuana. Over the last decade various federal amendments (e.g., Hinchey-Rohrabacher) have been submitted that would prevent the Justice Department from using appropriated funds to interfere with the implementation of medical cannabis laws, and bills have been introduced that would reschedule marijuana and/or prevent provisions of the CSA and FFDCA from restricting activities in states that have adopted medical marijuana programs. These have all been defeated to date, but others are pending.

"Executive Order"

Resolution 229 (A-09) makes reference to a "Presidential/Executive" order. To the Council's knowledge no such order exists. As previously mentioned, in 1996, the Director of ONDCP issued a statement that threatened physicians with loss of certain privileges. However, this was not an Executive Order, but rather a compilation of strategies developed by several federal agencies. It never had the force of an Executive Order, and is nonetheless moot because of the permanent injunction issued against implementation of this strategy in *Conant v. Walters*.

During the 2008 Presidential campaign, then-Senator Obama pledged to avoid the use of federal resources in cracking down on medical marijuana activities in states where medical marijuana laws were in place. This view has since been reiterated by the Attorney General in press briefings, although DEA raids on a medical marijuana dispensaries in California have occurred in the same time frame. Resolution 229 (A-09) was prompted by pending medical marijuana legislation in the state of New York, and perhaps a provision authored by Congressman Maurice Hinchey (D-NY) that seeks to clarify the Obama administration's medical marijuana enforcement policy. The Hinchey provision was included in the report accompanying the Commerce, Justice, Science and related Agencies appropriation bill for fiscal year 2010. The provision (referring to the Department of Justice) reads:

> "There have been conflicting public reports about the Department's enforcement of medical marijuana policies. Within 60 days of enactment, the Department shall provide to the Committee clarification of the Department's policy regarding enforcement of federal laws and use of federal resources against individuals involved in medical marijuana activities."

CONDUCTING CLINICAL RESEARCH ON SCHEDULE I VS SCHEDULE II COMPOUNDS

Researchers who propose to conduct investigations in humans on Schedule I drugs must obtain FDA review of the protocol and fulfill the FDA's Investigational New Drug (IND) requirements for safety. They also must submit the protocol to the DEA as part of the process to obtain a valid registration for a Schedule I substance. When DEA receives the Schedule I research application, they forward it to another division within FDA for scientific review as part of their decision-making process. Investigators conducting research with a Schedule I substance must submit a protocol for each study involving each Schedule I substance to obtain approval to conduct that research. If a new protocol for a research study, even with the same substance is devised, the DEA registration must be amended by submitting the new protocol for review to the DEA. This is a requirement under the CSA and is separate from the FFDCA requirements for submitting INDs for human studies to the FDA, whereby FDA assesses whether the study design is safe.

Investigators seeking to do human research on Schedule II substances must still procure FDA safety review of the protocol and apply for a Schedule II registration with the DEA. Once granted, this Schedule II license is sufficient for all future studies on that substance.

The only legal federal source of marijuana is grown under the auspices of the National Institute on Drug Abuse (NIDA), and prior to 1999 only NIH-funded studies on marijuana could qualify for access to the NIDA supply. In May 1999, the Department of Health and Human Services announced a new guidance on procedures for the provision of marijuana for medical purposes on a cost-reimbursable basis.[45] For protocols submitted by non-NIH funded sources, institutional peer review and IRB approval precede the submission, after which the scientific merits of each protocol are evaluated through a Public Health Service interdisciplinary review process. This guidance created an avenue for externally funded investigators to acquire marijuana for research purposes, but retains additional review and approval steps that are not required of other traditional IND-sponsors.

In an effort to promote research on medical cannabis, California's State Assembly appropriated $3 million to establish a university-based Center for Medicinal Cannabis Research, to be administered jointly by the University of California's San Diego and San Francisco campuses.[46] Subsequently, many of the randomized controlled trials on smoked cannabis have been supported by this program. The cannabis used in such studies is obtained from NIDA in accordance with the procedures outlined above.

BOTANICALS AS DRUG PRODUCTS

Many drugs have been derived from plants, and the *National Formulary* and *U.S. Pharmacopoiea* formerly contained numerous botanical agents. Interest in the use of such agents waned with advances in the understanding of physiologic, biochemical, and cellular functioning. Pharmaceutical development evolved with a focus on identifying specific cellular targets (receptors) amenable to drug intervention, although plants may provide the starting material for certain products. The 1994 passage of the Dietary Supplement and Health Education Act fostered a return to the public's use of botanical products in the form of "dietary supplements." Such products are regulated as foods, and are not subject to FDA approval for safety and efficacy. They can use so called "structure and function" claims but cannot claim to be useful in the treatment of a disease or condition. In order to make a disease-based claim, the product must go through the FDA drug approval process.

In 2004, the FDA issued a *Guidance for Industry Botanical Drug Products* monograph.[47] This document provides the pathway by which botanical agents can be approved as prescription drugs. The crude botanical substance can become a "botanical drug substance" through processes of extraction, blending, addition of excipients, formulation, and packaging in a defined manner. Particular attention is devoted to product composition because botanicals are complex mixtures of chemical/structural components. Similar to conventional products, a botanical drug substance must undergo animal toxicity studies, and demonstrate its safety and efficacy in randomized, double-blind, placebo-controlled trials. Additional pharmacologic and toxicologic studies are required if a non-oral route (e.g., inhalation) of administration is contemplated. If the substance is intended to treat chronic conditions, 6 to 12 months in long-term safety extension studies is considered sufficient.

