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Marijuana Legalization; A Non-Starter
ONDCP Director R. Gil Kerlikowske
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The Department of Justice earlier this week issued guidelines for Federal prosecutors regarding laws authorizing the use of marijuana for medical purposes. This prompted a flurry of news reports, analysis and commentary, some arguing that the guidelines could be read as the Federal government's tacit approval of "medical" marijuana. Advocates of marijuana legalization tried to cast the guidelines as a victory, portraying them as a step toward full legalization. Neither of these analyses is correct.

Marijuana legalization, for any purpose, remains a non-starter in the Obama Administration. It is not something that the President and I discuss; it isn't even on the agenda. Attorney General Holder issued very clear guidelines to U.S. Attorneys about the appropriate use of Federal resources. He did not open the door to legalization.

Regarding state ballot initiatives concerning "medical" marijuana, I believe that medical questions are best decided not by popular vote, but by science. The Food and Drug Administration (FDA), which studies and approves all medicines in the United States, has made very clear that the raw marijuana plant is not medicine, and any state considering medical marijuana should look very carefully at what has happened in California.

Legalization is being sold as being a cure to ending violence in Mexico, as a cure to state budget problems, as a cure to health problems. The American public should be skeptical of anyone selling one solution as a cure for every single problem. Legalized, regulated drugs are not a panacea—pharmaceutical drugs in this country are tightly regulated and government controlled, yet we know they cause untold damage to those who abuse them.

To test the idea of legalizing and taxing marijuana, we only need to look at already legal drugs—alcohol and tobacco. We know that the taxes collected on these substances pale in comparison to the social and health care costs related to their widespread use.

In a little over three months, my office will deliver to President Obama a National Drug Control Strategy that will strike a balance between public health and public safety, recognizing that reducing demand through a community-wide approach is critical to our success. Legalization would only thwart our efforts and increase the economic and social costs that result from greater drug acceptance and use.

—R. Gil Kerlikowske

Who is REALLY smoking "medical" marijuana?

The following data is from the "medical" marijuana states that provide information on the types of conditions that people claim they want to smoke marijuana for.

California

There are an estimated 300,000 to 400,000 "medical" marijuana "patients" in California. In cities like San Diego where the issue has been closely examined, **only 2% of those smoking marijuana under the guise of medicine have serious conditions such as AIDS, glaucoma and cancer.** A full 98% are claiming more minor conditions such as back and neck pain, anxiety, muscle spasms, insomnia, headaches and other conditions. But even more troubling is that 12% of the users are under 21!

Source: California Police Chiefs Association. Medical Marijuana Dispensary Information, Medical Marijuana Dispensaries-San Diego (Power Point). http://www.californiapolicechiefs.org/nav_files/medical_marijuana.html

Source: CNN Money.com How marijuana became legal by Roger Parloff. September 18, 2009

Oregon

As of October 1, 2009, the Oregon Medical Marijuana Program has 23,873 individuals that legally hold "medical" marijuana ID cards, and of those, 88% are claiming "severe pain" **(an indefinable term that is being used to cover medical conditions such as menstrual cramps, headaches, and minor arthritis)** rather than conditions such as cancer (4.4%), glaucoma (1.5%) and HIV+/AIDS (2.2%).

Source: Oregon.gov, Oregon Medical Marijuana Program (OMMP) http://oregon.gov/DHS/ph/ommp/index.shtml

Colorado

As of July 31, 2009, the Marijuana Registry Program has 8,918 individuals that legally hold registry ID cards, up 1,288 since May 30, 2009. Of the 11,094 ID card holders, 90% are claiming "severe pain" (as explained above), and 27% are claiming "muscle spasms" rather than conditions such as cancer (3%), glaucoma (1%) and HIV+/AIDS (1%).

Source: Colorado Department of Public Health and Environment, Medical Marijuana Registry Update. http://www.cdphe.state.co.us/hs/Medicalmarijuana/marijuanaupdate.html

Hawaii

As of December 2008 the program has 4,560 participants. Of the 4,560 participants, 68 % are claiming the condition of severe pain (as explained above). That was followed by 1.5% for persistent muscle spasms, 1.4% for HIV or AIDS, 1.2% for cancer, 1.1% for severe nausea, .05% for seizures and .03% for wasting syndrome.

Source: Article in the Maui News titled Careful what you ask for, dated 2/9/09. http://www.mauinews.com/page/content.detail/id/514619.html

Montana

Of the 1,989 participants in the registry program, 72.6% are claiming chronic pain or chronic pain with muscle spasms. Combined, the conditions such as cancer, glaucoma and HIV only represent 3.6% of the program's participants.

Source: Montana Department of Public Health and Human Services, medical marijuana program coordinator. March 27, 2009.

Rhode Island

As of December 30, 2008, 561 individuals are participating in the program. Of those, 63.71% are claiming a chronic disease or condition (chronic pain, severe nausea and severe persistent muscle spasms) rather than conditions such as cancer (11.95%), glaucoma (1.69%), HIV+/AIDS (4.50%) and Hepatitis C (9.7%).

Source: Rhode Island Department of Health http://www.health.ri.gov/hsr/mmp

FACTS ON DRUG LEGALIZATION

The argument that the only solution to the drug problem is to legalize illicit drugs continues with a fiery vengeance. Those concerned and involved in fighting drug abuse must be prepared to deal with the issue.

Simply asking the question, "should drugs be legalized?" sends a confusing message to young people. Kids today have enough demands made on them trying to resist drugs and peer pressure without having to sort through the mixed message and inconsistency that legalizing drugs would offer.

Many of those advocating drug legalization do not realize the damage they are doing. They have never talked with the kids who bravely refuse to use or to the young addicts struggling to renew a shattered life. To many people the legalization issue is idle chitchat as cocktail glasses knock together at social events.

There is both an old and a new school of thought on why drugs should be legalized. The older rationale dates back to the "hippy"era during the sixties and argues that drug use should be allowed as a matter of individual liberty and that people should have the right to use whatever drugs they want, regardless of the consequences to society. This liberal school of thought supported almost any argument to legalize drugs – that drugs are not dangerous, that there is a compelling medicinal need for illicit drugs, that drug laws are an evil plot by "big brother" government, or that people only use drugs because they are illegal.

The inability of law enforcement to solve America's drug problem in cited as evidence of the futility of imposing legal prohibition on drugs. The costs of enforcement, it is argued, outweigh the benefit society derives from such enforcement. Faulty economic theory is simplistically applied to support the argument for legalization.

This theory overlooks historical experience, neglects social and economic realities, ignores the biological and physiological effects of illicit drugs, and misinterprets lessons from recent experience with these deadly substances.

Liberalizing drug laws only brings about an increase in drug use, drug addiction, and drug-related criminal activity. It is true that law enforcement cannot win this war alone. Prevention education and treatment efforts have just started to work in conjunction with enforcement. Just because certain aspects of a battle are going poorly does not mean that surrender is inevitable.

Most legalization proponents would continue to prohibit drug use by youth. They believe that funds formerly used for law enforcement could be used for education to prevent drug use and for treatment. It is unrealistic to expect to discourage young people from using a drug that is legal for adults. Our experience with alcohol supports this. It is ludicrous to think that the temptation of trying legal, cheap drugs would not be a problem in dealing with our young people.

Research has demonstrated that those who drink alcohol to become intoxicated are more prone to alcoholism than those who drink and avoid intoxication. Illegal drugs are used solely for their intoxicating effect. Drugs such as crack can addict the user with the first use. Another thing to remember is there is no such thing as "responsible use" of illicit drugs. Illegal drugs are always used for the purpose of intoxication and the users pose an even greater risk of causing death from accidents, suicide and criminal behavior.

In summing up, one should remember that many Americans have been personally affected by the drug abuse problem. None have suffered as much as our youth, whether a baby born addicted, a child murdered by drug-crazed parents, or a teenage abuser destroying his mind and future.

Young people are not to blame for the problem they inherited. The drug epidemic began in the permissive era of the late sixties and early seventies. If we didn't know it then, we know it now; *Freedom is not free.* Responsibility, self-control, and self-sacrifice are necessary to maintain it. Our free society cannot survive if we sit idly by as our children unwarily enslave themselves. We must set limits and raise standards. Each of us must do our part.

The FDA Tobacco Markup Amendment Introduced by Senator Tom Coburn, M.D. at the Federal Level

The following is being offered as excellent information and resource material in order to defeat medical marijuana in Pennsylvania:

Hello Everyone!

I wanted to let you know that Sen. Coburn is offering an amendment during the FDA Tobacco markup this afternoon to subject any State-legalized marijuana to the same regulatory requirements and penalties as an FDA-approved drug, as well as apply the new tobacco regulations and user fees to marijuana intended to be consumed as a cigarette. Sen. Coburn will emphasize that State legalization of marijuana is illegal and undermines Federal authority. States cannot legalize a drug squarely under the jurisdiction of the FDA-a drug the agency has clearly stated is not FDA-approved because it has no accepted medical use. Subjecting marijuana to the tobacco regulations is particularly interesting, because distributors would have to pay user fees, which would mean turn themselves in for an illegal act.

Sen. Coburn offered a similar amendment to the 2007 FDA Revitalization Act in committee, which passed 11-9 with all of the present Republicans voting for it and 2 Democrats (Harkin and Bingaman) voting for it. Attached is the amendment and below find some talking points. Let me know if you have any questions or would like to discuss further.

Thanks!

Evan Feinberg

Coburn Amendment 6 -- Requires 'medical' marijuana products to be regulated in the same manner as other drugs marketed for medical purposes, and marijuana products intended to be consumed as a cigarette in the same manner as tobacco products.

S. 982 requires the FDA to regulate harmful tobacco products-cigarettes and smokeless tobacco. My amendment would ensure that State-legalized "medical" or even recreational marijuana would also be subject to the appropriate FDA regulations.

Marijuana is a Schedule I Controlled Substance, which means it is classified as "having a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use of the drug or other substance under medical supervision." The FDA has officially stated that, "Efforts that seek to bypass the FDA drug approval process would not serve the interests of public health.. FDA has not approved smoked marijuana for any condition or disease indication."

Yet thirteen states[1] have passed laws allowing cannabis to be sold as medication despite the fact that the drug has not been approved by FDA. As a result, manufacturers are exempt from the patient safety precautions that apply to all other drugs that are marketed for medical uses. This amendment would require those who produce, market or sell marijuana for so-called medical uses comply with the same rules that pharmaceutical manufacture are legally bound to follow.

This amendment would also require smoked marijuana to be subject to all the same safety regulations and requirements as tobacco products under this act. Smoked marijuana poses similar, yet more harmful effects as smoked tobacco products. There is little reason to exclude marijuana manufacturers from the regulations and user fees that tobacco companies must comply with to attempt to ensure safe use of their product.

'MEDICAL' MARIJUANA SHOULD NOT BE EXEMPT FROM THE RULES APPLIED TO OTHER DRUGS

This bill would amend the Federal Food, Drug, and Cosmetic Act to provide for the regulation of tobacco products by the FDA, including disclosure, annual registration, inspection, recordkeeping, and user fee requirements. The bill also allows the Secretary to require prior

approval of all label statements and to restrict the sale or distribution of tobacco products, including advertising and promotion, if the Secretary determines that such regulation would be appropriate for the protection of the public health.

Patients deserve to be fully informed about the dangers of a drug and the adverse events experienced by other patients. There is no logical reason why patients should be protected from misleading statements about one drug but not another.

If anyone truly believes that smoked marijuana is a legitimate medical therapy, they should support this amendment because it would treat the drug in the same manner as all other products sold with medical claims.

MARIJUANA AND TOBACCO POSE COMPARABLE HEALTH RISKS

There are striking similarities between the health risks of smoked marijuana and cigarettes, though smoking cannabis is a greater threat to an individual's health.

Marijuana smoke contains some of the same cancer-causing compounds as tobacco, sometimes in higher concentrations. Studies show that someone who smokes five joints per day may be taking in as many cancer-causing chemicals as someone who smokes a full pack of cigarettes every day. Tobacco smoke and marijuana smoke may work together to change the tissues lining the respiratory tract. Marijuana smoking could contribute to early development of head and neck cancer in some people.

People who smoke marijuana regularly may develop many of the same breathing problems that tobacco smokers have, such as daily cough and phlegm production, more frequent chest colds, a heightened risk of lung infections, and a greater tendency toward obstructed airways. Cancer of the respiratory tract and lungs may also be promoted by marijuana smoke, since it contains irritants and carcinogens. Marijuana smokers usually inhale more deeply and hold their breath longer, which increases the lungs' exposure to carcinogenic smoke. Thus, puff for puff, smoking marijuana may increase the risk of cancer more than smoking tobacco does.

According to a recent report, Marijuana smoke is actually more toxic than cigarettes. Researchers who compared marijuana smoke to tobacco smoke found that ammonia levels were 20 times higher in the marijuana smoke, and that hydrogen cyanide and nitrogen-related chemicals also were more prevalent in the marijuana smoke.

A 2007 study done by British researchers found that Smoking one cannabis joint is as harmful to a person's lungs as having up to five cigarettes. Those who smoked cannabis damaged both the lungs' small fine airways, used for transporting oxygen, and the large airways, which blocked air flow, the researchers said. It meant cannabis smokers complained of wheezing, coughing, and

chest tightness, the study by experts at the Medical Research Institute of New Zealand found.

Other studies have found that long-term marijuana smokers are prone to develop bullous lung disease at a much younger age than cigarette smokers, because they tend to inhale more deeply and hold hot smoke in their lungs up to four times longer. A January 2008 found that Marijuana smokers get bullous lung disease 20 years before tobacco smokers. Bullous lung disease is a condition where air trapped in the lungs causes obstruction to breathing and eventual destruction of the lungs.

A 2008 Johns Hopkins study found that withdrawal from heavy marijuana use is about as harsh for users as withdrawal from nicotine addiction is for tobacco users.

If this Committee believes that the FDA should regulate tobacco because of public health concerns, there is no doubt that the FDA should regulate a similar illegal product that poses an even greater threat to public health.

STATE APPROVED 'MEDICAL' MARIJUANA UNDERMINES FDA AUTHORITY AND DRUG SAFETY

All drugs bought, sold and prescribed in the U.S. must first undergo rigorous clinical trials and be proven to be safe and effective by the Food and Drug Administration (FDA) before they can be made legally available to patients. This process ensures patient safety, protects the public health and, in cases of injury, ensures accountability and liability.

Making any drug available without FDA review or proof of safety and effectiveness sets a dangerous precedent that threatens patient safety.

Smoked marijuana has never been approved for medical use by the FDA. For several years, in fact, FDA allowed a limited number of seriously ill patients to use smoked marijuana. The program was terminated in 1992 when the Public Health Service (PHS) stated there was no scientific evidence that the drug was assisting patients, and issued a warning that using smoked marijuana as a form of medical therapy may actually be harmful to some patients.

Like marijuana, other drugs in their raw form, such as tobacco and cocaine, contain beneficial ingredients. Many proponents of allowing marijuana to be available for patient use without FDA review and approval have advocated FDA regulation of tobacco as well as additional regulation of pharmaceuticals awaiting FDA approval. This contradiction is inconsistent and undermines the credibility and validity of both arguments.

Proponents of marijuana legalization-- for medical or other purposes-have bypassed the standard legal and scientific procedures required to determine a drug's safety and effectiveness.

If states are permitted to use political means rather than scientific standards to approve drugs and bypass FDA authority for one drug, why not others? What will stop a State from determining

their tobacco products will not be subject to FDA-regulations?

A vote against this amendment is essentially a vote to provide an exemption from FDA rules and regulations for all drugs and drug makers who can simply seek state level approval without undergoing the rigors of clinical trials or even having to prove safety or effectiveness.

'MEDICAL' MARIJUANA IS VIRTUALLY UNREGULATED

Unlike nearly every other product sold in the U.S. for human, or even animal, consumption, so-called 'medical' marijuana is virtually unregulated.

In recent years, the FDA has reviewed and approved drugs to treat dogs for obesity and car sickness. The agency is examining whether or not the butter flavoring of microwave popcorn poses any dangers and mulling which types of seafood can be labeled as "lobsters," according to news reports.

The Associated Press reported in May 2007 that a Las Vegas company selling an energy drink using the name "Cocaine," was sent a warning letter by the FDA and given 15 days to notify the agency of its plans to correct the violations of federal law. Otherwise, it can face seizure of its products, injunctions and possible criminal prosecution. While the "Cocaine" energy drink contains no actual cocaine, it is being marketed as "The Legal Alternative" to the illegal drug, according to its Web site. Its logo appears to be spelled out in a white powder that resembles the drug.

Regardless, the FDA said Redux Beverages LLC was illegally marketing the drink as both a street drug alternative and a dietary supplement, according to a warning letter dated April 4, 2007. The FDA cites as evidence the drink's own labeling and Web site, which include the statements "Speed in a Can," "Liquid Cocaine" and "Cocaine - Instant Rush," according to the letter.

Yet FDA has made no similar threats to the countless growers and sellers of 'medical' marijuana.

In June 2005, the *New York Times* published an expose on 'medical' marijuana in San Francisco:

"The best sellers at the Green Cross medical marijuana dispensary here are whipped up in the kitchen of Kevin Reed, the founder and president. Fresh-baked marijuana cakes. Marijuana cookies with Ghirardelli chocolate chips. Marijuana peanut butter, lollipops, peanut brittle and espresso truffles. Each comes packaged with a warning: 'Please keep out of the reach of children and pets.'

"Mr. Reed, 31, a former mobile home salesman from Alabama who moved here after being arrested twice for marijuana possession, said the warning was added to the sweets when a customer reported that 'their grandma ate one of them.'

"The Incredible Edibles, as the confections are called, account for 40 percent of sales at the Green

Cross, a thriving nonprofit organization in a neighborhood of hip bars, trendy restaurants and Victorian row houses. The 150 or so customers it serves each day can pay with Visa or MasterCard and need only a doctor's recommendation to gain entry.

"It has been nine years since voters in California passed the first state law allowing sick people to use marijuana for medical purposes. The measure passed in San Francisco with 78 percent of the vote, the largest percentage in the state. But the city, where dozens of dispensaries like the Green Cross, known as pot clubs, have sprouted, is now among many struggling with the excesses of the law. .

"Even in states where its use for medical purposes is legal, city officials, dispensary owners and medical marijuana advocates in San Francisco had begun questioning how much of the drug was enough.

"The San Francisco Board of Supervisors imposed a six-month moratorium on new dispensaries after health officials counted at least 43 unregulated facilities, including one in a building where formerly homeless people were receiving drug and alcohol abuse counseling. Even with the moratorium, there have been reports of new clubs setting up shop.

"'The absence of laws has allowed adverse opportunities to emerge,' said Supervisor Ross Mirkarimi, who proposed the moratorium.

"Capt. Rick Bruce of the San Francisco police said more marijuana was on the streets than at any other time in his 30 years with the department. Captain Bruce said that while there were many sick people who legitimately turned to the drug for treatment, countless dealers had used the dispensaries as a cover for illegal sales.

"'It's a huge scam,' said Captain Bruce, who heads the city's Bayview station, which covers some of the highest-crime neighborhoods. 'We see guys coming out of these places, and the only description I can come up with is that.... they are what you would call your traditional potheads; whether they have a medical condition beyond that is subject to debate.' .

"An estimated 100,000 people in California use the drug for medicinal purposes, far more than in any other state, according to the Drug Policy Alliance, a group that supports medical uses of marijuana. .

"Getting inside the dispensaries, many patients say, is not difficult. Under the state law, would-be marijuana users seeking relief from a range of ailments, from chronic pain or nausea to cancer or AIDS-related symptoms, must receive a doctor's recommendation, which is roughly the equivalent of a prescription for federally approved medicines. If their usual doctors are reluctant to make a referral, patients can turn to "compassionate physicians" who advertise their services in newspapers and on the Web.

"One of those physicians, Dr. R. Stephen Ellis, whose practice is explained on www.potdoc.com,

promises to refund examination fees if an appointment does not result in a recommendation. MediCann, a chain of 10 clinics in the state run by a Santa Cruz doctor, Jean Talleyrand, processes about 700 patients a week, with about three-quarters of them getting a recommendation, said a spokesman, Nicholas Jarrett. .

"Dr. Joshua Bamberger, the medical director for housing and urban health at the San Francisco Department of Public Health, said . the county had no ability under the law to control how much marijuana patients buy. . The county does not keep records of who has received a card or the name of the doctor who provided the recommendation, but it does number each card for tracking purposes.

"When some drug dealers are arrested, even with large quantities of marijuana, Captain Bruce said, many of them produce a medical marijuana card and insist they have done nothing wrong."

SMOKED MARIJUANA IS NOT 'MEDICAL' MARIJUANA

Marijuana is a Schedule I controlled substance, meaning that it has no commonly accepted medical use.

In considering potential medical uses of marijuana, it is important to distinguish between whole marijuana and pure tetrahydrocannabinol (THC) or other specific chemicals derived from cannabis.

Whole marijuana contains hundreds of chemicals, some of which are clearly harmful to health.

The Food and Drug Administration has approved THC, manufactured into a pill (marinol) that is taken by mouth-- not smoked-- to treat the nausea and vomiting that go along with certain cancer treatments and is available by prescription. Another chemical related to THC (nabilone) has also been approved for treating cancer patients who suffer nausea. The oral THC is also used to help AIDS patients eat more to keep up their weight.

Despite anecdotal claims, smoked marijuana has not been found to be safe or effective for treating any medical condition, primarily because its alleged therapeutic utility has yet to be sufficiently demonstrated in well-controlled clinical trials.

For several years, FDA allowed a limited number of seriously ill patients to use smoked

marijuana. The program was terminated in 1992 when the Public Health Service (PHS) stated there was no scientific evidence that the drug was assisting patients, and issued a warning that using smoked marijuana as a form of medical therapy may actually be harmful to some patients.

In 1997, the National Institutes for Health (NIH) convened an Ad Hoc Group of Experts, which concluded that scientific evidence was insufficient to definitively assess marijuana's therapeutic potential and advised that the traditional scientific process should be followed to evaluate the drug's use for certain disorders. In its 1999 report *Marijuana and Medicine: Assessing the Science Base*, the Institute of Medicine (IOM) concluded that any therapeutic effects of smoking marijuana were modest. IOM recommended marijuana's active components should be tested rigorously in controlled clinical trials.

According to the Food and Drug Administration, "In 2001, [the Department of Health and Human Services (HHS or DHHS)] completed an extensive analysis in response to a request to reschedule marijuana to a less restrictive schedule. After looking at all the relevant data on marijuana, HHS concluded that the weight of the scientific evidence supported the findings that marijuana should continue to be scheduled as Schedule I because it has a high potential for abuse, no currently accepted medical use in the United States, and a lack of accepted evidence about the safety of using marijuana under medical supervision."

On April 20, 2006, FDA released a statement noting "a past evaluation by several Department of Health and Human Services (HHS) agencies, including the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA) and National Institute for Drug Abuse (NIDA), concluded that no sound scientific studies supported medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use. There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana."

SMOKING MARIJUANA IS HARMFUL TO PATIENTS' HEALTH

While all of the long-term effects of marijuana use are not yet known, there are studies showing serious health concerns, including those analogous to smoked tobacco already detailed. The volume of literature detailing the harmful effects of whole, smoked marijuana, in fact, continues to grow. Marijuana can be harmful in a number of ways, through both immediate effects and damage to health over time.

Marijuana hinders the user's short-term memory, and may cause trouble for a user in handling complex tasks. With the use of more potent varieties of marijuana, even simple tasks can be difficult. Because of the drug's effects on perceptions and reaction time, users could be involved in auto crashes.

Under the influence of marijuana, students may find it hard to study and learn. A new study presented at a conference on global health economics in San Francisco earlier this year found that

high school students who smoke marijuana are likely to see lower math scores, and ultimately, lower wages, than peers.

The immune system protects the body from many agents that cause disease. Both animal and human studies have shown that marijuana impairs the ability of T-cells in the lungs' immune defense system to fight off some infections.

Scientists have found that marijuana smokers studied have more sick days and more doctor visits for respiratory problems and other types of illness than did a similar group who did not smoke.

Findings show that the regular use of marijuana or THC may play a role in cancer and problems in the respiratory, and immune systems.

Marijuana abuse is also linked to social problems. "Recent research has indicated that for some people there is a correlation between frequent marijuana use and aggressive or violent behavior," according to the National Crime Prevention Council.

Drug users also may become involved in risky sexual behavior. There is a strong link between drug abuse and the spread of HIV.

According to the National Institute on Drug Abuse (NIDA), "High doses of marijuana can induce psychosis (disturbed perceptions and thoughts), and marijuana use can worsen psychotic symptoms in people who have schizophrenia. There is also evidence of increased rates of depression, anxiety, and suicidal thinking in chronic marijuana users."

"Marijuana use may trigger panic attacks, paranoia, even psychoses, especially if you suffering from anxiety, depression or having thinking problems," according to the American Psychiatric Association. A majority of patients who smoke marijuana do so for mental health reasons according to a recent study. Patients suffering from mental health problems that have turned to marijuana as a form of medicine are, however, worsening both their mental and physical health while forgoing real treatment that could improve their lives.

ACCEPTED MEDICAL ALTERNATIVES EXIST TO ADDRESS HEALTH PROBLEMS MARIJUANA IS BEING PROMOTED TO TREAT

Proponents of marijuana claim patients suffering from weight loss or AIDS wasting can benefit from smoking marijuana. This claim has never been substantiated by the FDA and smoking marijuana has never been deemed safe or effective for these or other medical conditions. Legal alternatives that have been evaluated and approved as safe and effective to treat these conditions do, however, exist.

Serono Inc. received FDA approval for Serostim, which treats wasting in AIDS patients. The drug has been on the market since 1996 under the FDA's orphan drug program. Serono said it got final approval after confirmatory multi-center, placebo-controlled study substantiated previous

findings of increased lean body mass and improvement in physical endurance in AIDS patients. Megestrol acetate (Megace) is also approved by the FDA for the management of anorexia, cachexia and unexplained weight loss in patients with AIDS. In clinical trials, Megestrol led to increased appetite and weight gain. AIDS patients also reported improvement in their sense of well being.

HIV-associated wasting is a chronically debilitating and potentially life- threatening condition. It is a metabolic disorder that causes the body to use vital muscle and organ tissue, which is critical for survival, for energy instead of primarily using the body's stored fat. Loss of lean body mass, which consists of muscle tissue, important body organ tissue and blood cells, can lead to increased risk of opportunistic infections, illness, and extreme fatigue and can profoundly diminish a person's quality of life.

Dronabinol, a synthetic version of THC, may reduce agitation and lead to weight gain in patients with Alzheimer disease, according to data presented at the annual meeting of the International Psychogeriatric Association.

"Our research suggests dronabinol may reduce agitation and improve appetite in patients with Alzheimer's disease, when traditional therapies are not successful," said Joshua Shua-Haim, MD, lead investigator in the study and medical director of the Meridian Institute for Aging, a continuum of senior health programs and services in Central New Jersey affiliated with Meridian Health System. "In the study, dronabinol appeared to be safe and effective for these patients."

Other drugs approved by the FDA used alone or in combination to prevent nausea and vomiting after cancer chemotherapy include: Ondansetron, metoclopramide (reglan, and others), cortico-steriods, prochlorperazine (Compazine, and others), lorazepam (Ativan), granisetron and aprepitant (Emend).

"MEDICAL" MARIJUANA IS BEING LARGELY USED FOR "RECREATIONAL" OR EMOTIONAL REASONS RATHER THAN FOR MEDICAL PURPOSES

Data from a survey of patients at California's San Mateo Medical Center presented this year at the American Psychiatric Association conference revealed that one-third of HIV patients who smoked "medical" marijuana do so for "recreational" reasons.

"We expected to see people smoking marijuana to alleviate nausea, pain and to increase their appetite-- all the reasons that are commonly cited," said Diane Prentiss, a research epidemiologist with the Medical Center. "We were surprised that 57 percent say they smoked to relieve anxiety or depression."

Ironically and tragically, patients suffering from mental health problems that have turned to marijuana believing it to be a legitimate form of medicine are actually worsening both their mental and physical health while forgoing real treatment that could improve their lives. The

National Institute on Drug Abuse (NIDA) has found that "High doses of marijuana can induce psychosis (disturbed perceptions and thoughts), and marijuana use can worsen psychotic symptoms in people who have schizophrenia. There is also evidence of increased rates of depression, anxiety, and suicidal thinking in chronic marijuana users." "Marijuana use may trigger panic attacks, paranoia, even psychoses, especially if you suffering from anxiety, depression or having thinking problems," according to the American Psychiatric Association.

OTHER HARMFUL SUBSTANCES HAVE BENEFICIAL COMPONENTS BUT ARE NOT ADVOCATED FOR MEDICAL USE IN THEIR RAW FORM

Like marijuana, there are other drugs and substances that are harmful but have properties that can if extracted can have beneficial effects depending upon the circumstances under which they are taken. Examples include nicotine, cocaine, amphetamine, opiates, benzodiazepines, barbiturates, and many others.

First, it is important to note that at this time, there is insufficient scientific data to conclude that smoked marijuana has therapeutic benefits, or that any benefits it may have will outweigh the risks of harm due to the inhalation of the marijuana smoke.

NIH conducted a workshop in 1997 and the Institute of Medicine (IOM) did an exhaustive 18-month study that was released in 1999 (commissioned by the Office of National Drug Control Policy) of the extant research on the medical uses of marijuana and its active constituents, primarily tetrahydrocannabinol (THC). Both reports found that there was insufficient data to determine marijuana's therapeutic utility, but that more research is needed to determine the benefits of marijuana or related compounds for certain conditions or diseases including pain, neurological and movement disorders, nausea in patients who are undergoing chemotherapy for cancer, and loss of appetite and weight (cachexia) related to AIDS. Dronabinol, an oral form of THC, currently has FDA approval for use is the latter two conditions.

- Prescription medicines that are clearly beneficial can nevertheless be harmful if abused. When used for legitimate medical purposes and managed by properly trained clinicians, medications such as ritalin, methadone, oxycontin, morphine, and countless others, improve the quality of life for millions of Americans with debilitating diseases and conditions. All medications can cause side effects and when intentionally or carelessly misused they can pose significant risks.

- Nicotine, the main addictive component of tobacco, also has beneficial properties when used in replacement products, such as the therapeutic patch, gum, spray and inhalers, to assist with smoking cessation.

- Cocaine has legitimate medical use in eye and nasal surgeries.

- Amphetamines and other stimulant drugs can be useful in the treatment of ADD (attention deficit disorder) or ADHD (attention deficit hyperactivity disorder) and narcolepsy.

- Some cancers Chemotherapeutic drugs have been isolated from dangerous sources. Paclitaxel (taxol) was initially isolated from a poisonous plant pacific yew (*Taxus brevifolia* Nutt.) and was later find in other *Taxus* plants. Vinblastine, Vincristine and other vinca alkaloids have been extracted from *Vinca rosea* L.

- Opioids Analgesics such as Morphine (and analogs) from *Papaver somniferum* L.

- The antimalarial agent artemisinin (Qing-hao-su) from *Artemisia annua* L.

ERRONEOUSLY PROMOTING MARIJUANA AS MEDICINE MAY ENCOURAGE DRUG ABUSE

As of 2002, around 21 percent of teens and 54 percent of young people aged 18 to 25 said they had used marijuana at least once. Marijuana remains the most commonly used illegal drug, with 14.6 million users, according to new data from the National Survey on Drug Use and Health prepared by the Substance Abuse and Mental Health Services Administration (SAMHSA).

Giving the false impression that smoking marijuana has been approved as being safe and effective may be contributing to its abuse, especially among young people. More young people are now in treatment for marijuana dependency than for alcohol or for all other illegal drugs combined. Of all teenagers in drug treatment, about 60 percent have a primary marijuana diagnosis. The average age of initiation for marijuana use generally has been getting younger. In 2001, 84 percent reported first using marijuana between the ages of 12 and 17. A 1999 survey found that 57 percent of kids age 12-17 agreed that marijuana would be "fairly easy" or "very easy" to obtain and was available from a wide variety of sources.

Additionally, a new report from the National Center on Addiction and Substance Abuse (CASA) confirms recent federal reports claiming that marijuana has become more potent over the past decade and a half, adding that treatment admissions for marijuana problems increased dramatically during the same time frame.

The report, dubbed "Non-Medical Marijuana III: Rite of Passage or Russian Roulette?," cites a 175-percent increase in the THC content of marijuana between 1992 and 2006, alongside a 492-percent rise in teen treatment admissions involving marijuana abuse or dependence and a 188-percent increase in treatment admissions where marijuana was named as the primary drug of abuse.

"The message for teens is clear -- today's pernicious pot is not your parent's pot," said CASA

chairman and CEO Joseph A. Califano, Jr. "

[1] Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont and Washington

Subject: FROM DAVE EVANS - CALIFORNIA DECLARES THAT SMOKING POT CAUSES CANCER

Dear Friends:

A few days ago, the State of California Office of Environmental Health Hazard Assessment declared that marijuana smoke causes cancer. This was after an extensive review of over 30 scientific papers and a hearing. The state agency found marijuana smoke contains 33 of the same harmful chemicals as tobacco smoke. Their statement is attached.

Smoking marijuana is not medicine. It will make sick people sicker and healthy people sick. It may cause Kaposi's sarcoma in people with AIDS (see below link to a study from Harvard Medical School). This is a fatal form of cancer. This is not compassionate.

No FDA approved medicines are smoked. It is difficult to administer safe, regulated dosages of medicines in smoked form. Furthermore, the harmful chemicals and carcinogens that are byproducts of smoking create entirely new health problems. [FN1]
Internet links to studies are below.

The respiratory difficulties associated with marijuana use preclude the inhaled route of administration as a medicine. Smoked marijuana is associated with higher concentrations of tar, carbon monoxide, and carcinogens than even cigarette smoke.[FN2]

Marijuana adversely impairs some aspects of lung function, causes abnormalities in the cells lining the airways of the upper and lower respiratory tract and in the airspaces deep within the lung, and it causes cancer.[FN3].

In addition to these cellular abnormalities and consequences, contaminants of marijuana smoke are known to include certain forms of bacteria and fungi. Those at particular risk for the development of disease and infection when these substances are inhaled, are those users with impaired immunity such as those with AIDS. [FN4]

Smoking marijuana can cause intoxication, precipitation of anxiety or acute psychotic reactions, orthostatic hypotension and bronchial inflammation. For a drug to be acceptable, its beneficial results must outweigh the adverse effects, especially when the claim is that it can be used repeatedly for symptomatic relief of chronic disorders.[FN5]

In recent years there has been a great public effort to curtail tobacco because of its effects on health yet the advocates of legalization promote smoking marijuana. Yet, a recent study shows that marijuana smoke has ammonia levels 20 times higher than tobacco smoke. Marijuana has hydrogen cyanide, nitric oxide, and aromatic amines at 3-5 times higher than tobacco smoke. [FN6]

Another study shows that that marijuana smokers face rapid lung destruction - as much as 20 years ahead of tobacco smokers. [FN7]

A just released study shows that marijuana damages DNA and that it is toxic to the body. [FN8]

LINKS TO STUDIES

Marijuana Damages DNA And May Cause Cancer, New Test Reveals

http://www.sciencedaily.com/releases/2009/06/090615095940.htm

Marijuana Smoke Contains Higher Levels Of Certain Toxins Than Tobacco Smoke

http://www.sciencedaily.com/releases/2007/12/071217110328.htm

Marijuana Smokers Face Rapid Lung Destruction -- As Much As 20 Years Ahead Of Tobacco Smokers

http://www.sciencedaily.com/releases/2008/01/080123104017.htm

Impact On Lungs Of One Cannabis Joint Equal To Up To Five Cigarettes

http://www.sciencedaily.com/releases/2007/07/070731085550.htm

Marijuana Component Opens The Door For Virus That Causes Kaposi's Sarcoma (link to Harvard study)

http://www.sciencedaily.com/releases/2007/08/070801112156.htm

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[FN5] "Smoked Marijuana as Medicine: Not Much Future," Clinical Pharmacology & Therapeutics (2008), H Kalant, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada

[FN6] Marijuana Smoke Contains Higher Levels of Certain Toxins Than Tobacco Smoke, Science Daily, December 18, 2007

[FN7] Marijuana Smokers Face Rapid Lung Destruction - As Much as 20 Years Ahead of Tobacco Smokers, Science Daily, January 27, 2008

[FN8] Marijuana Damages DNA and May Cause Cancer, New Test Reveals, Science Daily, June 15, 2009

From: <AmerCares@aol.com>
To: <ktrue@pahousegop.com>
Date: 11/25/2009 7:52 AM
Subject: Fwd: FUNCTIONS OF THE U.S. ATTORNEY GENERAL
Attachments: Fwd: FUNCTIONS OF THE U.S. ATTORNEY GENERAL

Dear Representative True,

I would like to submit the following memo for distribution to the appropriate committee that is considering the bill on "medical marijuana."

TO: THE HONORABLE ERIC HOLDER, U.S. ATTORNEY GENERAL

FROM: JOYCE NALEPKA (PRESIDENT OF AMERICACARES PH: 301-681-7861)

RE: WHAT WILL YOU ANSWER WHEN THEY ASK?

YOU KNEW MARIJUANA WAS HARMFUL TO EVERY MAJOR BODY SYSTEM?

YOU KNEW MARIJUANA NEGATIVELY AFFECTS THE BRAIN, LUNGS, REPRODUCTIVE AND IMMUNE SYSTEMS?