An example of a drug that is seeking FDA approval through this pathway is an extract prepared from two different breeds of cannabis that have been genetically developed to produce either high quantities of THC or cannabidiol. Chemovars of cannabis were selected via Mendelian genetics to express one predominant phytocannabinoid. Cloned plants undergo extraction to produce botanical drug substances that contain predominately THC or cannabidiol, or an approximate 1:1 combination of the two. The final product is a botanical extract (Nabiximols) comprising an oromucosal spray that delivers 2.7 mg of THC and 2.5 mg of cannabidiol per spray. Patients self-

titrate their overall dose and pattern of dosing according to their response and tolerance of the medicine. This botanical drug substance is approved in Canada (Sativex®) for the symptomatic relief of neuropathic pain in patients with multiple sclerosis, and as an adjunctive analgesic to opioids in patients with advanced cancer pain.[48-50] Nabiximols is progressing through the FDA pathway for botanical drug substance approval as a treatment for patients with advanced cancer whose pain has not been adequately relieved by optimized treatment with opioid medications.

Other cannabinoid based botanical drug substances have been developed in other countries (e.g., Cannador®), and several are in development in the U.S. with various modes of action (botanical extracts; CB receptor agonists or antagonists; inhibitors of endocannabinoid uptake or degradation). Cannador® is an extract delivered in an oral dosage form containing primarily 2.5 mg THC and 1 mg cannabidiol. It has demonstrated benefit in randomized controlled trials involving patients with multiple sclerosis experiencing pain due to spasm, and in decreasing post-operative pain.[51,52] The development of pharmaceutical grade cannabis-based extracts with proven medical benefits provides further evidence on the therapeutic potential of components of the cannabis plant.

SMOKED CANNABIS STUDIES

Currently cannabinoids are "available" in three different categories:[41] FDA approved oral preparations of THC (Dronabinol; Marinol®) and a synthetic analogue (Nabilone; Cesament®); *Cannabis sativa* extracts (e.g., Nabiximols [Sativex®], [Cannador®]) not currently approved in the U.S.; and crude botanical sources made available under state laws. Since 2001, systematic reviews have been conducted on smoked cannabis and other cannabinoids (mostly oral THC and botanical extracts).[53-56] The following discussion focuses on randomized, placebo-controlled human trials that have evaluated smoked cannabis. Table 1 summarizes the characteristics and findings of such trials.

Randomized Trials on Smoked Cannabis

Cancer chemotherapy. Three randomized, double-blind, controlled trials involving a total of 43 patients have evaluated the efficacy of smoked cannabis to alleviate nausea and vomiting accompanying cancer chemotherapy; one directly compared smoked cannabis with oral THC but was never published in a peer reviewed journal.[57-59] These trials revealed a modest antiemetic effect of smoked cannabis greater than placebo.

Several research/treatment studies were conducted by state departments of health during the late 1970s and early to mid-1980s under protocols approved by the FDA. These open label studies involved patients who had responded inadequately to other antiemetics. In such patients, smoked cannabis was reported to be comparable to or more effective than oral THC, and considerably more effective than prochlorperazine or other previous antiemetics in reducing nausea and emesis. Results of these studies generally were based on patients' and/or physicians' subjective ratings. These programs were noted in the 1997 Council report and another independent review that was published in 2001.[56] Smoked cannabis (as well as THC and other synthetic cannabinoids) is more effective than older antiemetic drugs (neuroleptics) and placebo.[53] All of these trials in cancer patients were conducted before the advent of 5-HT_3 and neurokinin-1 receptor antagonists. Smoked cannabis has been compared with the 5-HT_3 receptor antagonist ondansetron in an experimental emesis model. This randomized double-blind included 13 healthy volunteers who received syrup of ipecac.[60] Smoked cannabis significantly reduced ratings of queasiness and slightly reduced the vomiting induced by the syrup compared with placebo. Ondansetron completely eliminated episodes of vomiting.

Appetite stimulation. Three randomized, placebo-controlled trials involving a total of 97 HIV+ adult patients have compared the effects of smoked cannabis with oral THC or dronabinol; two used a "within subjects" design. Generally, the effects of smoked cannabis (2% or 3.9% THC) were comparable to oral cannabinoids in increasing caloric intake and triggering weight gain, although the dose of oral THC was substantially higher than normally recommended.[61-63] HIV viral load and the pharmacokinetics of concurrent protease inhibitors were unaffected over a three week period.[61]

Pain Management. Two randomized, double-blind, placebo-controlled trials involving a total of 89 patients with HIV-associated peripheral neuropathy, and one (n = 38) involving an experimental pain model (capsaicin) have been reported.[64,65] The latter was a randomized, double-blind, placebo-controlled crossover trial in 15 healthy volunteers examining the effects of cannabis cigarettes (2%, 4%, or 8%) on pain and cutaneous hyperalgesia induced by intradermal capsaicin.[65] The medium dose exhibited delayed analgesia, significantly inhibiting capsaicin-induced pain at 45 minutes after drug exposure; the low dose was ineffective, and the high dose increased capsaicin-induced pain at 45 minutes. Smoked cannabis did not significantly affect acute painful heat, cold, and mechanical thresholds.[64]

In patients with HIV-associated neuropathic pain, cannabis cigarettes of varying concentration and number consumed over a 5-day period significantly reduced pain intensity. Approximately half of patients experienced more than a 30% reduction, which is a standard benchmark for efficacy. Analysis of the number-needed-to-treat also compared favorably with historic values associated with other drugs used to treat neuropathic pain.[66,67]

Generally, side effects typically attributable to THC (anxiety, sedation, confusion, dizziness, fatigue, tachycardia, dry mouth) were noticeable in these studies but were tolerable and not considered dose-limiting. The use of higher potency cigarettes was more likely to be associated with drug-related cognitive decline on psychological testing.