YOU KNEW MARIJUANA COLLECTS IN THE FATTY TISSUES OF THE BRAIN AND OTHER ORGANS?

YOU KNEW MARIJUANA WAS RELATED TO DEPRESSION, PSYCHOSIS, AND IN MORE THAN 15 NATIONS, IT HAS BEEN SHOWN THAT "SKUNK" THE MORE POTENT MARIJUANA IS LINKED TO SCHIZOPHRENIA?

THAT FORMER HHS SECRETARY, JOSEPH CALIFANO, COLUMBIA UNIVERSITY REPORTED THAT MARIJUANA IS NOW 175 % MORE POTENT THAN IT WAS IN THE 70'S?

YOU HAVE HAD MOST OF THIS INFORMATION SINCE 1974 WHEN FORMER SENATOR JAMES O. EASTLAND CONDUCTED FIVE DAYS OF HEARINGS ON THE HEALTH EFFECTS OF MARIJUANA?

AND SHOULD HAVE LEARNED IT AGAIN IN 1980 WHEN NOW VICE PRESIDENT BIDEN AND DECEASED SENATOR CHARLES MATHIAS HELD TWO DAYS OF HEARINGS WHERE PARENTS FROM TEN STATES TESTIFIED TO THE MEDICAL, SCIENTIFIC AND PERFORMANCE EFFECTS OF MARIJUANA.

AT THE VARIOUS HEARINGS, DOZENS OF RESEARCHERS, TREATMENT EXPERTS, EDUCATORS AND PARENTS TESTIFIED TO THE HORROR STORIES CAUSED BY MARIJUANA.

THAT THE UNITED KINGDOM IS NOW WORKING TO RECRIMINALIZE MARIJUANA AFTER REALIZING THEY HAD OVER 250,000 SCHIZOPHRENICS IN THEIR COUNTRY.

THAT THE MAJOR UK NEWSPAPER RAN A 4-PAGE APOLOGY FOR THEIR PART IN PRESSURING THE UK TO WEAKEN THEIR LAWS. OR, THAT THE PAPER, "THE INDEPENDENT" WROTE, "IF ONLY WE HAD KNOWN THEN WHAT WE KNOW NOW---WE WOULD NEVER HAVE PARTICIPATED. VIEW ARTICLE AT: WWW.UKCANNABISANAPOLOGY

THAT OUR OWN CENTERS FOR DISEASE CONTROL'S MOST RECENT FIGURES INDICATE AMERICA IS LOSING OVER 3,000 YOUNG PEOPLE PER MONTH--ALMOST AS MANY AS HAVE BEEN LOST IN THE RECENT WARS.

THAT THE ONLY AGENCY THAT CAN APPROVE MEDICINE IS THE U.S. FOOD AND DRUG ADMINISTRATION WHICH STATES:

"FDA HAS NOT APPROVED SMOKED MARIJUANA FOR ANY CONDITION OR DISEASE INDICATION."

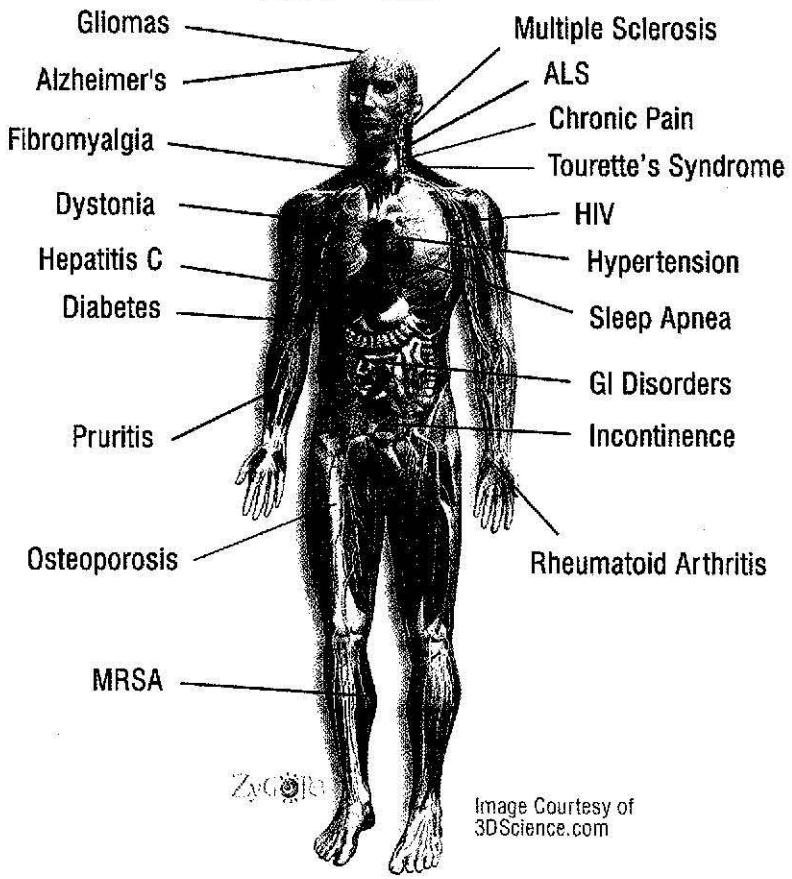
MEDICINE----I DON'T THINK SO.

WHY DIDN'T YOU CONDUCT AN OUT-OUT CAMPAIGN TO TELL ALL AMERICA AND THE WORLD? WHAT WILL YOU SAY?

Emerging Clinical Applications for Cannabis and Cannabinoids:

A Review of the Recent Scientific Literature

2000 – 2009



NORML Foundation
Washington, DC
Paul Armentano
Deputy Director

"There can be no doubt that a plant that has been in partnership with man since the beginnings of agricultural efforts, that has served man in so many ways, and that, under the searchlight of modern chemical study, has yielded many new and interesting compounds will continue to be a part of man's economy. It would be a luxury that we could ill afford if we allow prejudices, resulting from abuse of Cannabis, to deter scientists from learning as much as possible about this ancient and mysterious plant."

-Richard Evans Schultes (1973)

Table of Contents

Introduction

Despite the ongoing political debate regarding the legality of medicinal marijuana, clinical investigations of the therapeutic use of cannabinoids are now more prevalent than at any time in history. A search of the National Library of Medicine's PubMed website quantifies this fact. A keyword search using the terms "cannabis, 1996" (the year California voters became the first of 13 states to allow for the drug's medical use under state law) reveals just 258 scientific journal articles published on the subject during that year. Perform this same search for the year 2008, and one will find over 2,100 published scientific studies.

While much of the renewed interest in cannabinoid therapeutics is a result of the discovery of the endocannabinoid regulatory system, some of this increased attention is also due to the growing body of testimonials from medicinal cannabis patients and their physicians. Nevertheless, despite this influx of anecdotal reports, much of the modern investigation of medicinal cannabis remains limited to preclinical (animal) studies of individual cannabinoids (e.g. THC or cannabidiol) and/or synthetic cannabinoid agonists (e.g., dronabinol or WIN 55,212-2) rather than clinical trial investigations involving whole plant material. Predictably, because of the US government's strong

public policy stance against any use of cannabis, the bulk of this modern cannabinoid research is taking place outside the United States.

As clinical research into the therapeutic value of cannabinoids has proliferated – there are now more than 17,000 published papers in the scientific literature analyzing marijuana and its constituents — so too has investigators' understanding of cannabis' remarkable capability to combat disease. Whereas researchers in the 1970s, 80s, and 90s primarily assessed cannabis' ability to temporarily alleviate various disease symptoms — such as the nausea associated with cancer chemotherapy — scientists today are exploring the potential role of cannabinoids to modify disease.

Of particular interest, scientists are investigating cannabinoids' capacity to moderate autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, as well as their role in the treatment of neurological disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (a.k.a. Lou Gehrig's disease.)

Investigators are also studying the anti-cancer activities of cannabis, as a growing body of preclinical and clinical data concludes that cannabinoids can reduce the spread of specific

cancer cells via apoptosis (programmed cell death) and by the inhibition of angiogenesis (the formation of new blood vessels). Arguably, these latter trends represent far broader and more significant applications for cannabinoid therapeutics than researchers could have imagined some thirty or even twenty years ago.

THE SAFETY PROFILE OF MEDICAL CANNABIS

Cannabinoids have a remarkable safety record, particularly when compared to other therapeutically active substances. Most significantly, the consumption of marijuana – regardless of quantity or potency -- cannot induce a fatal overdose. According to a 1995 review prepared for the World Health Organization, "There are no recorded cases of overdose fatalities attributed to cannabis, and the estimated lethal dose for humans extrapolated from animal studies is so high that it cannot be achieved by ... users."

In 2008, investigators at McGill University Health Centre and McGill University in Montreal and the University of British Columbia in Vancouver reviewed 23 clinical investigations of medicinal cannabinoid drugs (typically oral THC or liquid cannabis extracts) and eight observational studies conducted between 1966 and 2007. Investigators "did not find a higher incidence rate of serious

adverse events associated with medical cannabinoid use" compared to non-using controls over these three decades.

That said, cannabis should not necessarily be viewed as a 'harmless' substance. Its active constituents may produce a variety of physiological and euphoric effects. As a result, there may be some populations that are susceptible to increased risks from the use of cannabis, such as adolescents, pregnant or nursing mothers, and patients who have a family history of mental illness. Patients with Hepatitis C, decreased lung function (such as chronic obstructive pulmonary disease), or who have a history of heart disease or stroke may also be at a greater risk of experiencing adverse side effects from marijuana. As with any medication, patients should consult thoroughly with their physician before deciding whether the medicinal use of cannabis is safe and appropriate.

HOW TO USE THIS REPORT

As states continue to approve legislation enabling the physician-supervised use of medicinal marijuana, more patients with varying disease types are exploring the use of therapeutic cannabis. Many of these patients and their physicians are now discussing this issue for the first time, and are seeking guidance on whether the therapeutic use of

cannabis may or may not be advisable. This report seeks to provide this guidance by summarizing the most recently published scientific research (2000-2009) on the therapeutic use of cannabis and cannabinoids for 19 clinical indications:

* Alzheimer's disease
* Amyotrophic lateral sclerosis
* Chronic Pain
* Diabetes mellitus
* Dystonia
* Fibromyalgia
* Gastrointestinal disorders
* Gliomas
* Hepatitis C
* Human Immunodeficiency Virus
* Hypertension
* Incontinence
* Methicillin-resistant Staphyloccus aureus (MRSA)
* Multiple sclerosis
* Osteoporosis
* Pruritis
* Rheumatoid arthritis
* Sleep apnea
* Tourette's syndrome

In some of these cases, modern science is now affirming longtime anecdotal reports of medicinal cannabis users (e.g., the use of cannabis to alleviate GI disorders). In other cases, this research is

highlighting entirely new potential clinical utilities for cannabinoids (e.g., the use of cannabinoids to modify the progression of diabetes.)

The conditions profiled in this report were chosen because patients frequently inquire about the therapeutic use of cannabis to treat these disorders. In addition, many of the indications included in this report may be moderated by cannabis therapy. In several cases, preclinical data and clinical indicates that cannabinoids may halt the progression of these diseases in a more efficacious manner than available pharmaceuticals. In virtually all cases, this report is the most thorough and comprehensive review of the recent scientific literature regarding the therapeutic use of cannabis and cannabinoids.

For patients and their physicians, let this report serve as a primer for those who are considering using or recommending medicinal cannabis. For others, let this report serve as an introduction to the broad range of emerging clinical applications for cannabis and its various compounds.

Paul Armentano
Deputy Director
NORML | NORML Foundation
Washington, DC
January 15, 2009

* The author would like to acknowledge Drs. Dale Gieringer, Gregory Carter, Steven Karch, and Mitch Earleywine, as well as Bernard Ellis, MPH, NORML interns John Lucy, Christopher Rasmussen, and Rita Bowles, for providing research assistance for this report. The NORML Foundation would also like to acknowledge Dale Gieringer, Paul Kuhn, and Richard Wolfe for their financial contributions toward the publication of this report.

** Important and timely publications such as this are only made possible when concerned citizens become involved with NORML. For more information on joining NORML or making a donation, please visit: http://www.norml.org/join. Tax-deductible donations in support of NORML's public education campaigns should be made payable to the NORML Foundation.

Foreword

Gregory T. Carter, MD

Department of Rehabilitation Medicine
University of Washington School of Medicine

Marijuana is a colloquial term used to refer to the dried flowers of the female *Cannabis Sativa* and *Cannabis Indica* plants. Marijuana, or cannabis, as it is more appropriately called, has been part of humanity's medicine chest for almost as long as history has been recorded.

All forms of cannabis plants are quite complex, containing over 400 chemicals. Approximately 60 of these chemicals are classified as cannabinoids. Among the most psychoactive of the cannabinoids is delta-9-tetrahydrocannabinol (THC), the active ingredient in the prescription medications dronabinol (Marinol) and naboline (Cesamet). Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which are non-psychoactive but possess distinct pharmacological effects.

Cannabis was formally introduced to the United States Pharmacopoeia (USP) in 1854, though written references regarding the plant's therapeutic use date back as far as 2800 B.C. By 1900, cannabis

was the third leading active ingredient, behind alcohol and opiates, in patent medicines for sale in America. However, following the Mexican Revolution of 1910, Mexican immigrants flooded into the United States, introducing to American culture the recreational use of marijuana. Anti-drug campaigners warned against the encroaching, so-called "Marijuana Menace," and alleged that the drug's use was responsible for a wave of serious, violent criminal activity. In 1937, after testimony from Harry Anslinger -- a strong opponent of marijuana and head of the Federal Bureau of Narcotics in the 1930s -- and against the advice of the American Medical Association, the Marijuana Tax Act was pushed through Congress, effectively outlawing all possession and use of the drug.

At the time of the law's passage, there were no fewer than 28 patented medicines containing cannabis available in American drug stores with a physician's prescription. These cannabis-based medicines were produced by reputable drug companies like Squibb, Merck, and Eli Lily, and were used safely by tens of thousands of American citizens. The enactment of the Marijuana Tax Act abruptly ended the production and use of medicinal cannabis in the United States, and by 1942 cannabis was officially removed from the *Physician's Desk Reference.*

Fortunately, over the past few decades there has been a significant rebirth of interest in the viable medicinal uses of cannabis. Much of the renewed interest in cannabis as a medicine lies not only in the drug's effectiveness, but also because of its remarkably low toxicity. Lethal doses in humans have not been described. This degree of safety is very rare among modern medicines, including most over-the-counter medications. As a result, the National Institutes of Health (NIH), the National Academy of Sciences Institute of Medicine, and even the US Food and Drug Administration have all issued statements calling for further investigation into the therapeutic use of cannabis and cannabinoids.

The discovery of an endogenous cannabinoid system, with specific receptors and ligands, has progressed our understanding of the therapeutic actions of cannabis from folklore to valid science. It now appears that the cannabinoid system evolved with our species and is intricately involved in normal human physiology -- specifically in the control of movement, pain, reproduction, memory, and appetite, among other biological functions. In addition, the prevalence of cannabinoid receptors in the brain and peripheral tissues suggests that the cannabinoid system represents a previously unrecognized ubiquitous network in the nervous system.

Cannabinoid receptor sites are now known to exist in the nervous systems of all animals more advanced than hydra and mollusks. This is a result of at least 500 million years of evolution. The human body's neurological, circulatory, endocrine, digestive, and musculoskeletal systems have now all been shown to possess cannabinoid receptor sites. Indeed, even cartilage tissue has cannabinoid receptors, which makes cannabis a prime therapeutic agent to treat osteoarthritis. Cannabinoids have been shown to produce an anti-inflammatory effect by inhibiting the production and action of tumor necrosis factor (TNF) and other acute phase cytokines, which also makes them ideal compounds to treat the autoimmune forms of arthritis. It is now suggested by some researchers that these widely spread cannabinoid receptor systems are the mechanisms by which the body maintains homeostasis (the regulation of cell function), allowing the body's tissues to communicate with one another in this intricate cellular dance we call "life." With this knowledge of the widespread action of cannabinoids within all these bodily systems, it becomes much more easy to conceptualize how the various forms of cannabinoids might have a potentially therapeutic effect on diseases ranging from osteoarthritis to amyotrophic lateral sclerosis (ALS).

Another one of the exciting therapeutic areas that cannabis may impact is chronic pain. Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids (anandamide) and synthetic cannabinoids (methanandamide). Ideally, cannabinoids could be used alone or in conjunction with opioids to treat people with chronic pain, improve their quality of life, and allow them to return to being a productive citizen.

When discussing the therapeutic use of cannabis and cannabinoids, opponents inevitably respond that patients should not smoke their medicine. Patients no longer have to. Medicinal cannabis patients who desire the rapid onset of action associated with inhalation, but who are concerned about the potential harms of noxious smoke can dramatically cut down on their intake of carcinogenic compounds by engaging in vaporization rather than smoking. Cannabis vaporization limits respiratory toxins by heating cannabis to a temperature where cannabinoid vapors form (typically around 180-190 degrees Celsius), but below the point of combustion where noxious smoke and associated toxins (e.g., carcinogenic hydrocarbons) are produced (near 230

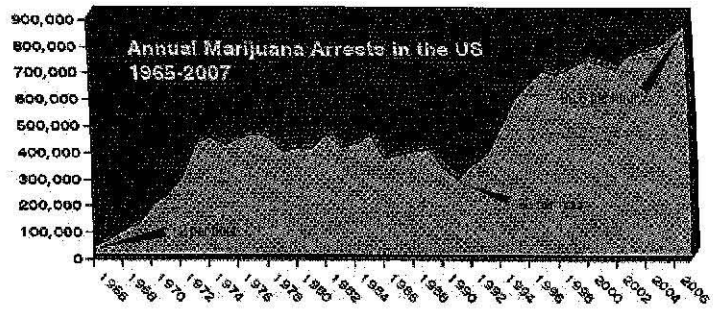
degrees Celsius). This eliminates the inhalation of any particulate matter and removes the health hazards of smoking. In clinical trials, vaporization has been shown to safely and effectively deliver pharmacologically active, aerosolized cannabinoids deeply into the lungs, where the rich vascular bed will rapidly deliver them to tissues throughout the body.

The following report summarizes the most recently published scientific research on the therapeutic use of cannabis and cannabinoids for more than a dozen diseases, including Alzheimer's, amyotrophic lateral sclerosis, diabetes, hepatitis C, multiple sclerosis, rheumatoid arthritis, and Tourette's syndrome. It is my hope that readers of this report will come away with a fair and balanced view of cannabis -- a view that is substantiated by scientific studies and not by anecdotal opinion or paranoia. Cannabis is neither a miracle compound nor the answer to everyone's ills. However, it does appear to have remarkable therapeutic benefits that are there for the taking if the governmental barriers for more intensive scientific study are removed.