The overall evaluation of the clinical effects of smoked cannabis in stimulating appetite and relieving neuropathic pain (and to a certain degree, nausea) correlates with patterns of use reported in surveys of HIV+ patients. In this population, cannabis use also has been associated with adherence to antiretroviral therapy in patients who experience nausea, and for the self management of HIV-associated peripheral neuropathy.[68,69] In one consecutive series, 23% of HIV+ patients reported smoking cannabis in the prior 30 days to improve appetite or relieve pain, but also to relieve anxiety or depression or "increase pleasure" which are characteristics of substance misuse or recreational use.[70] Another survey found a similar percentage of HIV-positive patients (27%) used cannabis to improve appetite, relieve nausea and pain, and for anxiety and depression. Nearly half of these users reported memory deterioration.[71]

Multiple Sclerosis and Spasticity. Surveys reveal that 36% to 68% of patients with multiple sclerosis have experimented with smoked cannabis for symptom relief, and approximately 15% are continuing users.[72,73] Two randomized, double-blind, placebo-controlled trials involving a total of 40 patients have been reported in patients with multiple sclerosis and spasticity.[74,75] In a pilot study involving 10 patients who smoked one cannabis cigarette of low potency (1.54% THC) some patients reported subjective improvements, but exhibited impairment of posture and balance.[74] When higher potency cannabis cigarettes were used for three days, reduced scores for pain (50%) and spasticity (30%) were observed, along with some cognitive impairment, dizziness, and fatigue; the majority of these patients had prior experience smoking cannabis.[75]

Glaucoma. In one randomized, double-blind, placebo-controlled crossover study of 18 adults with glaucoma, smoking one cannabis cigarette (2% THC) caused a significant reduction in intraocular pressure, along with alterations in sensory perception, tachycardia/palpitations, and postural hypotension.[76]

ADVERSE EFFECTS OF SMOKED CANNABIS

Determining the adverse effects of smoked cannabis used as medicine is problematic since only short-term controlled trials have been conducted. Most research on the harmful consequences of cannabis use has been conducted in simulated laboratory environments and in individuals who use cannabis for nonmedical purposes. One independent health assessment of four of the remaining seven patients obtaining cannabis cigarettes through the federal government's Compassionate Use Treatment IND (see Council report from 1997),[1] showed no demonstrable adverse outcomes related to their chronic medicinal cannabis use. Some of cannabis' adverse effects differ in experienced versus inexperienced users, and it is not clear to what extent the adverse effects reported in recreational users are applicable to those who use cannabis for the self-management of disease or symptoms. Most data on adverse effects has come from observational population-based cohort studies of recreational cannabis users, an unknown portion of whom may be using the substance for medicinal purposes. Adverse reactions observed in short-term randomized, placebo-controlled trials of smoked cannabis to date are mostly mild without substantial impairment. A systematic review of the safety studies on medical cannabinoids published over the last 40 years (not including studies on smoked cannabis) found that short term use was associated with a number of adverse events, but less than 4% were considered serious.[77]

Nonmedical Use

Nonmedical use of marijuana continues to be problematic in society. Approximately one third of all Americans over 12 years of age have tried marijuana, usually experimenting first during adolescence.[4] According to the most recent NSDUH Survey, marijuana continues to be the most commonly used illicit drug (14.4 million past month users).[78] Among persons aged 12 or older, the rate of past month marijuana use in 2007 (5.8 percent) was similar to the rate in 2006 (6.0 percent). The prevalence of past month marijuana use among adolescents (i.e., youths aged 12 to 17) generally decreased from 2002 (8.2 percent) to 2005 (6.8 percent), and then remained constant between 2005 and 2007. Adolescents who perceived great risk from smoking marijuana once a month were much less likely to have used marijuana in the past month than those who perceived moderate to no risk (1.4 vs. 9.5 percent). The specific illicit drugs that had the highest levels of past year dependence or abuse in 2007 were marijuana (3.9 million), followed by pain relievers (1.7 million) and cocaine (1.6 million). It is not clear how any of these trends have been influenced by the medical cannabis debate.

Acutely, smoked cannabis increases heart rate, and blood pressure may decrease on standing. Cannabis intoxication is associated with impairment of short-term memory, attention, motor skills, reaction time, and the organization and integration of complex information.[1] Although dependent on the setting, smoked cannabis can cause relaxation and enhance mood. However, some individuals experience acute anxiety or panic reactions, confusion, dysphoria, paranoia, and psychotic symptoms (e.g., delusions, hallucinations).[1]

Substance Dependence

Chronic cannabis use is associated with development of tolerance to some effects and the appearance of withdrawal symptoms (restlessness, irritability, mild agitation, insomnia, sleep disturbances, nausea, cramping) with the onset of abstinence. Depending on the measures and age group studied, 4% to 9% of cannabis users fulfill diagnostic criteria for substance dependence. Although some cannabis users develop dependence, they are considerably less likely to do so than users of alcohol and nicotine, and withdrawal symptoms are less severe.[4,79,80] Like other drugs, dependence is more likely to occur in individuals with co-morbid psychiatric conditions.

Whether or not cannabis is a "gateway" drug to other substance misuse is controversial and whether the medical availability of cannabis would increase drug abuse is not known. Analysis of trends in emergency room visits for marijuana do not support the view that state authorization for medical cannabis use leads to increased signals of substance misuse.[81] The IOM concluded that marijuana use is not the cause or even the most serious predictor of serious substance use disorders.[4] A systematic review of longitudinal studies on the use of cannabis concluded its use was consistently associated with reduced educational achievement and the use of other drugs, but not other measures of psychosocial harm.[82]

Cognitive Deficits and Mental Health

Other concerns about long-term cannabis use include cognitive effects, and its intersection with mental disorders. Acute intoxication with cannabis causes marked changes in subjective mental status, brain functioning, and neuropsychological performance. A meta-analysis conducted in 2003 found evidence of subtle impairments in the ability to learn and remember new information in chronic cannabis smokers, but no general persistent neuropsychological deficits.[83] Neuropsychological deficits and differences in brain functioning are most consistently observed among frequent, heavy users.[84]

A recent systematic review on cannabis use and the risk of psychotic or affective mental health outcomes renewed the debate about the potential role of smoked cannabis as a cause or sequelae of mental disorders.[85] Whether cannabis use contributes to mental disorders, is used for self-management of mental disorders, or the mental disorder itself lends to cannabis use is not clear. The recent discontinuation of clinical trials on a CB1 receptor antagonist because of suicidal ideation indicates some involvement of endocannabinoids in the regulation of mood.

Respiratory Illness and Cancer

Like tobacco, chronic cannabis smoking is associated with markers of lung damage and increased symptoms of chronic bronchitis.[86-88] However, results of a population-based case control study of cannabis smokers found no evidence of increased risk for lung cancer or other cancers affecting the oral cavity and airway.[89] Another population-based case-control study of marijuana use and head and neck squamous cell carcinoma (HNSCC) concluded that moderate marijuana use is associated with reduced risk of HNSCC.[90] Furthermore, although smoking cannabis and tobacco may synergistically increase the risk of respiratory symptoms and COPD, smoking only cannabis is not associated with an increased risk of developing COPD.[91] One recent study suggests that use of smoked cannabis is associated with an increased risk for testicular cancers.[92]

The use of a vaporizing device may mitigate some of these symptoms. Cannabis vaporization is a technique aimed at suppressing the formation of irritating respiratory toxins by heating cannabis to a temperature where active cannabinoids are volatilized, but below the point of combustion where

smoke and associated toxins form. The use of a vaporizer is associated with higher plasma THC concentrations than smoking marijuana cigarettes, little if any carbon monoxide production, and significantly fewer triggered respiratory symptoms.[93,94]

Immunosuppression

Cannabinoids exert immunosuppressive and anti-inflammatory effects.[95-97] Plant-derived and synthetic cannabinoids exert antiproliferative effects on a wide spectrum of human tumor cell lines in culture, although mitogenic responses also have been observed.[98,99] Apoptosis, inhibition of proliferation, suppression of cytokine and chemokine product and induction of T regulatory cells have been identified. CB2 receptors are associated with activated microglia in the CNS.[100] Clearly endocannabinoids are immune modulators, but how they regulate various elements of the human immune response is unclear, and how exogenous cannabinoids may interact with these processes also is not established. Short-term use of smoked cannabis did not affect viral load in HIV-positive patients and also is associated with adherence to therapy and reduced viral loads in patients with hepatitis C infections.[61,101]

SUMMARY AND CONCLUSION

Despite more than 30 years of clinical research, only a small number of randomized, controlled trials have been conducted on smoked cannabis. These trials were short term and involved a total of ~300 patients. Results of these trials indicate smoked cannabis reduces neuropathic pain, improves appetite and caloric intake especially in patients with reduced muscle mass, and may relieve spasticity and pain in patients with multiple sclerosis. Substantially better alternatives than smoked cannabis are available to treat patients with glaucoma or chemotherapy-induced nausea and vomiting. Smoked cannabis has not been subject to any sort of rigorous study in any other indication. Results obtained from oral cannabinoid products (including botanical extracts) are not directly applicable to smoked cannabis for a number of reasons including substantial differences in constituents, pharmacokinetics of active ingredients, and active metabolite patterns. However, development of botanical extracts as prescription medications lends further credence to the therapeutic potential of components of the cannabis plant.

There is a contrast between the relatively small number of patients who have been studied over the past 30 years in controlled clinical trials involving smoked cannabis and survey data from patients with chronic pain, multiple sclerosis, and amyotrophic lateral sclerosis that indicates a significant use of cannabis for self management. Additionally, surveys of patients with HIV or hepatitis C infection suggest that smoked cannabis is used to relieve a constellation of symptoms (pain, nausea, appetite suppression, sleep disorders) and as a source of palliation from antiviral medication side effects.

Marijuana is the most common illicit drug used by the nation's youth and young adults. However, the fact that cannabis is prone to nonmedical use does not obviate its potential for medical product development. Many legal pharmaceutical products that are used for pain relief, palliation, and sleep induction have more serious acute toxicities than marijuana, including death. Witness the evolving series of steps that the FDA has taken in recent months to address the inappropriate use and diversion of certain long-acting Schedule II opioid drugs. However, the patchwork of state-based systems that have been established for "medical marijuana" is woefully inadequate in establishing even rudimentary safeguards that normally would be applied to the appropriate clinical use of psychoactive substances. Recent documentaries have noted the ease with which individuals can "qualify" for access to cannabis products in certain parts of California.

The AMA supports the concept of drug approval by scientific and regulatory review to establish safety and efficacy, combined with appropriate standards for identity, strength, quality, purity, packaging, and labeling, rather than by ballot initiative or state legislative action. 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. To the extent that rescheduling marijuana out of Schedule I will benefit this effort, such a move can be supported. In the meantime, physicians who comply with their ethical obligations to "first do no harm" and to "relieve pain and suffering" should be protected in their endeavors, including advising and counseling their patients on the use of cannabis for therapeutic purposes.

RECOMMENDATION

The Council on Science and Public Health recommends that Policy H-95.952 be amended by insertion and deletion to read as follows:

H-95.952 Medical Marijuana

(1) Our American Medical Association (AMA) calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease.