The cannabis plant does not warrant the tremendous legal and societal commotion that has occurred over it. Over the past 30 years, the United States has spent billions in an effort to stem the use

of illicit drugs, particularly marijuana, with limited success. Many very ill people have had to fight long court battles to defend themselves for the use of a compound that has helped them. Rational minds need to take over the war on drugs, separating myth from fact, right from wrong, and responsible, medicinal use from other less compelling behavior.

The medicinal marijuana user should not be considered a criminal in any state. Most major medical groups, including the Institute of Medicine, agree that cannabis is a compound with significant therapeutic potential whose "adverse effects ... are within the range of effects tolerated for other medications." Over a decade ago, the Drug Enforcement Administration (DEA) studied the medicinal properties of cannabis. After considerable study, DEA Administrative Law Judge Francis L. Young concluded: "The evidence clearly shows that marijuana is capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision. ... It would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance."



Despite this conclusion, over a decade later the DEA and the rest of the federal government persist in their policy of total prohibition. Nevertheless, the scientific process continues to evaluate the therapeutic effects of cannabis through ongoing research and assessment of available data. With regard to the medicinal use of cannabis, our legal system should take a similar approach, using science and logic as the basis of policy making rather than relying on political rhetoric and false perceptions regarding the alleged harmful effects of recreational marijuana use.

Alzheimer's Disease

Alzheimer's disease (AD) is a neurological disorder of unknown origin that is characterized by a progressive loss of memory and learned behavior. Patients with Alzheimer's are also likely to experience depression, agitation, and appetite loss, among other symptoms. Over 4.5 million Americans are estimated to be afflicted with the disease. No approved treatments or medications are available to stop the progression of AD, and few pharmaceuticals have been FDA-approved to treat symptoms of the disease.

A review of the recent scientific literature indicates that cannabinoid therapy may provide symptomatic relief to patients afflicted with AD while also moderating the progression of the disease.

Writing in the February 2005 issue of the *Journal of Neuroscience*, investigators at Madrid's Complutense University and the Cajal Institute in Spain reported that the intracerebroventricular administration of the synthetic cannabinoid WIN 55,212-2 prevented cognitive impairment and decreased neurotoxicity in rats injected with amyloid-beta peptide (a protein believed to induce Alzheimer's). Additional cannabinoids were also found to reduce the inflammation associated with

Alzheimer's disease in human brain tissue in culture. "Our results indicate that ... cannabinoids succeed in preventing the neurodegenerative process occurring in the disease," investigators concluded.[1]

Investigators at The Scripps Research Institute in California in 2006 reported that THC inhibits the enzyme responsible for the aggregation of amyloid plaque — the primary marker for Alzheimer's disease — in a manner "considerably superior" to approved Alzheimer's drugs such as donepezil and tacrine. "Our results provide a mechanism whereby the THC molecule can directly impact Alzheimer's disease pathology," researchers concluded. "THC and its analogues may provide an improved therapeutic [option] for Alzheimer's disease [by]... simultaneously treating both the symptoms and the progression of [the] disease."[2]

Most recently, investigators at Ohio State University, Department of Psychology and Neuroscience, reported that older rats administered daily doses of WIN 55,212-2 for a period of three weeks performed significantly better than non-treated controls on a water-maze memory test. Writing in the journal *Neuroscience* in 2007, researchers reported that rats treated with the compound experienced a 50 percent improvement

in memory and a 40 to 50 percent reduction in inflammation compared to controls.[3]

Previous preclinical studies have demonstrated that cannabinoids can prevent cell death by anti-oxidation.[4] Some experts believe that cannabinoids' neuroprotective properties could also play a role in moderating AD.[5] Writing in the September 2007 issue of the *British Journal of Pharmacology*, investigators at Ireland's Trinity College Institute of Neuroscience concluded, "[C]annabinoids offer a multi-faceted approach for the treatment of Alzheimer's disease by providing neuroprotection and reducing neuroinflammation, whilst simultaneously supporting the brain's intrinsic repair mechanisms by augmenting neurotrophin expression and enhancing neurogenesis. ... Manipulation of the cannabinoid pathway offers a pharmacological approach for the treatment of AD that may be efficacious than current treatment regimens."[6]

In addition to potentially modifying the progression of AD, clinical trials also indicate that cannabinoid therapy can reduce agitation and stimulate weight gain in patients with the disease. Most recently, investigators at Berlin Germany's Charite Universitatmedizin, Department of Psychiatry and Psychotherapy, reported that the daily administration of 2.5 mg of synthetic THC

over a two-week period reduced nocturnal motor activity and agitation in AD patients in an open-label pilot study.[7]

Clinical data presented at the 2003 annual meeting of the International Psychogeriatric Association previously reported that the oral administration of up to 10 mg of synthetic THC reduced agitation and stimulated weight gain in late-stage Alzheimer's patients in an open-label clinical trial.[8] Improved weight gain and a decrease in negative feelings among AD patients administered cannabinoids were previously reported by investigators in the *International Journal of Geriatric Psychiatry* in 1997.[9] Additional study of the use of cannabinoids and Alzheimer's would appear to be warranted.

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Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a fatal neurodegenerative disorder that is characterized by the selective loss of motor neurons in the spinal cord, brain stem, and motor cortex. An estimated 30,000 Americans are living with ALS, which often arises spontaneously and afflicts otherwise healthy adults. More than half of ALS patients die within 2.5 years following the onset of symptoms.

A review of the scientific literature reveals an absence of clinical trials investigating the use of cannabinoids for ALS treatment. However, recent preclinical findings indicate that cannabinoids can delay ALS progression, lending support to anecdotal reports by patients that cannabinoids may be efficacious in moderating the disease's development and in alleviating certain ALS-related symptoms such as pain, appetite loss, depression and drooling.[1]

Writing in the March 2004 issue of the journal *Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders*, investigators at the California Pacific Medical Center in San Francisco reported that the administration of THC both before and after the onset of ALS symptoms staved disease progression

and prolonged survival in animals compared to untreated controls.[2]

Additional trials in animal models of ALS have shown that the administration of other naturally occurring and synthetic cannabinoids can also moderate ALS progression, but not necessarily impact survival.[3-4] One recent study demonstrated that blocking the CB1 cannabinoid receptor did extend life span in an ALS mouse model, suggesting that cannabinoids' beneficial effects on ALS may be mediated by non-CB1 receptor mechanisms.[5]

Preclinical data has also shown that cannabinoids are neuroprotective against oxidative damage both *in vitro*[6] and in animals.[7] Cannabinoids' neuroprotective action may be able to play a role in moderating ALS, which is characterized by excessive glutamate activity in the spinal cord.[8] At least one cannabinoid, delta-9-THC, has been shown to protect cultured mouse spinal neurons against excitotoxicity.[9]

As a result, some experts now recommend that "marijuana ... be considered in the pharmacological management of ALS,"[10] and they believe that "further investigation into the usefulness of marijuana and ... synthetic cannabinoid receptor agonists is warranted."[11]

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Chronic Pain

As many as one in five Americans lives with chronic pain.[1] Many of these people suffer from neuropathic pain (nerve-related pain) -- a condition that is associated with numerous diseases, including diabetes, cancer, multiple sclerosis, and HIV. In most cases, the use of standard analgesic medications such as opiates and NSAIDS (non-steroidal anti-inflammatory drugs) is ineffective at relieving neuropathic pain.

Survey data indicates that the use of cannabis is common in chronic pain populations[2], and several recent clinical trials indicate that inhaled marijuana can significantly alleviate neuropathic pain. A pair of clinical trials recently demonstrated that smoking cannabis reduces neuropathic pain in patients with HIV by more than 30 percent compared to placebo.[3-4] (Additional details on these studies appear in the HIV section of this book.)

In 2008 investigators at the University of California at Davis assessed the efficacy of inhaled cannabis on pain intensity among 38 patients with central or peripheral neuropathic pain in a randomized, placebo-controlled, crossover trial. They reported: "[C]annabis reduced pain intensity and unpleasantness equally. Thus, as with opioids,

cannabis does not rely on a relaxing or tranquilizing effect, but rather reduces both the core component of nociception (nerve pain) and the emotional aspect of the pain experience to an equal degree."[5]

Preclinical data indicates that cannabinoids, when administered in concert with one another, are more effective at ameliorating neuropathic pain than the use of a single agent. Investigators at the University of Milan reported in 2008 that the administration of single cannabinoids such as THC or CBD produce limited relief compared to the administration of plant extracts containing multiple cannabinoids, terpenes (oils), and flavonoids (pigments).

Researchers concluded: "[T]he use of a standardized extract of Cannabis sativa ... evoked a total relief of thermal hyperalgesia, in an experimental model of neuropathic pain, ... ameliorating the effect of single cannabinoids," investigators concluded. ... Collectively, these findings strongly support the idea that the combination of cannabinoid and non-cannabinoid compounds, as present in [plant-derived] extracts, provide significant advantages in the relief of neuropathic pain compared with pure cannabinoids alone. ... Further studies of cannabis-based medicines in neuropathic pain are now

required to demonstrate a clinically relevant improvement in the treatment of this condition."[6]

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Diabetes Mellitus

Diabetes mellitus is a group of autoimmune diseases characterized by defects in insulin secretion resulting in hyperglycemia (an abnormally high concentration of glucose in the blood). There are two primary types of diabetes. Individuals diagnosed with type 1 diabetes (also known as juvenile diabetes) are incapable of producing pancreatic insulin and must rely on insulin medication for survival. Individuals diagnosed with type 2 diabetes (also known as adult onset diabetes) produce inadequate amounts of insulin. Type 2 diabetes is a less serious condition that typically is controlled by diet. Over time, diabetes can lead to blindness, kidney failure, nerve damage, hardening of the arteries, and death. The disease is the third leading cause of death in the United States after heart disease and cancer.

A search of the scientific literature reveals no clinical investigations of cannabis for the treatment of diabetes, but does identify a small number of preclinical studies indicating that cannabinoids may modify the disease's progression and provide symptomatic relief to those suffering from it.[1-2] Most recently, a study published in the journal *Autoimmunity* reported that injections of 5 mg per day of the non-psychoactive cannabinoid CBD

significantly reduced the incidence of diabetes in mice. Investigators reported that 86% of untreated control mice in the study developed diabetes. By contrast, only 30% of CBD-treated mice developed the disease.[3] In a separate experiment, investigators reported that control mice all developed diabetes at a median of 17 weeks (range 15-20 weeks), while a majority (60 percent) of CBD-treated mice remained diabetes-free at 26 weeks.[4]

Investigators also found that CBD significantly lowered plasma levels of the pro-inflammatory cytokines (proteins) INF-gamma and TNF-alpha and significantly reduced the severity of insulitis (an infiltration of white blood cells resulting in swelling) compared to non-treated controls. "Our results indicate that CBD can inhibit and delay destructive insulitis and inflammatory ... cytokine production in ... mice resulting in decreased incidence of diabetes," authors concluded.

Other preclinical trials have demonstrated cannabinoids to possess additional beneficial effects in animal models of diabetes. Writing in the March 2006 issue of the *American Journal of Pathology*, researchers at the Medical College of Virginia reported that rats treated with CBD for periods of one to four weeks experienced significant protection from diabetic retinopathy.[5] This condition, which is characterized by retinal

oxygen deprivation and a breakdown of the blood-retinal barrier, is the leading cause of blindness in working-age adults.

Cannabinoids have also been shown to alleviate neuropathic pain associated with the disease. A pair of studies published in the journal *Neuroscience Letters* in 2004 reported that mice administered a cannabis receptor agonist experienced a reduction in diabetic-related tactile allodynia (pain resulting from non-injurious stimulus to the skin) compared to non-treated controls.[6-7] The findings suggest that "cannabinoids have a potential beneficial effect on experimental diabetic neuropathic pain."

Finally, a 2001 trial demonstrated that delta-9-THC could moderate an animal model of the disease by reducing artificially-elevated glucose levels and insulitis in mice compared to non-treated controls.[8] With the incidence of diabetes steadily increasing in both the adult and juvenile population, it would appear that further cannabinoid research is warranted in the treatment of these diseases.

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Dystonia

Dystonia is a neurological movement disorder characterized by abnormal muscle tension and involuntary, painful muscle contractions. It is the third most common movement disorder after Parkinson's disease and tremor, affecting more than 300,000 people in North America.

A small number of case reports and preclinical studies investigating the use of cannabis and cannabinoids for symptoms of dystonia are referenced in the recent scientific literature. A 2002 case study published in the July issue of the *The Journal of Pain and Symptom Management* reported improved symptoms of dystonia after smoking cannabis in a 42-year-old chronic pain patient. Investigators reported that subject's subjective pain score fell from 9 to zero (on a zero-to-10 visual analog scale) following cannabis inhalation, and that the subject did not require any additional analgesic medication for the following 48 hours. "No other treatment intervention to date had resulted in such dramatic overall improvement in [the patient's] condition," investigators concluded.[1]

A second case study reporting "significant clinical improvement" following cannabis inhalation in a single 25-year-old patient with generalized

dystonia due to Wilson's disease was documented by an Argentinian research team in the August 2004 issue of the journal *Movement Disorders*.[2]

Also in 2004, a German research team at the Hannover Medical School reported successful treatment of musician's dystonia in a 38-year-old professional pianist following administration of 5 mg of THC in a placebo-controlled single-dose trial.[3] Investigators reported "clear improvement of motor control" in the subject's affected hand, and noted, "[Two] hours after THC intake, the patient was able to play technically demanding literature, which had not been possible before treatment." Prior to cannabinoid treatment, the subject had been unresponsive to standard medications and was no longer performing publicly. "The results provide evidence that ... THC intake ... significantly improves [symptoms of] ... focal dystonia," investigators concluded.

By contrast, a 2002 randomized, placebo-controlled study investigating the use of the synthetic oral cannabinoid naboline (Cessamet) in 15 patients afflicted with generalized and segmental primary dystonia did not show a significant reduction in dystonic symptoms.[4] Investigators speculated that this result may have been dose-related, and that administration of a higher dosage may have yielded a different outcome.

At least one recent preclinical trial indicates that both synthetic cannabinoids as well as high doses of the natural non-psychoactive cannabinoid cannabidiol (CBD) could moderate the disease progression of dystonia in animals.[5] Limited references regarding the use of cannabinoids for dystonia in humans[6] and animals[7] in the 1980s and the 1990s also appear in the scientific literature. It would appear that additional, larger clinical trials are warranted to investigate the use of cannabis and cannabinoids for this indication.

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Fibromyalgia

Fibromyalgia is a chronic pain syndrome of unknown etiology. The disease is characterized by widespread musculoskeletal pain, fatigue, and multiple tender points in the neck, spine, shoulders, and hips. An estimated 3 to 6 million Americans are afflicted by fibromyalgia, which is often poorly controlled by standard pain medications.

Fibromyalgia patients frequently self-report using cannabis therapeutically to treat symptoms of the disease,[1-2] and physicians – where legal to do so – often recommend the use of cannabis to treat musculoskeletal disorders.[3-4] To date however, only one clinical trial is available in the scientific literature assessing the use of cannabinoids to treat the disease.

Writing in the July 2006 issue of the journal *Current Medical Research and Opinion*, investigators at Germany's University of Heidelberg evaluated the analgesic effects of oral THC in nine patients with fibromyalgia over a 3-month period. Subjects in the trial were administered daily doses of 2.5 to 15 mg of THC, but received no other pain medication during the trial. Among those participants who completed the trial, all reported a significant

reduction in daily recorded pain and electronically induced pain.[5]

Previous clinical and preclinical trials have shown that both naturally occurring and endogenous cannabinoids hold analgesic qualities,[6-9] particularly in the treatment of cancer pain [10] and neuropathic pain, [11-13] both of which are poorly treated by conventional opioids. As a result, some experts have suggested that cannabinoid agonists would be applicable for the treatment of chronic pain conditions unresponsive to opioid analgesics such as fibromyalgia, and they theorize that the disease may be associated with an underlying clinical deficiency of the endocannabinoid system.[14]

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Gastrointestinal Disorders

Gastrointestinal (GI) disorders, including functional bowel diseases such as irritable bowel syndrome (IBS) and inflammatory bowel diseases such as Crohn's disease and colitis, afflict more than one in five Americans, particularly women. While some GI disorders may be controlled by diet and pharmaceutical medications, others are poorly moderated by conventional treatments. Symptoms of GI disorders often include cramping, abdominal pain, inflammation of the lining of the large and/or small intestine, chronic diarrhea, rectal bleeding, and weight loss.

Although several anecdotal reports[1-2] and a handful of case reports[3-4] exist in the scientific literature supporting the use of cannabinoids to treat symptoms of GI disorders, virtually no clinical trial work has been performed in this area, aside from a 2007 clinical study assessing the impact of oral THC on colonic motility.[5]

However, numerous preclinical studies demonstrate that activation of the CB1 and CB2 cannabinoid receptors exert biological functions on the gastrointestinal tract.[6] Effects of their activation in animals include suppression of gastrointestinal motility,[7] inhibition of intestinal secretion,[8] reduced acid reflux,[9] and protection

from inflammation[10], as well as the promotion of epithelial wound healing in human tissue.[11] As a result, many experts now believe that cannabinoids and/or modulation of the endogenous cannabinoid system represents a novel therapeutic target for the treatment of numerous GI disorders — including inflammatory bowel diseases, functional bowel diseases, gastro-oesophagael reflux conditions, secretory diarrhea, gastric ulcers, and colon cancer.[12-13]

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Gliomas

Gliomas (tumors in the brain) are especially aggressive malignant forms of cancer, often resulting in the death of affected patients within one to two years following diagnosis. There is no cure for gliomas and most available treatments provide only minor symptomatic relief.

A review of the modern scientific literature reveals numerous preclinical studies and one pilot clinical study demonstrating cannabinoids' ability to act as antineoplastic agents, particularly on glioma cell lines.