(2) ~~Our AMA recommends that marijuana be retained in Schedule I of the Controlled Substances Act pending the outcome of such studies.~~ Our AMA urges that marijuana's status as a federal Schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines, and alternate delivery methods. This should not be viewed as an endorsement of state-based medical cannabis programs, the legalization of marijuana, or that scientific evidence on the therapeutic use of cannabis meets the current standards for a prescription drug product. (New HOD Policy)

(3) Our AMA urges the National Institutes of Health (NIH) to implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research into the medical utility of marijuana. This effort should include: a) disseminating specific information for researchers on the development of safeguards for marijuana clinical research protocols and the development of a model informed consent on marijuana for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of marijuana for clinical research purposes; c) confirming that marijuana of various and consistent strengths and/or placebo will be supplied by the National Institute on Drug Abuse to investigators registered with the Drug Enforcement Agency who are conducting bona fide clinical research studies that receive Food and Drug Administration approval, regardless of whether or not the NIH is the primary source of grant support.

~~(4) Our AMA believes that the NIH should use its resources and influence to support the development of a smoke-free inhaled delivery system for marijuana or delta-9 tetrahydrocannabinol (THC) to reduce the health hazards associated with the combustion and inhalation of marijuana.~~

~~(5)~~ (4) Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between

physicians and patients should not subject either party to criminal sanctions. (CSA Rep. 10, I-97; Modified: CSA Rep. 6, A-01)

Fiscal Note: Less than $500

REFERENCES

1. Council on Scientific Affairs Report 10. Medical marijuana. American Medical Association, Interim Meeting, Dallas, Texas; December 1997.

2. Council on Scientific Affairs Report 6. Medical marijuana. American Medical Association, Annual Meeting, Chicago, Illinois; June 2001.

3. Joy JE, Watson S Jr, Benson JA Jr, eds. *Marijuana and Medicine. Assessing the Science Base.* Division of Neuroscience and Behavioral Health, Institute of Medicine. National Academy Press: Washington, DC; 1999.

4. American College of Physicians. Supporting research into the therapeutic role of marijuana. American College of Physicians; 2008: Position Paper. http://www.acponline.org/advocacy/where_we_stand/other_issues/medmarijuana.pdf. Accessed August 8, 2009.

5. O'Shaughnessy WB. On the preparation of the Indian hemp or gunjah (*Cannabis indica*): the effects on the animal system in health and their utility in the treatment of tetanus and other convulsive diseases. *Trans Med Phys Soc Bombay.* 1839;8:421-461.

6. Mikuriya TH, ed. Marijuana: Medical Papers, 1839-1972. Oakland, Calif: MediComp; 1973.

7. Reynolds JR. On the therapeutic uses and toxic effects of Cannabis indica. *Lancet.* 1890;1:637-638.

8. US Congress, House Ways and Means Committee, Hearings on H.R. 6385: Taxation of Marihuana, 75th Cong, 1st session, April 27, 1937.

9. Report of the Committee on Legislative Activities. *JAMA.* 1937;108:2214-2215.

10. Mechoulam R, Gaoni Y. A total synthesis of d,1-delta-1-tetrahydrocannabinol, the active constituent in hashish. *J Am Chem Soc.* 1965;87:3273-3275.

11. Turner CE, Elsohly MA, Boeren EG. Constituents of Cannabis sativa. XVII. A review of natural constituents. *J Nat Prod.* 1980;43:169-234.

12. Isbell H. Clinical pharmacology of marihuana. *Pharmacol Rev.* 1971;23:337-338.

13. Razdan RK. Structure-activity relationships in cannabinoids. *Pharmacol Rev.* 1986;38:75-149.

14. Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animal and humans. *Addiction.* 1996;91:1585-1614.

15. Garrett ER, Hunt CA. Physicochemical properties, solubility, and protein binding of delta9-THC. *J Pharm Sci.* 1974;63:1056-1064.

16. Dewey WL, Martin BR, May EL. Cannabinoid stereoisomers: pharmacologic effects In: Smith DF, ed. *CRC Handbook of Stereoisomers: Drugs in Psychopharmacology*, Boca Raton, FL: CRC Press; 1984:317-326.

17. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature.* 1990;346:561–564.

18. Biegon A, Kerman IA. Autoradiographic study of pre- and postnatal distribution of cannabinoid receptors in human brain. *Neuroimage.* 2001;14:1463-1468.

19. Glass M, Dragunow M, Faull, R.L. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience.* 1997;77:299-318.

20. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* 2002;54:161-202.

21. Mackie K. Signaling via CNS cannabinoid receptors. *Mol Cell Endocrinol.* 2008;286:S60-S65.

22. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature.* 1993;365:61–65.

23. Onaivi ES, Ishiguro H, Gong JP, et al. Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Ann. N. Y. Acad. Sci.* 2006;1074:514-536.

24. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science.* 2005;310:329-332.

25. Walter L, Stella N. Cannabinoids and neuroinflammation. *Br J Pharmacol.* 2004;141:775–785.

26. Pertwee RG. The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids. *AAPS J.* 2005;7:E625–E654.

27. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science.* 1992;258:1946–1949.

28. Sugiura T, Kondo S, Sukagawa A, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun.* 1995;215:89–97.

29. Pacher P, Batkal S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Reviews.* 2006;58:389-462.

30. Sugiura T, Waku K. Cannabinoid receptors and their endogenous ligands. *J Biochem.* 2002; 132:7–12.

31. Alexander SPH, Kendall DA. The complications of promiscuity: endocannabinoid action and metabolism. *Brit J Pharmacol.* 2007;152:602-623.

32. Pertwee RG. GPR55: a new member of the cannabinoid receptor clan? *Br J Pharmacol.* 2007;152:984-986.

33. Vemuri VK, Janero DR, Makriyannis A. Pharmacotherapeutic targeting of the endocannabinoid signaling system: drugs for obesity and the metabolic syndrome. *Physiol Behav.* 2008;93:671-686.

34. Richardson D, Pearson RG, Kurina N, et al. Characterization of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Res Ther.* 2008;10(2):R43 (Epub).

35. Wright KL, Duncan M, Sharkey KA. Cannabinoid CB2 receptors in the gastrointestinal tract: a regulatory system in sites of inflammation. *Brit J Pharmacol.* 2008;153:263-270.

36. Mangiieri RA, Piomelli D. Enhancement of endocannabinoid signaling and the pharmacotherapy of depression. *Pharmacol Res.* 2007;56:360-366.

37. Solinas M, Yasar S, Goldberg SR. Endocannabinoid system involvement in brain reward processes related to drug abuse. *Pharmacol Res.* 2007;56:393-405.

38. Jhaveri MD, Richardson D, Chapman V. Endocannabinoid metabolism and uptake: novel targets for neuropathic and inflammatory pain. *Brit J Pharmacol.* 2007;152:624-632.

39. Thirteen legal medical marijuana states. Laws, fees and possession limits. http://medicalmarijuana.procon.org/viewresource.asp?resourceID=000881

40. Thirteen states with pending legislation or ballot measures to legalize medical marijuana (as of July 19, 2009). http://medicalmarijuana.procon.org/viewresource.asp?resourceID=002481.

41. Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD. Medicinal use of cannabis in the United States. Historical perspective, current trends and future directions. *J Opioid Management.* 2009;5:153-168.

42. Conant v. Walters, 309 F.3d 629 (9th Cir. 2002).

43. USA v. Oakland Buyers Cooperative 532 U.S. 483 (2001).

44. Gonzales v. Raich 545 U.S. 1, (2005).

45. Announcement of the Department of Health and Human Services Guidance on Procedures for Provision of Marijuana for medical Research. http://grants.nih.gov/grants/guide/notice-files/not99-091.html.

46. Center for Medical Cannabis Research. University of California. http://www.cmcr.ucsd.edu/geninfo/research.htm.

47. US Food and Drug Administration. Guidance for Industry Botanical Drug Products. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070491.pdf.

48. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double blind, placebo-controlled trial. *Pain.* 2007;133:210-220.

49. Rog DJ, Nurimikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannbidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open label, 2-year extension trial. *Clin Ther.* 2007;29:2068-2079.

50. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology.* 2005;65:812-819.

51. Holdcroft A, Maze M, Dore C, et al. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology.* 2006;104:1040-1046.

52. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. *Lancet.* 2003;362:1517-1526.

53. Rocha FC, Stefano SC, de Cassia Haiek R, Rosa Oliveira L, da Silveira D. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care.* 2008;17:431-443.

54. Bagshaw SM. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. *J Palliative Care.* 202;18:111-122

55. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *J Ethnopharmacology.* 2006;105:1-25.

56. Musty RE, Rossi R. Effects of smoked cannabis and oral Δ9tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. *J Cannabis Therap.* 2001;1:2956.

57. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate: a prospective, randomized evaluation. *Ann Intern Med.* 1979;91:819-824.

58. Chang AE, Shiling DJ, Stillman RC, et al. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer.* 1981;47:1746-1751.

59. Levitt M, Faiman C, Hawks R, Wilson A. Randomized double-blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics. Proceedings of the Annual Meeting of the American Society of Clinical Oncology, Toronto, May 6-8, 1984.

60. Soderpalm A, Schuster A, de Wit H. Antiemetic efficacy of smoked marijuana. Subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacol Biochem Behav.* 2001;69:343-350.

61. Abrams DI, Hilton JF, Leiser R et al. Short-term effects of cannabinoids in patients with HIV-1 infection. *Ann Intern Med.* 2003;139:258-266.

62. Haney M, Rabkin J, Gunderson E. Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood. *Psychopharmacology.* 2005;181:170-178.

63. Haney M, Gunderson EW, Rabkin J, et al. Dronabinol and marijuana in HIV-positive marijuana smokers. *J Acquir Immune Defic Syndr.* 2007;45:545-554.

64. Wilsey B, Marcotte T, Tsodkiov A, et al. A randomized, placebo-controlled crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008;9:506-521.

65. Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in health volunteers. *Anesthesiology.* 2007;107:785-796.

66. Abrams DI, Jay CA, Shade SB et al. Cannabis in painful HIV-associated sensory neuropathy. *Neurology.* 2007;68:515-521.

67. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology.* 2009;34:672-680.

68. Nicholas PK, Kemppainen JK, Canaval GE, et al. Symptom management and self-care for peripheral neuropathy in HIV/AIDS. AIDS Care. 2007;19:179-189.

69. De Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected person with moderate to severe nausea. J Acquir Immune Defic Syndr. 2005;38:43-46.

70. Prentiss D, Power R, Balmas G, Tzuang G, Israelski DM. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr.* 2004;35:38-45.

71. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. *J Pain Symptom Manage.* 2005;29:358-367.

72. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. *Multiple Sclerosis.* 2006;12:646-651.

73. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. *Neurology.* 2004;62:2098-2100.

74. Cory-Bloom J, Wolfson TJ, Gams AC, et al. Short-term effects of medicinal cannabis on spasticity in multiple sclerosis. Abstract.

75. Greenberg HS, Werness SA, Pugh JE, Andrus RO, Anderson DJ, Domino EF. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clin Pharmacol Ther.* 1994;55:324-328.

76. Merrit JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marijuana on intraocular and blood pressure in glaucoma. *Ophthalmology.* 1980;87:222-228

77. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *CMAJ.* 2008;178:1669-1678.

78. Substance Abuse and Mental Health Administration—Office of Applied Studies. Results from the 2007 National Survey on Drug Use and Health: national findings. http://www.oas.samhsa.gov/nsduh/2k7nsduh/2k7Results.pdf. Accessed August 10, 2009.