Writing in the September 1998 issue of the journal *FEBS Letters*, investigators at Madrid's Complutense University, School of Biology, first reported that delta-9-THC induced apoptosis (programmed cell death) in glioma cells in culture.[1] Investigators followed up their initial findings in 2000, reporting that the administration of both THC and the synthetic cannabinoid agonist WIN 55,212-2 "induced a considerable regression of malignant gliomas" in animals.[2] Researchers again confirmed cannabinoids' ability to inhibit tumor growth in animals in 2003.[3]

That same year, Italian investigators at the University of Milan, Department of Pharmacology,

Chemotherapy and Toxicology, reported that the non-psychoactive cannabinoid, cannabidiol (CBD), inhibited the growth of various human glioma cell lines *in vivo* and *in vitro* in a dose dependent manner. Writing in the November 2003 issue of the *Journal of Pharmacology and Experimental Therapeutics Fast Forward*, researchers concluded, "Non-psychoactive CBD ... produce[s] a significant anti-tumor activity both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as an antineoplastic agent."[4]

In 2004, Guzman and colleagues reported that cannabinoids inhibited glioma tumor growth in animals and in human glioblastoma multiforme (GBM) tumor samples by altering blood vessel morphology (e.g., VEGF pathways). Writing in the August 2004 issue of *Cancer Research*, investigators concluded, "The present laboratory and clinical findings provide a novel pharmacological target for cannabinoid-based therapies."[5]

More recently, investigators at the California Pacific Medical Center Research Institute reported that the administration of THC on human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced cell death more rapidly than did the administration of WIN 55,212-2. Researchers also noted that THC selectively targeted malignant cells while ignoring

healthy ones in a more profound manner than the synthetic alternative.[6]

Most recently, Guzman and colleagues reported that THC administration decreases recurrent glioblastoma multiforme tumor growth in patients diagnosed with recurrent GBM. In the first ever pilot clinical trial assessing the use of cannabinoids and GBM, investigators found that the intratumoral administration of THC was associated with reduced tumor cell proliferation in two of nine subjects. "The fair safety profile of THC, together with its possible anti-proliferative action on tumor cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids," investigators concluded.[7] Several additional investigators have also recently called for further exploration of cannabis-based therapies for the treatment of glioma.[8-10]

In addition to cannabinoids' ability to moderate glioma cells, separate studies demonstrate that cannabinoids and endocannabinoids can also inhibit the proliferation of other various cancer cell lines, including breast carcinoma,[11-14] prostate carcinoma,[15-17] colorectal carcinoma,[18] gastric adenocarcinoma,[19] skin carcinoma,[20] leukemia cells,[21-22] nueroblastoma,[23] lung carcinoma,[24-25] uterus carcinoma,[26] thyroid

epithelioma,[27] pancreatic adenocarcinoma,[28-29], cervical carcinoma[30] and lymphoma.[31-32]

Studies also indicate that the administration of cannabinoids, in conjunction with conventional anti-cancer therapies, can enhance the effectiveness of standard cancer treatments.[33]

Consequently, many experts now believe that cannabinoids "may represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis and the metastatic spreading of cancer cells,"[34-35] and have recommended that at least one cannabinoid, cannabidiol, now be utilized in cancer therapy.[36]

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Hepatitis C

Hepatitis C is a viral disease of the liver that afflicts an estimated four million Americans. Chronic hepatitis C is typically associated with fatigue, depression, joint pain and liver impairment, including cirrhosis and liver cancer.

Patients diagnosed with hepatitis C frequently report using cannabis to treat both symptoms of the disease as well as the nausea associated with antiviral therapy.[1-2] An observational study by investigators at the University of California at San Francisco (UCSF) found that hepatitis C patients who used cannabis were significantly more likely to adhere to their treatment regimen than patients who didn't use it. [3] Nevertheless, no clinical trials assessing the use of cannabinoids for this indication are available in the scientific literature.

Preclinical data indicates that the endocannabinoid system may moderate aspects of chronic liver disease[4-5] and that cannabinoids may reduce inflammation in experimental models of hepatitis.[6] However, other clinical reviews have reported a positive association between daily cannabis use and the progression of liver fibrosis (excessive tissue build up) and steatosis (excessive fat build up) in select hepatitis C patients. [7-9]

As a result, experts hold divergent opinions regarding the therapeutic use of cannabinoids for hepatitis C treatment. Writing in the October 2006 issue of the *European Journal of Gastroenterology*, investigators from Canada and Germany concluded that cannabis' "potential benefits of a higher likelihood of treatment success [for hepatitis c patients] appear to outweigh [its] risks." [10] By contrast, other experts discourage the use of cannabis in patients with chronic hepatitis until further studies are performed.[11-14]

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Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus is a retrovirus that invades cells in the human immune system, making it highly susceptible to infectious diseases. According to the World Health Organization, over 500,000 Americans have died from HIV/AIDS and over one million US citizens are living with the disease.

Survey data indicates that cannabis is used by as many one in three North American patients with HIV/AIDS to treat symptoms of the disease as well as the side-effects of various antiretroviral medications,[1-4] with one recent study reporting that more than 60 percent of HIV/AIDS patients self-identify as "medical cannabis users."[5] Patients living with HIV/AIDS most frequently report using cannabis to counter symptoms of anxiety, appetite loss, and nausea, and at least one study has reported that patients who use cannabis therapeutically are 3.3 times more likely to adhere to their antiretroviral therapy regimens than non-cannabis users.[6]

Clinical trial data indicates that cannabis use does not adversely impact CD4 and CD8 T cell counts,[7] and may even improve immune function.[8-9]

In 2007, investigators at Columbia University published clinical trial data in 2007 reporting that HIV/AIDS patients who inhaled cannabis four times daily experienced "substantial ... increases in food intake ... with little evidence of discomfort and no impairment of cognitive performance." They concluded, "Smoked marijuana ... has a clear medical benefit in HIV-positive [subjects]"[10]

That same year, investigators at San Francisco General Hospital and the University of California's Pain Clinical Research Center reported in the journal *Neurology* that inhaling cannabis significantly reduced HIV-associated neuropathy compared to placebo. Researchers reported that inhaling cannabis three times daily reduced patients' pain by 34 percent. They concluded, "Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated neuropathy [in a manner] similar to oral drugs used for chronic neuropathic pain."[11]

In 2008, researchers at the University of California at San Diego reported similar findings. Writing in the journal *Neuropsychopharmacology*, they concluded: "Smoked cannabis ... significantly reduced neuropathic pain intensity in HIV-associated ... polyneuropathy compared to placebo, when added to stable concomitant analgesics. ...

Mood disturbance, physical disability, and quality of life all improved significantly during study treatment. ... Our findings suggest that cannabinoid therapy may be an effective option for pain relief in patients with medically intractable pain due to HIV."[12]

As a result, many experts now believe that "marijuana represents another treatment option in [the] health management" of patients with HIV/AIDS.[13]

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Hypertension

High blood pressure, or hypertension, afflicts an estimated 1 in 4 American adults. This condition puts a strain on the heart and blood vessels and greatly increases the risk of stroke and heart disease.

Emerging research indicates that the endogenous cannabinoid system plays a role in regulating blood pressure, though its mechanism of action is not well understood.[1] Animal studies demonstrate that anandamide and other endocannabinoids profoundly suppress cardiac contractility in hypertension and can normalize blood pressure,[2-3] leading some experts to speculate that the manipulation of the endocannabinoid system "may offer novel therapeutic approaches in a variety of cardiovascular disorders."[4]

The administration of natural cannabinoids has yielded conflicting cardiovascular effects on humans and laboratory animals.[5-9] The vascular response in humans administered cannabis in experimental conditions is typically characterized by a mild increase in heart rate and blood pressure. However, complete tolerance to these effects develops quickly and potential health risks appear minimal.[10-11]

In animals, cannabinoid administration in animals is typically associated with vasodilation, transient bradycardia and hypotension,[12] as well as an inhibition of atherosclerosis (hardening of the arteries) progression.[13-15] The administration of synthetic cannabinoids have also been shown to lower blood pressure in animals and have not been associated with cardiotoxicity in humans.[16]

At this time, research assessing the clinical use of cannabinoids for hypertension is in its infancy though further investigation appears warranted.[17]

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Incontinence

Urinary incontinence is defined as a loss of bladder control. Incontinence can result from several biological factors, including weak bladder muscles and inflammation, as well as from nerve damage associated with diseases such as multiple sclerosis (MS) and Parkinson's disease. More than one in ten Americans over age 65 is estimated to suffer from incontinence, particularly women.

Several recent clinical trials indicate that cannabinoid therapy may reduce incidents of incontinence. Writing in the February 2003 issue of the journal *Clinical Rehabilitation*, investigators at Oxford's Centre for Enablement in Britain reported that self-administered doses of whole-plant cannabinoid extracts improved bladder control compared to placebo in patients suffering from MS and spinal cord injury.[1]

Investigators at London's Institute for Neurology followed up these initial findings in an open-label pilot study of cannabis-based extracts for bladder dysfunction in 15 patients with advanced multiple sclerosis. Following cannabinoid therapy, "urinary urgency, the number of and volume of incontinence episodes, frequency and nocturia all decreased significantly," investigators determined. "Cannabis-based medicinal extracts are a safe and

effective treatment for urinary and other problems in patients with advanced MS."[2]

These findings were confirmed in 2006 in a multi-center, randomized placebo-controlled trial involving 630 patients administered oral doses of cannabis extracts or THC. Researchers reported that subjects administered cannabis extracts experienced a 38 percent reduction in incontinence episodes from baseline to the end of treatment, while patients administered THC experienced a 33 percent reduction, suggesting a "clinical effect of cannabis on incontinence episodes."[3]

Most recently, preclinical data presented at the 2006 annual meeting of the American Urological Association indicated that cannabis analogs can reduce bladder inflammation and bladder over-activity in animals.[4]

In light of these findings, experts have recommended the use of cannabinoids as potential 'second-line' agents for treating incontinence.[5]

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Methicillin-resistant *Staphyloccus aureus* (MRSA)

Many bacterial infections possess multi-drug resistance. Arguably the most significant of these bacteria is methicillin-resistant *Staphyloccus aureus*, more commonly known as MRSA or 'the superbug.' This bacterium is resistant to standard antibiotics, including penicillin. According to the *Journal of the American Medical Association*, MRSA is responsible for nearly 20,000 hospital-stay related deaths annually in the United States.[1]

Published data demonstrates that cannabinoids possess strong antibacterial properties. In 2008, investigators at Italy's Universita del Piemonte Orientale and Britain's University of London, School of Pharmacy assessed the germ-fighting properties of five separate cannabinoids against various strains of multidrug-resistant bacteria, including MRSA. They reported that all of the compounds tested showed "potent antibacterial activity," and that cannabinoids were "exceptional" at halting the spread of MRSA.[2]

A second study published that same year reported that non-cannabinoid constituents in the plant also possess antibacterial properties against MRSA and malaria.[3]

Clinical trials regarding the use of cannabinoids for MRSA have been recommended, with some experts stating, "Cannabis sativa ... represents an interesting source of antibacterial agents to address the problem of multidrug resistance in MRSA and other pathogenic bacteria."[4]

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Multiple Sclerosis

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system that causes inflammation, muscular weakness, and a loss of motor coordination. Over time, MS patients typically become permanently disabled, and in some cases the disease can be fatal. According to the US National Multiple Sclerosis Society, about 200 people are diagnosed every week with the disease — often striking those 20 to 40 years of age.

Clinical and anecdotal reports of cannabinoids' ability to reduce MS-related symptoms such as pain, spasticity, depression, fatigue, and incontinence are plentiful in the scientific literature[1-12] — leading many MS-associated patient organizations, including the Multiple Sclerosis Societies of Britain and Canada, to take positions in favor of the drug's prescription use.[13] Patients with multiple sclerosis typically report engaging in cannabis therapy[14], with one survey indicating that nearly one in two MS patients use the drug therapeutically.[15]

Recent clinical and preclinical studies also suggest that cannabinoids may inhibit MS progression. Writing in the July 2003 issue of the journal *Brain*, investigators at the University College of London's Institute of Neurology reported that administration

of the synthetic cannabinoid agonist WIN 55,212-2 provided "significant neuroprotection" in an animal model of multiple sclerosis. "The results of this study are important because they suggest that in addition to symptom management, ... cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis and probably other disease," researchers concluded.[16]

Investigators at the Netherland's Vrije University Medical Center, Department of Neurology, also reported for the first time in 2003 that the administration of oral THC can boost immune function in patients with MS. "These results suggest pro-inflammatory disease-modifying potential of cannabinoids [for] MS," they concluded.[17]

Clinical data reported in 2006 from an extended open-label study of 167 multiple sclerosis patients found that use of whole plant cannabinoid extracts relieved symptoms of pain, spasticity, and bladder incontinence for an extended period of treatment (mean duration of study participants was 434 days) without requiring subjects to increase their dose.[18] Results from a separate two-year open label extension trial in 2007 also reported that the administration of cannabis extracts was associated with long-term reductions in neuropathic pain in

select MS patients. On average, patients in the study required fewer daily doses of the drug and reported lower median pain scores the longer they took it. [19] These results would be unlikely in patients suffering from a progressive disease like MS unless the cannabinoid therapy was halting its progression, investigators have suggested.

As a result, the British government is now sponsoring a three-year clinical trial to assess the long-term effects of cannabinoids on both MS-associated symptom management as well as disease progression. Health Canada also recently approved the prescription use of cannabis abstracts for the treatment of MS-associated neuropathic pain.[20] Similar approval of cannabis extracts is pending in Britain and Europe.

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Osteoporosis

Osteoporosis is a degenerative skeletal disease characterized by a deterioration of bone tissue. Patients with osteoporosis are at risk for suffering multiple fractures and other serious disabilities. Approximately 10 million Americans over age 50 suffer from osteoporosis, according to the US Surgeon General's office, and another 34 million are at risk for developing the disease.

Initial references regarding the potential use of cannabinoids to protect against the onset of osteoporosis are available in the scientific literature beginning in the early 1990s.[1] To date, however, no clinical work has taken place investigating the use of cannabis for this indication.

Writing in the January 2006 issue of the *Proceedings of the National Academy of Sciences*, investigators at the Bone Laboratory of the Hebrew University in Jerusalem reported that the administration of the synthetic cannabinoid agonist HU-308 slowed the development of osteoporosis, stimulated bone building, and reduced bone loss in animals.[2] Follow up research published in the *Annals of the New York Academy of Sciences* in 2007 reported that the activation of the CB2 cannabinoid receptor reduced experimentally-induced bone loss and stimulated bone formation.[3] Investigators have

previously reported that mice deficient in the CB2 cannabinoid receptor experienced age-accelerated bone loss reminiscent of human osteoporosis.[4]

Though the role of the endocannabinoid system in the regulation of bone mass is not yet well understood,[5] experts are hopeful that cannabinoids and the cannabinoid receptor system may be "A promising target novel target for anti-osteoporotic drug development."[6]

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Pruritus

Itching (pruritus) is a common symptom associated with numerous skin diseases, as well as a secondary symptom of numerous serious conditions such as renal failure and liver disease. Itching, unlike other skin sensations, is generally a result of CNS activities, and typically goes untreated by standard medical therapies.

A review of the scientific literature reveals three clinical trials investigating the use of cannabinoids in the treatment of pruritus. Writing in the August 2002 issue of the *American Journal of Gastroentrology,* investigators from the University of Miami Department of Medicine reported successful treatment of pruritus with 5 mg of THC in three patients with cholestatic liver disease.[1] Prior to cannabinoid therapy, subjects had failed to respond to standard medications and had lost their ability to work. Following evening cannabinoid administration, all three patients reported a decrease in pruritus, as well as "marked improvement" in sleep and were eventually able to return to work. Resolution of depression was also reported in two out of three subjects. "Delta-9-tetrahydrocannabinol may be an effective alternative in patients with intractable cholestatic pruritus," investigators concluded.

The following year, British researchers reported in the June 2003 issue of the journal *Inflammation Research* that the peripheral administration of the synthetic cannabinoid agonist HU-211 significantly reduced experimentally-induced itch in 12 subjects.[2] Investigators had previously reported that topical application of HU-210 on human skin reduced experimentally-induced pain and acute burning sensations.[3]

Most recently, researchers at Wroclaw, Poland's University of Medicine, Department of Dermatology, reported that application of an endocannabinoid-based topical cream reduced uremic pruritus and xerosis (abnormal dryness of the skin) in hemodialysis patients.[4] Three weeks of twice-daily application of the cream "completely eliminated" pruritus in 38 percent of trial subjects and "significantly reduced" itching in others. Eighty-one percent of patients reported a "complete reduction" in xerosis following cannabinoid therapy.

In light of these encouraging preliminary results, some dermatology experts now believe that cannabinoids and the cannabinoid system may represent "promising new avenues for managing itch more effectively."[5]

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Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an inflammatory disease of the joints characterized by pain, stiffness, and swelling, as well as an eventual loss of limb function. Rheumatoid arthritis is estimated to affect about one percent of the population, primarily women.

Use of cannabis to treat symptoms of RA is commonly self-reported by patients with the disease. In a 2005 anonymous questionnaire survey of medicinal cannabis patients in Australia, 25 percent reported using cannabinoids to treat RA.[1] A survey of British medicinal cannabis patients found that more than 20 percent of respondents reported using cannabis for symptoms of arthritis.[2] Nevertheless, few clinical trials investigating the use of cannabis for RA appear in the scientific literature.

In January 2006, investigators at the British Royal National Hospital for Rheumatic Disease reported successful treatment of arthritis with cannabinoids in the first-ever controlled trial assessing the efficacy of natural cannabis extracts on RA.[3] Investigators reported that administration of cannabis extracts over a five week period produced statistically significant improvements in pain on

movement, pain at rest, quality of sleep, inflammation, and intensity of pain compared to placebo. No serious adverse effects were observed. Similar results had been reported in smaller, Phase II trials investigating the use of orally administered cannabis extracts on symptoms of RA.[4]

Preclinical data also indicates that cannabinoids can moderate the progression of RA. Writing in the August 2000 issue of the *Journal of the Proceedings of the National Academy of Sciences*, investigators at London's Kennedy Institute for Rheumatology reported that cannabidiol (CBD) administration suppressed progression of arthritis *in vitro* and in animals.[5] Administration of CBD after the onset of clinical symptoms protected joints against severe damage and "effectively blocked [the] progression of arthritis," investigators concluded. Daily administration of the synthetic cannabinoid agonist HU-320 has also been reported to protect joints from damage and to ameliorate arthritis in animals.[6]

Summarizing the available literature in the September 2005 issue of the *Journal of Neuroimmunology*, researchers at Tokyo's National Institute for Neuroscience concluded, "Cannabinoid therapy of RA could provide symptomatic relief of joint pain and swelling as

well as suppressing joint destruction and disease progression."[7]

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Sleep Apnea

Sleep apnea is a medical disorder characterized by frequent interruptions in breathing of up to ten seconds or more during sleep. The condition is associated with numerous physiological disorders, including fatigue, headaches, high blood pressure, irregular heartbeat, heart attack and stroke. Though sleep apnea often goes undiagnosed, it is estimated that approximately four percent of men and two percent of women ages 30 to 60 years old suffer from the disease.

One preclinical study is cited in the scientific literature investigating the role of cannabinoids on sleep-related apnea. Writing in the June 2002 issue of the journal of the American Academy of Sleep Medicine, researchers at the University of Illinois (at Chicago) Department of Medicine reported "potent suppression" of sleep-related apnea in rats administered either exogenous or endogenous cannabinoids.[1] Investigators reported that doses of delta-9-THC and the endocannabinoid oleamide each stabilized respiration during sleep, and blocked serotonin-induced exacerbation of sleep apnea in a statistically significant manner. No follow up investigations have taken place assessing the use of cannabinoids to treat this indication. However, several recent preclinical and clinical trials have reported on the use of THC, natural

cannabis extracts, and endocannabinoids to induce sleep[2,3] and/or improve sleep quality.[4]

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Tourette's Syndrome

Tourette's syndrome (TS) is a complex neuropsychiatric disorder of unknown etiology that is characterized by involuntary vocal tics. Severity of this condition varies widely among patients. Though there is no cure for Tourette's syndrome, the condition often improves with age. Experts estimate that 100,000 Americans are afflicted with TS.

A review of the scientific literature reveals several clinical trials investigating the use of cannabinoids for the treatment of TS. Writing in the March 1999 issue of the *American Journal of Psychiatry,* investigators at Germany's Medical School of Hanover, Department of Clinical Psychiatry and Psychotherapy, reported successful treatment of Tourette's syndrome with a single dose of 10 mg of delta-9-THC in a 25-year-old male patient in an uncontrolled open clinical trial.[1] Investigators reported that the subject's total tic severity score fell from 41 to 7 within two hours following cannabinoid therapy, and that improvement was observed for a total of seven hours. "For the first time, patients' subjective experiences when smoking marijuana were confirmed by using a valid and reliable rating scale," authors concluded.

Investigators again confirmed these preliminary results in a randomized double-blind placebo-controlled crossover single dose trial of THC in 12 adult TS patients. Researchers reported a "significant improvement of tics and obsessive-compulsive behavior (OCB) after treatment with delta-9-THC compared to placebo."[2] Investigators reported no cognitive impairment in subjects following THC administration[3] and concluded, "THC is effective and safe in treating tics and OCB in TS."[4]

Investigators confirmed these results in a second randomized double-blind placebo-controlled trial involving 24 patients administered daily doses of up to 10 mg of THC over a six-week period. Researchers reported that subjects experienced a significant reduction in tics following long-term cannabinoid treatment,[5] and suffered no detrimental effects on learning, recall or verbal memory.[6] A trend toward significant improvement of verbal memory span during and after therapy was also observed.

Summarizing their findings in the October 2003 issue of the journal *Expert Opinions in Pharmacotherapy,* investigators concluded that in adult TS patients, "Therapy with delta-9-THC should be tried ... if well established drugs either

fail to improve tics or cause significant adverse effects."[7]

REFERENCES

[1] Muller-Vahl et al. 1999. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. *American Journal of Psychiatry* 156: 495.

[2] Muller-Vahl et al. 2002. Treatment of Tourette's syndrome with Delta-9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 35: 57-61.

[3] Muller-Vahl et al. 2001. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry* 34: 19-24.

[4] Muller-Vahl et al. 2002. op. cit.

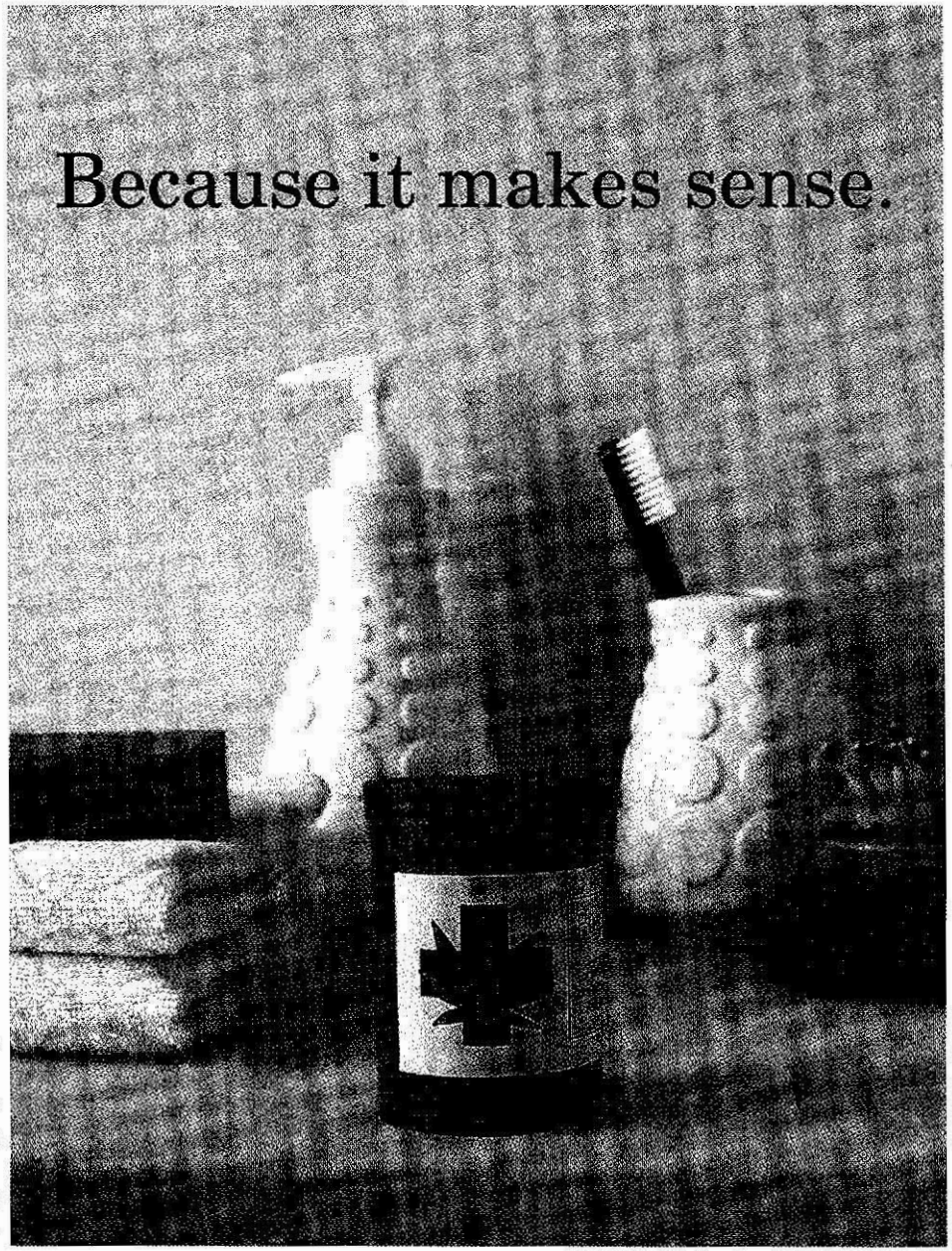
[5] Muller-Vahl et al. 2003. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *Journal of Clinical Psychiatry* 64: 459-65.

[6] Muller-Vahl et al. 2003. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. *Neuropsychopharmacology* 28: 384-8.

[7] Kirsten Muller-Vahl. 2003. Cannabinoids reduce symptoms of Tourette's syndrome. *Expert Opinions in Pharmacotherapy* 4: 1717-25.

"In strict medical terms marijuana is far safer than many foods we commonly consume ... Marijuana, in its natural form, is one of the safest therapeutically active substances known to man. By any measure of rational analysis marijuana can be safely used within a supervised routine of medical care."

-Drug Enforcement Administration
Chief Administrative Law Judge Francis Young
NORML v. DEA (1988)



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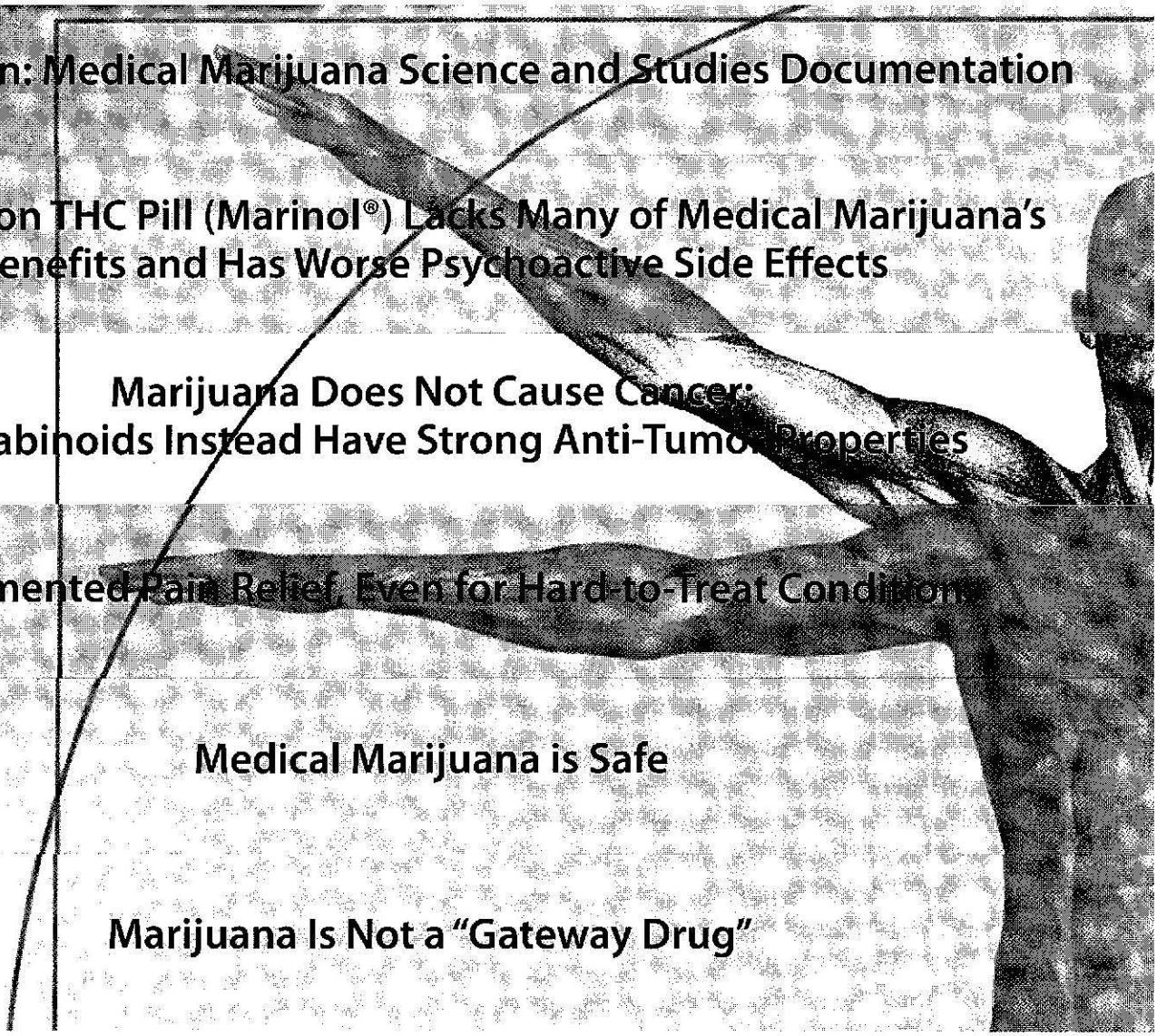

Prescription THC Pill (Marinol®) Lacks Many of Medical Marijuana's Benefits and Has Worse Psychoactive Side Effects

Marijuana Does Not Cause Cancer; Cannabinoids Instead Have Strong Anti-Tumor Properties

Documented Pain Relief, Even for Hard-to-Treat Conditions

Medical Marijuana is Safe

Marijuana Is Not a "Gateway Drug"

Institute of Medicine Says No Evidence for Gateway

"There is no evidence that marijuana serves as a stepping stone on the basis of its particular physiological effect."

"[I]t does not appear to be a gateway drug to the extent that it is the cause or even that it is the most significant predictor of serious drug abuse; that is, care must be taken not to attribute cause to association."

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

Gateway Theory Lacks Evidence

"[A]vailable evidence does not favor the marijuana gateway hypothesis over the alternative hypothesis that marijuana and hard drug initiation are correlated because both are influenced by individuals' heterogeneous liabilities to try drugs."

— A.R. Morral, et al., "Reassessing the Marijuana Gateway Effect," *Addiction*, December 2002

Drug Progression Not Related to Medical Use

"Marijuana has not been proven to be the cause or even the most serious predictor of serious drug abuse. It is also important to note that the data on marijuana's role in illicit drug use progression only pertains to its non-medical use."

—American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana," January 2008

Abusable Drugs Have No Predictable Sequence or Hierarchy

"Our key findings were that 1) there are no unique factors distinguishing the gateway sequence and the reverse sequence—that is, the sequence is opportunistic; 2) the gateway sequence and the reverse sequence have the same prognostic accuracy."

"The results of this study as well as other studies demonstrate that abusable drugs occupy neither a specific place in a hierarchy nor a discrete position in a temporal sequence."

— R.E. Tarter, et al., "Predictors of Marijuana Use in Adolescents Before and After Licit Drug Use: Examination of the Gateway Hypothesis," *American Journal of Psychiatry*, December 2006

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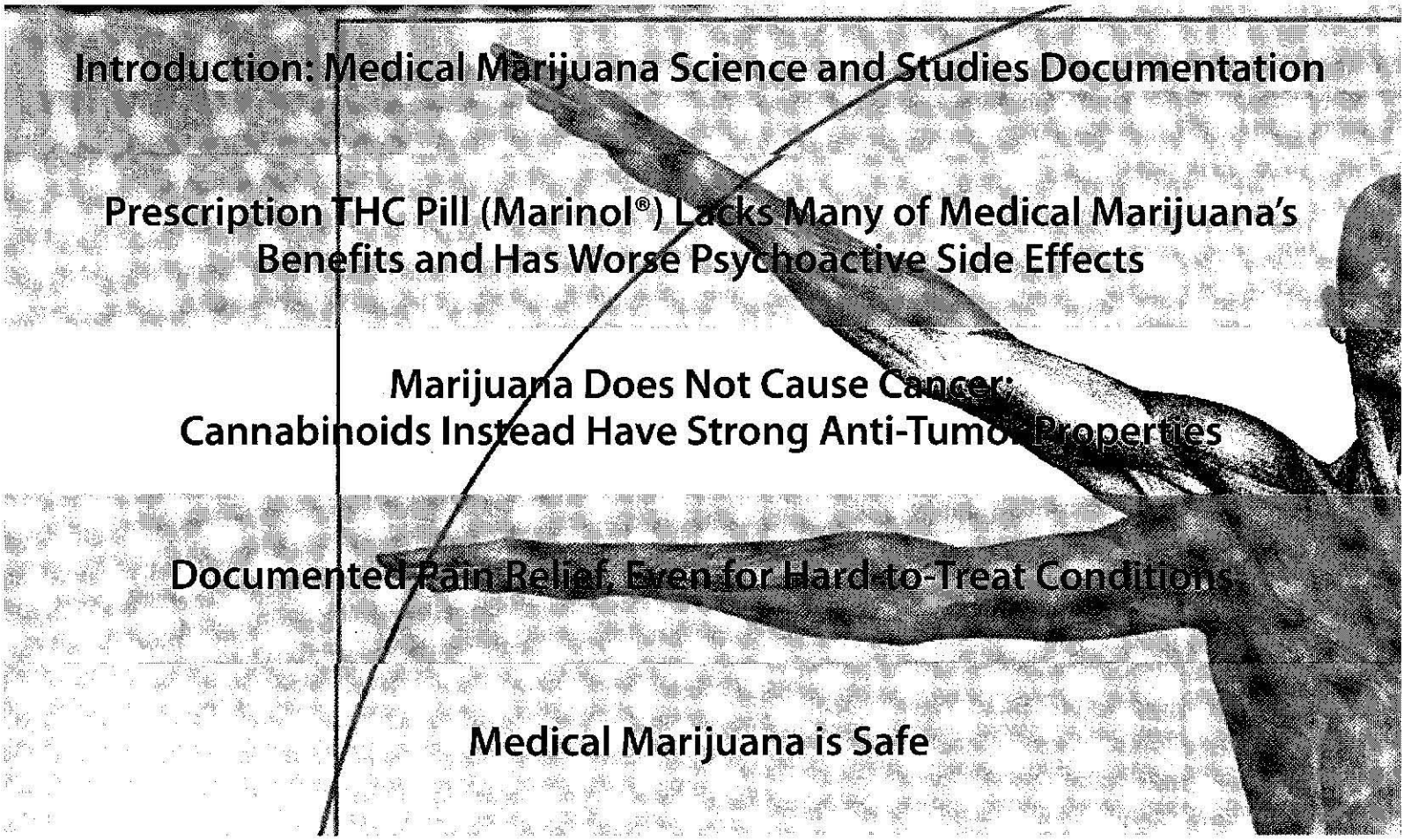

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Acceptable Safety in HIV/AIDS Patients

"The Institute of Medicine report, along with other recent reviews, suggest that if cannabis compounds can be shown to have therapeutic value then the margin of safety is acceptable. An acceptable safety margin has been shown in the present study as well as in a previous study of cannabinoids in patients with HIV-1 infection."

— Abrams D.I. et al., "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled trial," *Neurology*, February 13, 2007

Marijuana Cannot Cause Lethal Reactions

"...[M]arijuana has an extremely wide acute margin of safety for use under medical supervision and cannot cause lethal reactions.

"...[G]reater harm is caused by the legal consequences of its prohibition than possible risks of medicinal use."

— American Public Health Association, "Access to Therapeutic Marijuana/Cannabis," Resolution no. 9513, November 1995

No Harm to the Immune System

"Although cannabinoids are thought to exert a positive clinical benefit in some patients with HIV disease and wasting, concerns have been raised about their potential adverse effects on the immune system. Here, in the context of a randomized, placebo-controlled study comparing the short-term effects of cannabinoids in patients with HIV infection on a stable antiretroviral regimen, no such adverse effects have been observed."

— B.M. Bredt, et al., "Short-Term Effects of Cannabinoids on Immune Phenotype and Function in HIV-1-Infected Patients," *Journal of Clinical Pharmacology*, November 2002

Significant Margin of Safety

"There is a growing body of evidence that marijuana has a significant margin of safety when used under a practitioner's supervision when all of the patient's medications can be considered in the therapeutic regimen."

—American Nurses Association, "Providing Patients Safe Access to Therapeutic Marijuana/Cannabis," position statement, March 19, 2004

Clinical Trial Found No Negative Effect on Learning or Psychomotor Ability

"Compared with placebo, neither marijuana nor dronabinol significantly altered performance on any of the tasks (e.g. measures of learning, memory, vigilance, psychomotor ability)."

— Margaret Haney, et al., "Dronabinol and Marijuana in HIV-Positive Marijuana Smokers: Caloric Intake, Mood, and Sleep," *Journal of Acquired Immune Deficiency Syndromes*, May 16, 2007

Adverse Effects Comparable to Other Medications

"[E]xcept for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications."

[Note: See the section, "Vaporization Answers Concerns Regarding Heath Hazards of Smoking," for discussion of new technologies that eliminate the need for smoking medical marijuana.]