79. Chait LD, Pierri J. Effects of smoked marijuana on human performance: A critical review. In: Bartke A, Murphy L, eds. *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. CRC Press: Boca Raton, FL; 1992:387-424.

80. Hall W, Solowij N. Adverse effects of cannabis. *Lancet*. 1998;352:1611-1616.

81. Gorman DM, Huber CJ. Do medical cannabis laws encourage cannabis use? *Int J Drug Policy*. 2007;18:160-167.

82. Macleod J Oakes R, Copello A, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal general population studies. *Lancet*. 2004;363:1579-1588.

83. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta analytic study. *J Int Neurpsychol Soc*. 2003;9:679-689.

84. Gonzalez R. Acute and non-acute effects of cannabis on brain functioning and neuropsychological performance. *Neuropsychol Rev*. 2007;17:347-361.

85. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370:319-328.

86. Roth MD, Arora A, Barsky SH, et al. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med*. 1998;157:928-937.

87. Taylor DR, Fergusson DM, Milne BJ, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction*. 2002;97:1055-1061.

88. Aldington S, Williams M, Nowitz M, et al. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax*. 2007;62:1058-1063.

89. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiolo Biomarkers Prev*. 2006;15:1829-1834.

90. Liang C, McClean MD, Marsit C et al. A population-based case-control study of marijuana use and head and neck squamous cell carcinoma. *Cancer Prev Res*. 2009;2:759-768.

91. Tan WC, Lo C, Jong A et al. Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ*. 2009;180:814-820.

92. Daling JR, Doody DR, Sun X et al. Association of marijuana use on the incidence of testicular germ cell tumors. *Cancer*. 2009;115:1215-1223.

93. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Therapeut*.2007;82:572-578.

94. Earlywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users. *Harm Reduction J*. 2007;4:11.

95. Rieder SA, Chauhan A, Singh U, Nagarketti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. *Immunobiology*. 2009 May 18. Epub ahead of print.

96. Klein TW, Cabral GA. Cannabinoid-induced immune suppression and modulation of antigen presenting cells. *J Neuroimmune Pharmacol*. 2006;1:50-64.

97. McHugh D, Tanner C, Mechoulam R, Pertwee R, Ross R. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: Evidence for a site distinct form CB1 and CB2. *Molecular Pharmacology*. 73:441-450.

98. Guzman M, Sanchez C, Galve-Roperh I. Cannabinoids and cell fate. *Pharmacol Ther*. 2002;95:175-184.

99. McKallip RJ, Nagarkatti M, Nagarkatti PS. Delta-9–tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. *J Immunol*. 2005;174:3281-3289.

100. Cabaral GA, Raborn ES, Griffin L, ennis J, Marciano-Cabral. CB2 receptors in the brain: role in central immune function. *Brit J Pharmacol*. 2008;153:240-251.

101. Sylvestre DL, Clements BJ, Malibu Y. Cannabis use improves retention and virological outcomes in patients treatment for hepatitis C. *Eur J Gastroenterol Hepatol*. 2006;18:1057-1063.

APPENDIX A

AMA Policy On Medical Marijuana

H-95.952 Medical Marijuana

(1) Our AMA calls for further adequate and well-controlled studies of marijuana and related cannabinoids in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy and the application of such results to the understanding and treatment of disease. (2) Our AMA recommends that marijuana be retained in Schedule I of the Controlled Substances Act pending the outcome of such studies. (3) Our AMA urges the National Institutes of Health (NIH) to implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research into the medical utility of marijuana. This effort should include: a) disseminating specific information for researchers on the development of safeguards for marijuana clinical research protocols and the development of a model informed consent on marijuana for institutional review board evaluation; b) sufficient funding to support such clinical research and access for qualified investigators to adequate supplies of marijuana for clinical research purposes; c) confirming that marijuana of various and consistent strengths and/or placebo will be supplied by the National Institute on Drug Abuse to investigators registered with the Drug Enforcement Agency who are conducting bona fide clinical research studies that receive Food and Drug Administration approval, regardless of whether or not the NIH is the primary source of grant support. (4) Our AMA believes that the NIH should use its resources and influence to support the development of a smoke-free inhaled delivery system for marijuana or delta-9-tetrahydrocannabinol (THC) to reduce the health hazards associated with the combustion and inhalation of marijuana. (5) Our AMA believes that effective patient care requires the free and unfettered exchange of information on treatment alternatives and that discussion of these alternatives between physicians and patients should not subject either party to criminal sanctions. (CSA Rep. 10, I-97; Modified: CSA Rep. 6, A-01)

APPENDIX B

Institute of Medicine

Marijuana and Medicine: Assessing the Science Base

RECOMMENDATION 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoids research should include, but not be restricted to, effects attributable to THC alone.

Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect. (See Recommendation #2)

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recommended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues. If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems.

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- failure of all approved medications to provide relief has been documented,
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and
- involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 house of a submission by a physician to provide marijuana to a patient for a specified use.

Appendix C

American College of Physicians Position Statement

Position 1: ACP supports programs and funding for rigorous scientific evaluation of the potential therapeutic benefits of medical marijuana and the publication of such findings.

- Position 1a: ACP supports increased research for conditions where the efficacy of marijuana has been established to determine optimal dosage and route of delivery.

- Position 1b: Medical marijuana research should not only focus on determining drug efficacy and safety but also on determining efficacy in comparison with other available treatments.

Position 2: ACP encourages the use of nonsmoked forms of THC that have proven therapeutic value.

Position 3: ACP supports the current process for obtaining federal research-grade cannabis.

Position 4: ACP urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.

Position 5: ACP strongly supports exemption from federal criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for physicians who prescribe or dispense medical marijuana in accordance with state law. Similarly, ACP strongly urges protection from criminal or civil penalties for patients who use medical marijuana as permitted under state laws.