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

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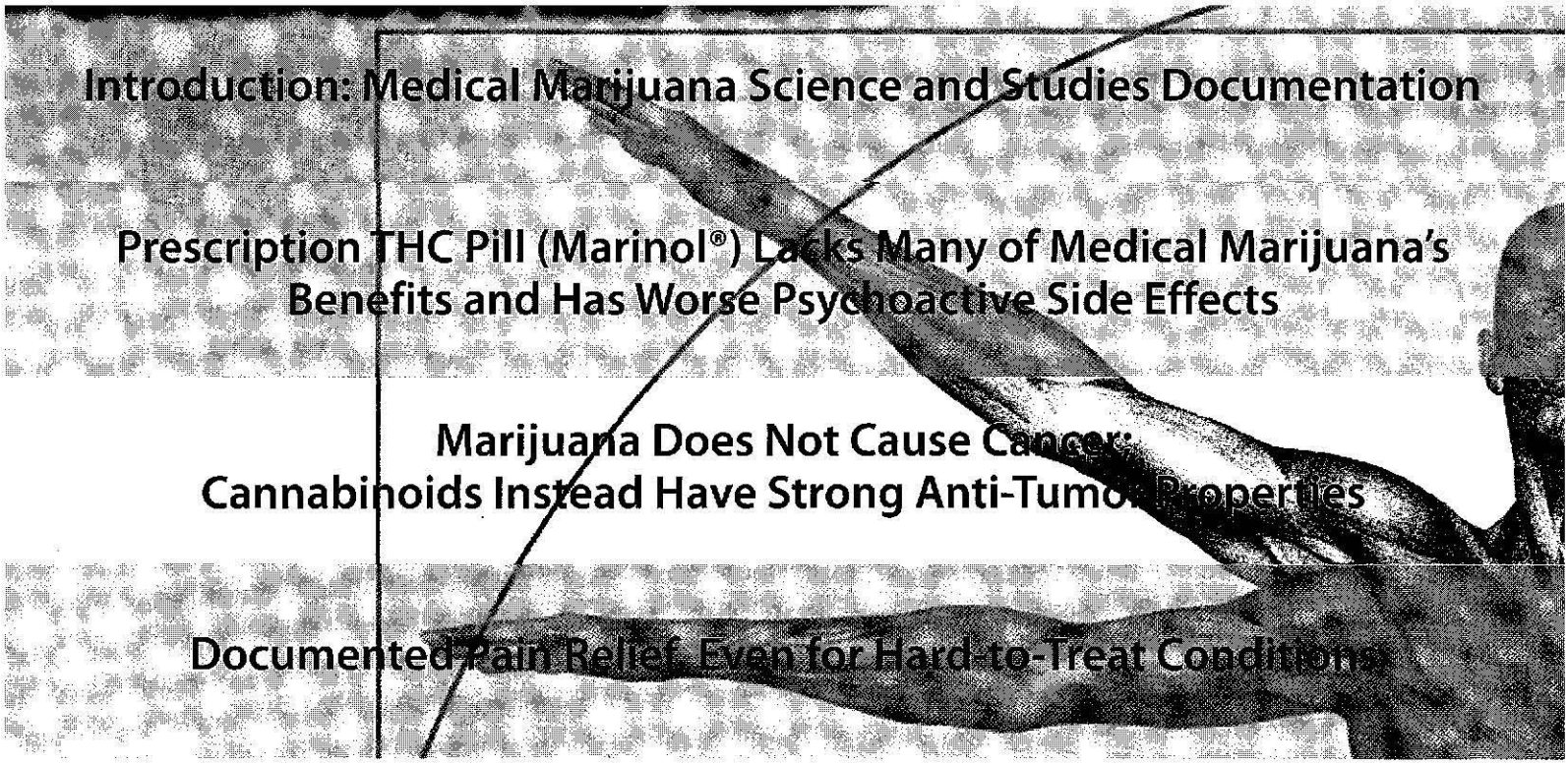

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Data from clinical and laboratory studies show medical marijuana to be effective at relieving certain types of pain, especially neuropathic pain (pain caused by damage to nerves). This type of pain, caused by a variety of conditions, is notoriously resistant to treatment with conventional pain drugs. Recently, a placebo-controlled trial of smoked marijuana demonstrated significant relief of peripheral neuropathy in patients with HIV/AIDS, a condition for which there are no FDA-approved treatments. Other research suggests cannabinoids may allow reduced doses of opiate pain drugs, reducing potential harm from narcotic painkillers.

Marijuana May Allow Reduced Doses of Morphine and Other Opioid Pain Drugs

"Chronic administration of morphine or THC produced antinociceptive tolerance [reduced pain relief] to the respective drugs, where as combination treatment did not produce tolerance."

"These results demonstrate that low dose THC-morphine combination treatment produces antinociception [pain relief] in the absence of tolerance or attenuation of receptor activity."

"The interaction of opioid and cannabinoid systems to produce antinociception in the absence of tolerance provides evidence that it may be possible to enhance the analgesic properties of these drugs clinically and minimize the side-effects associated with higher doses of either drug alone."

— Smith P., et al., "Low Dose Combination of Morphine and Δ9-Tetrahydrocannabinol Circumvents Antinociceptive Tolerance and Apparent Desensitization of Receptors," *European Journal of Pharmacology*, October 2007

Relief of Peripheral Neuropathy in HIV/AIDS

"Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy."

— Abrams D.I., et al., "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial," *Neurology*, February 13, 2007

American Medical Association Recognizes Marijuana for Pain Relief

"Smoked marijuana may benefit individual patients suffering from intermittent or chronic pain."

—American Medical Association, "Council on Scientific Affairs Report 10—Medical Marijuana," December 9, 1997

Inhibits Pain in Virtually Every Experimental Pain Paradigm

"The clinical potential of the cannabinoids is large; some people suggest that cannabis could be 'the aspirin of the 21st century' … Cannabinoids inhibit pain in virtually every experimental pain paradigm."

— David Baker, et al., "The Therapeutic Potential of Cannabis," *The Lancet Neurology*, May 2003

Therapeutic Benefits for MS and Neuropathic Pain

"[R]ecent randomised controlled clinical trials have pointed to potential therapeutic benefits of cannabinoids for patients with MS and chronic neuropathic pain. This suggests that patients' reports of the effectiveness of cannabis … could serve as a valid indicator of target diseases and symptoms for cannabinoid drug development."

— M.A. Ware, et al., "The Medicinal Use of Cannabis in the UK: Results of a Nationwide Survey," *International Journal of Clinical Practice*, March 2005

Multiple Sclerosis Pain Reduction

"The most commonly cited symptoms for cannabis use were pain and spasms … and the majority of persons using it for these symptoms reported benefit."

"Cannabinoids appear to have benefit in reducing pain in MS and other neuropathic pain syndromes."

—M.S. Chong, et al., "Cannabis use in patients with multiple sclerosis," *Multiple Sclerosis*, 2006

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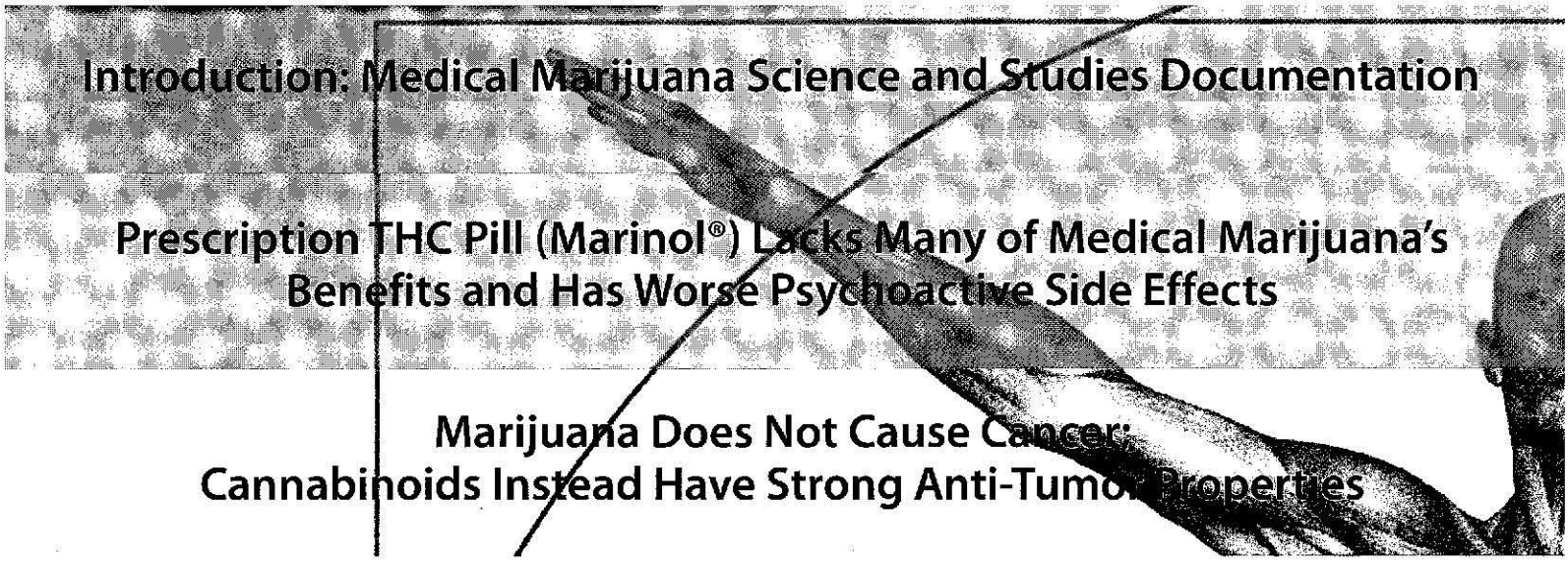

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Marijuana Does Not Cause Cancer; Cannabinoids Instead Have Strong Anti-Tumor Properties

Contrary to popular misconception, marijuana has never been shown to cause cancer in humans, and the largest, most definitive epidemiological studies have failed to find an association between marijuana use and lung cancer or other cancers typically associated with cigarette smoking. In fact, many of these studies have shown a trend toward lower lung cancer rates among marijuana smokers than among nonsmokers. This may be because cannabinoids, marijuana's active components, have well-documented anti-tumor activity.

65,000-Patient Study Finds No Association Between Marijuana Use and Cancer

The purpose of this retrospective cohort study was to examine the relationship of marijuana use to cancer incidence. The study population consisted of 64,855 examinees in the Kaiser Permanente multiphasic health checkup in San Francisco and Oakland.

"Compared with nonusers/experimenters (lifetime use of less than seven times), ever- and current use of marijuana were not associated witn increased risk of cancer at all sites in analyses adjusted for sociodemographic factors, cigarette smoking, and alcohol use."

—Sidney S. et al., "Marijuana Use and Cancer Incidence (California, United States)," *Cancer Causes and Control*, September 1997

UCLA Study Finds Lower Lung Cancer Rate Among Marijuana Smokers; Possible Protective Effect

"[W]e had ample numbers of such [heavy marijuana] users for oral and lung cancers. Nonetheless, and contrary to our expectations, we found no positive associations between marijuana use and lung or UAT [upper aerodigestive tract] cancers."

"In fact, we observed ORs <1 for all cancers except for oral cancer [i.e., the marijuana smokers had lower rates of cancer than those who didn't use marijuana]."

"Although purely speculative, it is possible that such inverse associations may reflect a protective effect of marijuana. There is recent evidence from cell culture systems and animal models that Δ9-tetrahydrocannabinol, the principal psychoactive ingredient in marijuana, and other cannabinoids may inhibit the growth of some tumors by modulating key signaling pathways leading to growth arrest and cell death, as well as by inhibiting tumor angiogenesis."

—M. Hashibe, et al., "Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study," *Cancer Epidemiology Biomarkers & Prevention*, October 2006

Plant Cannabinoids Have Anti-Tumor Effects in Breast Cancer

"A strong and statistically significant anti-tumor effect was observed … In particular, for a highly malignant human breast carcinoma cell line … cannabidiol and a cannabidiol-rich extract counteract cell growth both in vivo and in vitro as well as tumor metastasis in vivo."

—Alessia Ligresti, et al., "Anti-Tumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma," *Journal of Pharmacology And Experimental Therapeutics*, May 25, 2006

Cannabinoids Inhibit Lung Cancer Growth

"Our study suggests that cannabinoids like THC should be explored as novel therapeutic molecules in controlling the growth and metastasis of certain lung cancers."

"Furthermore, we have shown that THC [the active chemical in marijuana] inhibits lung cancer growth and metastasis in an in vivo murine model."

—A. Preet, Ganju R.K., and J.E. Groopman, "Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo," *Oncogene*, January 2008

Cannabinoids Inhibit Cancer Cells Without Harming Normal Cells

"Cannabinoids inhibit tumour growth in laboratory animals. They do so by modulating key cell-signalling pathways, thereby inducing direct growth arrest and death of tumour cells, as well as by inhibiting tumour angiogenesis and metastasis. Cannabinoids are selective antitumour compounds, as they can kill tumour cells without affecting their non-transformed counterparts. It is probable that cannabinoid receptors regulate cell-survival and cell-death pathways differently in tumour and nontumour cells."

— Manuel Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews: Cancer*, October 2003

Introduction: Medical Marijuana Science and Studies Documentation

Prescription THC Pill (Marinol®) Lacks Many of Medical Marijuana's Benefits and Has Worse Psychoactive Side Effects

Oral Route the Least Satisfactory Way to Administer Cannabinoids

"[O]ral administration is probably the least satisfactory route for cannabis owing to sequestration of cannabinoids in fat from which there is slow and variable release into plasma. In addition, significant first-pass metabolism in the liver, which degrades THC, contributes to the variability of circulating concentrations of orally administered cannabinoids, which makes dose titration more difficult and therefore increases the potential for adverse psychoactive effects. Smoking allows more accurate dose titration."

—David Baker et al., "The Therapeutic Potential of Cannabis," *The Lancet Neurology*, May 2003

Patient Experience With Marinol Matches What We Know Scientifically

"When we look at the pharmaecopia, when taken by mouth, delta-9 THC [Marinol] has a very low 6 to 20 percent absorption, and it's very variable from one person to another."

"Smoking THC, the THC is rapidly absorbed into the blood stream and redistributed with a considerable amount of it destroyed by combustion. Peak plasma levels are achieved at the very end of smoking and decline rapidly over 30 minutes, as if it were given intravenously, whereas, if taken by mouth, it's a slow [peak] and doesn't reach very high peaks and takes a long time to disappear.

"The amount of THC one is exposed to might be the same, but certainly the effects are much different. In patients who say, 'I can control the onset and the duration much easier if I smoke than if I swallow it,' [they] are telling us just what we know from the pharmaecopia."

—Donald Abrams, M.D., professor at the University of California, San Francisco, who has conducted U.S. government-approved research into the effects of smoked marijuana and AIDS patients, May 17, 1999

THC (Marinol) Doesn't Have the Same Benefits as Marijuana

"Not all the observed effects with cannabis can be ascribed to THC alone, other plant constituents may significantly modulate its action."

"Pure natural and synthetic [cannabinoid] compounds do not have disadvantages, but may not have the overall therapeutic effect of the herb."

—Barbara Costa, "On the Pharmacological Properties of Δ9-Tetrahydrocannabinol (THC)," *Chemistry & Biodiversity*, August 2007

CBD (a Cannabinoid Not Contained in Marinol) Has Medicinal Benefits and Reduces THC Side Effects

"Another important phytocannabinoid, the non-psychoactive cannabidiol (CBD), is not only an analgesic, anti-inflammatory, and antioxidant in its own right, but it is also reported to allay various THC side effects, including sedation, tachycardia, and anxiety."

— Russo E., Guy J., and Robson P.J., "Cannabis, Pain, and Sleep: Lessons From Therapeutic Clinical Trials of Sativex, a Cannabis-Based Medicine," *Chemistry & Biodiversity*, August 2007

Inhalation Improves Dose Control

"The benefits of smoked marijuana are that its effects peak rapidly (<20 minutes), allowing for dose titration and immediate symptom relief."

"Absorption of dronabinol is variable, however, and it has a slow rate of onset (peak effects in approximately 120 minutes) and a long duration of action, which make it difficult to titrate dose to achieve the desired effect. In addition, nauseated patients can have difficulty taking an oral medication."

[Note: in this study, also cited above, it took eight times the standard dose of dronabinol (Marinol) to produce effects roughly equal to low-potency smoked marijuana containing 3.9% THC]

—Margaret Haney, et al., "Dronabinol and Marijuana in HIV-Positive Marijuana Smokers: Caloric Intake, Mood, and Sleep," *Journal of Acquired Immune Deficiency Syndromes*, May 16, 2007

Marinol is Three Times More Psychoactive than Marijuana

"Marinol (a synthetic form of THC) is classified as a schedule III controlled substance while marijuana is classified as schedule I — despite the fact that Marinol contains a THC metabolite that is three times more psychoactive than the THC delivered to the lungs by smoked cannabis."

—American Pain Foundation, American Medical Women's Association, Lymphoma Foundation of America, American Nurses Association, California Nurses Association, AIDS Action Council, National Women's Health Network, Doctors of the World-USA, Gay Men's Health Crisis, Amici Curiae in Support of Petitioner, Ross v. Ragingwire, 2006 WL 3244938 Appellate Brief, August 7, 2006

Marinol's Slow Absorption Hampers Effectiveness

"It is well recognized that Marinol's oral route of administration hampers its effectiveness because of slow absorption and patients' desire for more control over dosing."

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

Introduction: Medical Marijuana Science and Studies Documentation

The following tabs include excerpts from numerous studies and scientific articles showing the medical efficacy of marijuana and its active components, known as cannabinoids, for a wide array of conditions, including cancer, HIV, multiple sclerosis, amyotrophic lateral sclerosis, and many others. Also included are scientific findings refuting common misconceptions about potential health hazards posed by marijuana use, most notably in relation to cancer and neurotoxicity. This is merely a representative sample of the large body of scientific evidence on the subject; it is not a comprehensive list.

Due to government interference and restrictions placed on the use of the actual marijuana plant for scientific studies in the U.S., some of these studies were conducted outside the U.S. or were able to examine only component compounds extracted from marijuana or synthetic versions of those compounds. Additional clinical trials, which would require the lifting of governmental roadblocks, are especially desirable because of the current availability of vaporizers, which allow the use of whole marijuana while eliminating the potential dangers of smoking.

Numerous Potential Medical Uses, But Politics Gets In the Way

"Preclinical and clinical research and anecdotal reports suggest numerous potential medical uses for marijuana."

"A clear discord exists between the scientific community and federal legal and regulatory agencies over the medicinal value of marijuana, which impedes the expansion of research... ACP urges review of marijuana's status as a Schedule I controlled substance and reclassification into a more appropriate schedule, given the scientific evidence regarding marijuana's safety and efficacy in some clinical conditions."

—American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana," January 2008

The Only Effective Relief for a Significant Number of Patients

"For a significant number of patients, clinical experience and research confirm that marijuana serves as the only effective medicine for relieving pain, suppressing nausea or stimulating appetite. Numerous studies by blue-ribbon government panels and federally funded, peer-reviewed scientific studies have consistently found that marijuana is effective for treating certain debilitating symptoms."