Table 1. Randomized, Placebo-Controlled Trials of Smoked Cannabis

Study	n	Design	Product and dosage	Efficacy	Adverse Effects
Antiemetic effects in patients receiving cancer chemotherapy					
Chang et al[57]	15 patients with osteogenic sarcoma undergoing high dose methotrexate chemotherapy (median age 24 years)	R, DB, CR,PC	Oral THC 10 mg/m^2 5 times daily or smoked cannabis (1.93% THC) cigarette substituted if vomiting occurred	Oral THC alone or the combination of oral and smoked cannabis had an antiemetic effect > placebo. THC reduced the number of retching and vomiting episodes, the degree and duration of nausea, and the volume of emesis. Clinical responses appeared to correlate with plasma THC values. Smoked THC yielded plasma concentrations more than 5 ng/mL on 70% of occasions compared with 44% of the time with oral THC.	Sedation in 80% of patients, most of whom had prior experience with smoked cannabis
Chang et al[58]	8 patients with various tumors undergoing adjuvant therapy with doxorubicin and cyclophosphamide (median age 41 years)	R, DB, CR, PC	Oral THC 10 mg/m^2 5 times daily or smoked cannabis (1.93% THC) cigarette substituted if vomiting occurred	No antiemetic effect. Seven of eight patients inexperienced in the use of cannabis.	Mood alteration and episodes of tachycardia
Levitt et al[59]	20 patients with various tumors	R, DB, CR, PC	One cannabis cigarette + placebo oral THC x 4; oral THC 15 mg + placebo cannabis cigarette x 4	Treatments were effective in only in 25% of patients; 35% preferred oral THC; 20% preferred smoked cannabis; 45% had nor preference.	Seven individuals exhibited distortions of time perception or hallucinations; four that had received THC; two with cannabis, and one with both
Appetite stimulation					
Abrams et al[61]	67 adults with HIV infection	R, DB for oral THC or P, PL	One to three cannabis cigarettes/day (3.95% THC) or oral THC 2.5 mg tid for 21 days	Smoked cannabis and oral THC equivalent on weight gain and superior to placebo; viral load and pharmacokinetics of protease inhibitors unaffected	Generally well tolerated; one cannabis recipient discontinued due to emergence of neuropsychiatric symptoms; two oral THC recipients dropped out due to side effects (paranoia; headache)

Haney et al[62]	30 HIV+ experienced cannabis smokers, half with less than 90% ideal body mass	R, DB, PC	Dronabinol zero to 30 mg or cannabis cigarettes zero to 3.9% THC), administered in eight 7 hour sessions over three to four weeks	Cannabis and dronabinol significantly increased caloric intake in the low body mass group	Few adverse effects reports, except intolerance of high (30 mg) dronabinol dose
Haney et al[63]	10 HIV+ experienced cannabis smokers	R, DB, PC	Dronabinol 5 or 10 mg, or cannabis cigarettes 2% or 3.9% THC each four times daily for four days	Cannabis and dronabinol increased calorie intake in a dose dependent fashion, and body weight at the highest doses	Relative absence of cognitive impairment. Improved mood and objective and subjective sleep measures.
Pain Management/Analgesia					
Abrams et al[66]	55 patients with HIV-associated neuropathic pain	R, DB, PC, PL	Up to three cannabis (3.95% THC) cigarettes daily for 5 days	Smoked cannabis relieved chronic neuropathic pain (34% reduction), and more than 50% of patients experienced at least a 30% reduction in pain intensity. Smoked cannabis also reduced experimentally induced hyperalgesia	All patients had prior cannabis smoking experience. Anxiety, sedation, disorientation, confusion, and dizziness occurred more often in cannabis recipients, but were rated as between "none" and mild.
Ellis et al[67]	34 adult patients with HIV-associated neuropathic pain	R, DB, CR, PC	Cannabis cigarettes of varying THC concentration (1-8%) administered 4 times daily for 5 days	46% more patients achieved at least a 30% reduction in pain relief with cannabis vs placebo	All patients were taking additional analgesics. Concentration difficulties, fatigue, sedation, dry mouth, tachycardia more frequent but not dose limiting. Two dropouts for "psychosis" and "cough"
Wilsey et al[64]	38 adult patients experienced cannabis smokers with central and peripheral neuropathic pain	R, DB, CR, PC	Cannabis cigarettes zero, 3.5% or 7% THC administered in graded puffs over 2 hours	Smoked cannabis reduced pain intensity at 4 hours compared with placebo; no difference was noted between the 2 doses. No effects observed on evoked pain responses. Most patients had complex regional pain syndrome.	Cannabis recipients were more likely to report subjective and psychoactive drug effects including impairment and sedation. General cognitive decline on psychological testing.

Multiple sclerosis					
Greenberg et al[75]	10 adult patients with multiple sclerosis and spasticity	R, DB, PC	One cannabis cigarette (1.54% THC) smoked over 10 minutes	Subjective feeling of clinical improvement in some patients	Impairment of posture and balance as measured by dynamic posturography
Cory-Bloom et al[74]	30 adult patients with multiple sclerosis and spasticity	R, DB, CR, PC	One cannabis cigarette (3.95%) daily for 3 days	Reduced pain (~50%) and spasticity (~30%) scores.	Cognitive impairment; dizziness; fatigue, "too high." 80% had prior cannabis use
Glaucoma					
Merritt et al[76]	18 adults with glaucoma (ages 28-71)	R, DB, CR, PC	One cannabis cigarette containing 2% THC	Significant reduction in intraocular pressure	Alteration in sensory perception (100%); tachycardia and palpitations (44%), postural hypotension (28%)

R = randomized; DB = double-blind; CR = crossover trials, PL = parallel group study; PC = placebo-controlled