— American Pain Foundation, American Medical Women's Association, Lymphoma Foundation of America, American Nurses Association, California Nurses Association, AIDS Action Council, National Women's Health Network, Doctors of the World-USA, Gay Men's Health Crisis, Amici Curiae in Support of Petitioner, *Ross v. Ragingwire*, 2006 WL 3244938 Appellate Brief, August 7, 2006

Life and Death

"These studies have consistently found (1) that marijuana is an effective anti-inflammatory, analgesic, appetite-stimulating, antiemetic, and antispasmodic agent; (2) that its side effects are often less debilitating than those of drugs currently approved for treating the same ailments; and (3) that for some individuals it is the only meaningful option. For certain persons, the medical use of marijuana can literally mean the difference between life and death."

— Lymphoma Foundation of America, HIV Medicine Association of the Infectious Diseases Society of America, American Medical Students Association, Dr. Barbara Roberts, Irvin Rosenfeld, Amici Curiae in Support of Respondents, *Gonzales v. Raich*, Supreme Court of the United States, October Term, 2004, No. 03-1454.

Institute of Medicine Recognizes Medical Use in Some Situations

"[W]e concluded that there are some limited circumstances in which we recommend smoking marijuana for medical uses."

—Principal Investigator John Benson, speaking at the Institute of Medicine news conference for release of "Marijuana and Medicine: Assessing the Science Base," March 1999

Extremely Wide Acute Margin of Safety

"[M]arijuana has an extremely wide acute margin of safety for use under medical supervision and cannot cause lethal reactions ... [G]reater harm is caused by the legal consequences of its prohibition than possible risks of medicinal use."

— American Public Health Association, Resolution #9513, "Access to Therapeutic Marijuana/Cannabis," 1995

Overwhelming Evidence that Marijuana Relieves Certain Symptoms

"The evidence is overwhelming that marijuana can relieve certain types of pain, nausea, vomiting and other symptoms caused by illnesses like multiple sclerosis, cancer and AIDS — or by the harsh drugs sometimes used to treat them. And it can do so with remarkable safety. Indeed, marijuana is less toxic than many of the drugs that physicians prescribe every day."

— Former U.S. Surgeon General Joycelyn Elders, M.D., "Myths About Medical Marijuana," *Providence Journal*, March 26, 2004

One of the Safest Therapeutically Active Substances Known

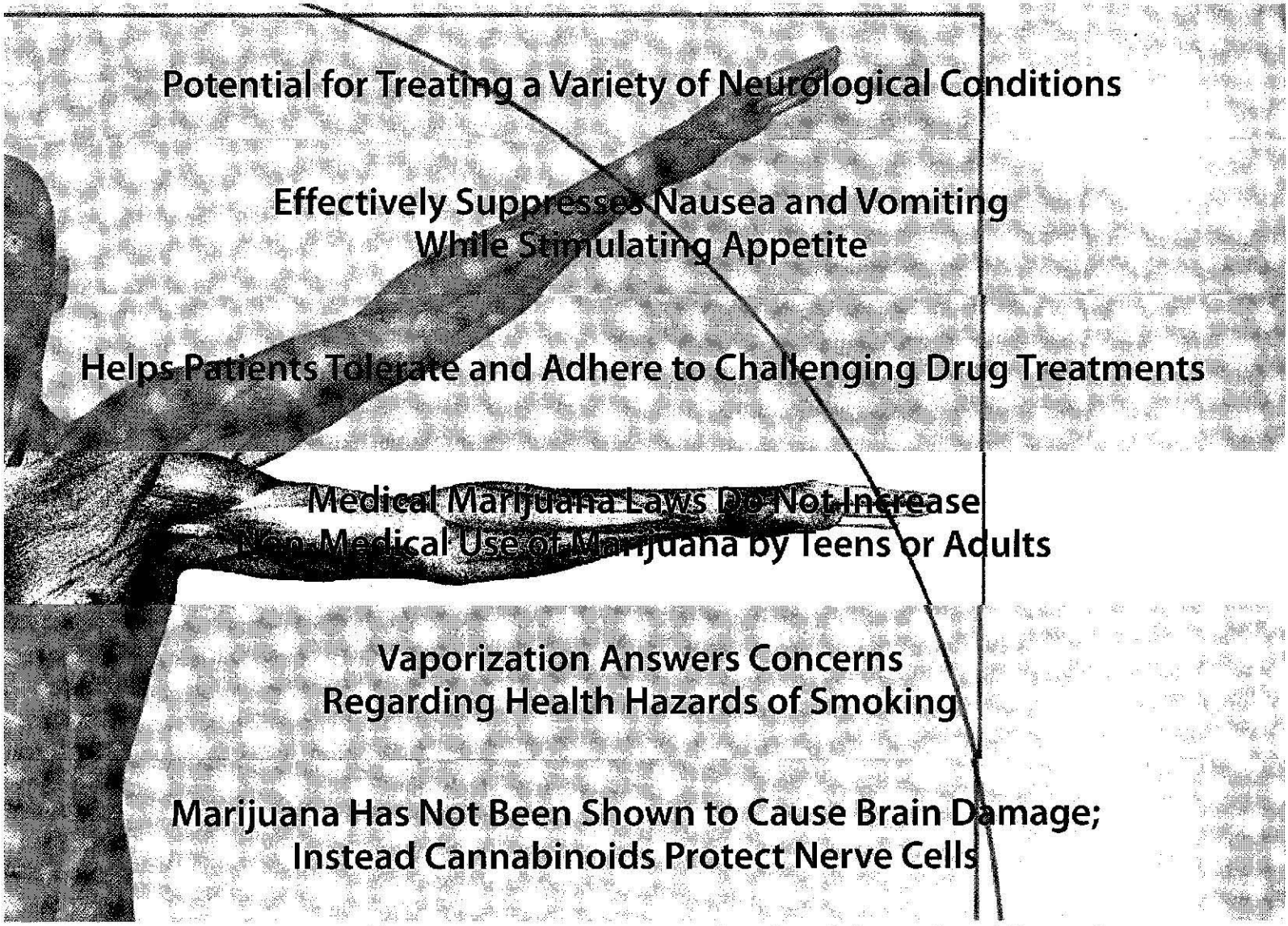
"Marijuana, in its natural form, is one of the safest therapeutically active substances known ... The evidence in this record clearly shows that marijuana has been accepted as capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision. It would be unreasonable, arbitrary and capricious for [the] DEA to continue to stand between those sufferers and the benefits of this substance."

— Francis L. Young, DEA Chief Administrative Law Judge, 1988

Improves Quality of Life for Advanced Cancer Patients

"[F]or cancer patients with advanced cancers who want to improve the quality of their life, a risk versus benefit analysis [of smoked medical marijuana] weighs heavily on the benefit side."

— *Cancer Monthly*, May 2006



U.S. Government Holds a Patent on Cannabinoids as Neuroprotectants

"The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke or trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and HIV dementia."

— The government of the United States of America, represented by the Secretary, Department of Health and Human Services, "Cannabinoids as AntiOxidants and Neuroprotectants," international application published under the Patent Cooperation Treaty, international publication no. WO 99/53916, October 1999

Marijuana Unlikely to be Neurotoxic to the Adolescent Brain

"[N]o pattern consistent with evidence of cerebral atrophy or loss of white matter integrity was detected. It is concluded that frequent cannabis use is unlikely to be neurotoxic to the normal developing adolescent brain."

— Lynn E. DeLisi, et al., "A Preliminary DTI Study Showing No Brain Structural Change Associated With Adolescent Cannabis Use," *Harm Reduction Journal*, May 9, 2006

Cannabinoids Protect Central Nervous System With Remarkably Low Toxicity

"In the CNS, most of the experimental evidence indicates that cannabinoids may protect neurons from toxic insults such as glutamatergic overstimulation, ischemia and oxidative damage. The neuroprotective effect of cannabinoids may have potential clinical relevance for the treatment of neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease,cerebrovascular ischemia and stroke. Both endogenous and exogenous cannabinoids appear to have neuroprotective and antioxidant effects."

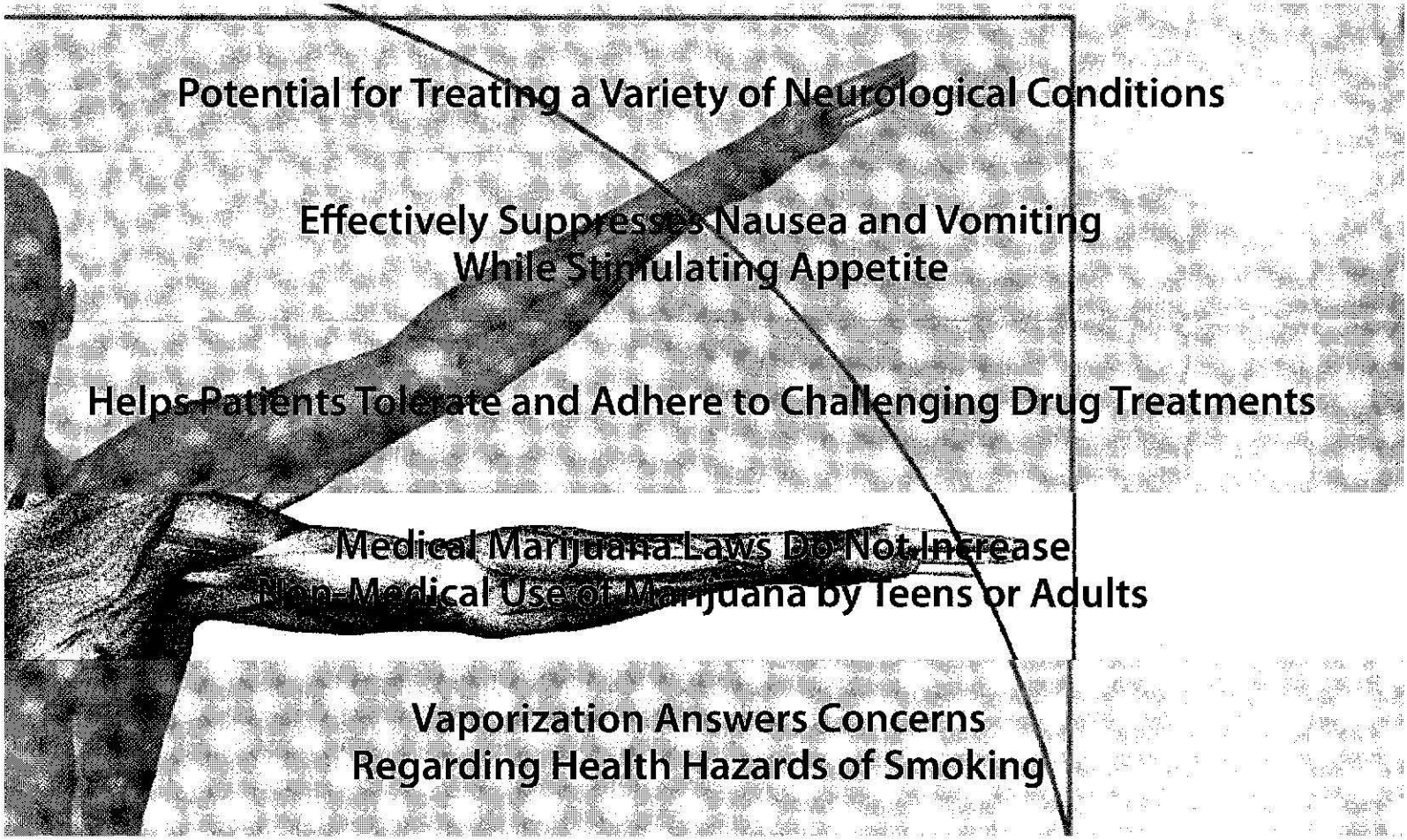
"This class of compounds not only holds tremendous therapeutic potential for neurological disease but is also confirmed as having remarkably low toxicity."

— Gregory Carter, et al., "Overview: Cannabis: Old Medicine With New Promise for Neurological Disorders," *Current Opinion in Investigational Drugs*, March 2002

Modern Research Refutes Claims of Brain Damage

"Earlier studies purporting to show structural changes in the brains of heavy marijuana users have not been replicated with more sophisticated techniques."

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



Because of concerns about smoking, the Institute of Medicine's 1999 review called for the development of "a nonsmoked, rapid-onset cannabinoid delivery system." Vaporization provides such a delivery system for whole marijuana, taking advantage of the fact that cannabinoids vaporize at a temperature well below that at which marijuana burns. By heating the material to the proper temperature, vaporizers can provide the advantages of inhalation — fast action and ease of dose titration — without the potentially harmful combustion products contained in smoke.

Fewer Respiratory Symptoms in Marijuana Users Who Vaporize

"We examined self-reported respiratory symptoms in participants who ranged in cigarette and cannabis use. Data from a large Internet sample revealed that the use of a vaporizer predicted fewer respiratory symptoms even when age, sex, cigarette smoking, and amount of cannabis used were taken into account."

"These results suggest that the respiratory effects of cannabis can decrease with the use of a vaporizer."

— S.S. Barnwell and M. Earleywine, "Decreased Respiratory Symptoms in Cannabis Users Who Vaporize," *Harm Reduction Journal*, April 2007

Vaporization is a Safe and Effective Delivery System

"Our results show that with the Volcano [vaporizer] a safe and effective cannabinoid delivery system seems to be available to patients. The final pulmonal uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking."

— A. Hazecamp, et al., "Evaluation of a Vaporizing Device (Volcano®) for the Pulmonary Administration of Tetrahydrocannabinol," *Journal of Pharmaceutical Sciences*, June 2006

Vaporization Offers Rapid Relief Without Smoking's Negative Effects

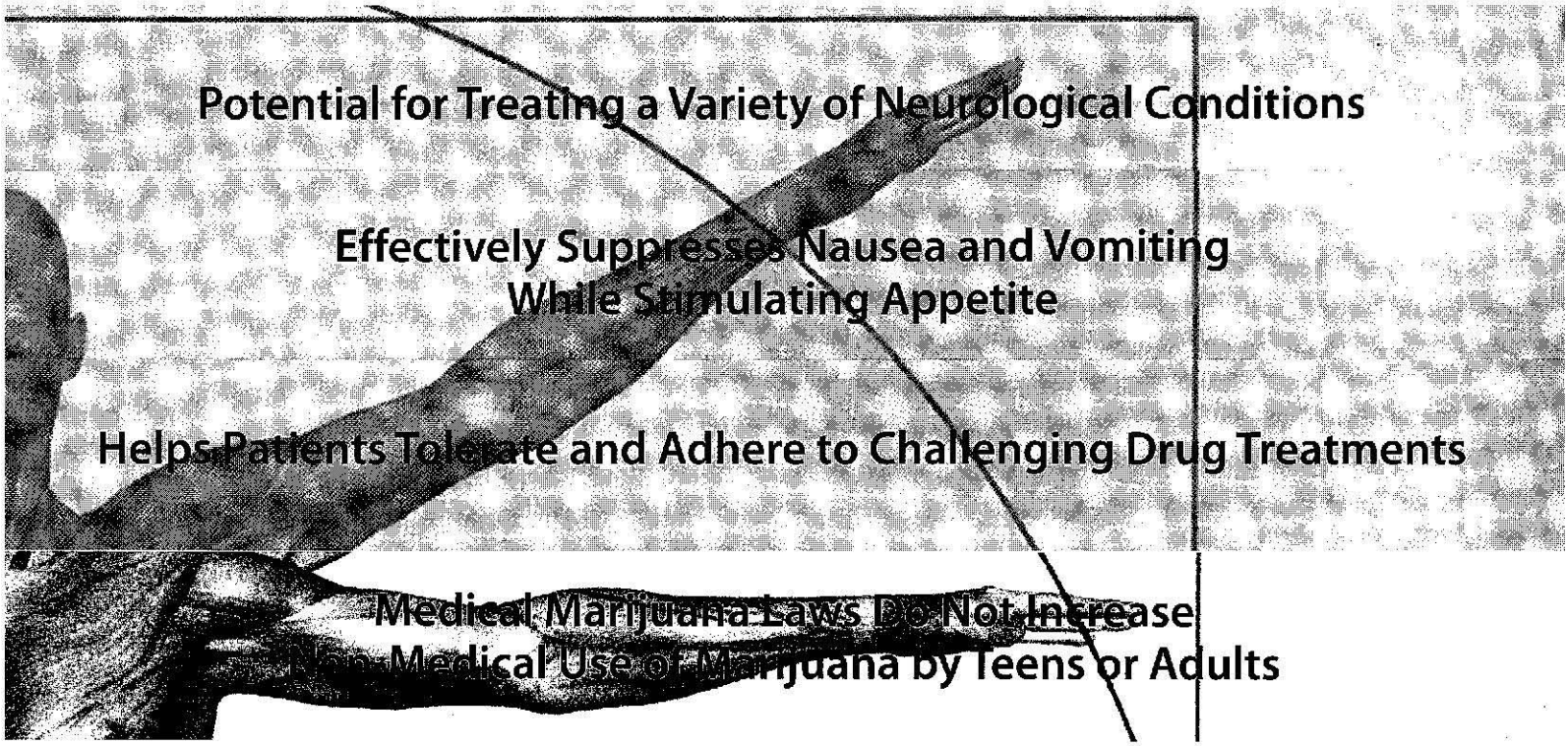
"The development of a vapor route for THC delivery offers promise for the future of medical marijuana research. A recent study found that THC administered through the Volcano vaporizer resulted in higher plasma THC levels compared to smoked marijuana at both 30 and 60 minutes post administration. It also found that exhaled carbon monoxide increased very little after vapor compared with smoking. Those findings, along with patient preference for the vapor method, indicate opportunities for future clinical trials. Vaporization of THC offers the rapid onset of symptom relief without the negative effects from smoking. It allows patients to self regulate their dosage immediately by ceasing inhalation when or if psychoactive effects become unpleasant."

— American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana," January 2008

Vaporization Avoids Exposure to Combustion Toxins

"Whereas smoking marijuana increased CO levels as expected for inhalation of a combustion product, there was little if any increase in CO after inhalation of THC from the vaporizer. This indicates little or no exposure to gaseous combustion toxins."

— D.I. Abrams, et al., "Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study," *Clinical Pharmacology & Therapeutics*, May 2007



A decade after the passage of the nation's first state medical marijuana law, California's Prop. 215, a considerable body of data shows that no state with a medical marijuana law has experienced a statistically significant increase in youth marijuana use since their laws' enactment. In fact, all states except Colorado have reported overall decreases — exceeding 50% in some age groups — strongly suggesting that state medical marijuana laws do not increase teen marijuana use.

Contrary to the fears expressed by opponents of medical marijuana laws, there is no evidence that the enactment of 12 state medical marijuana laws has produced an increase in adolescent marijuana use in those states or nationwide. Instead, data from those states suggest a modest decline overall, with very large declines in some age groups in some states. Overall, the decrease in teen marijuana use in medical marijuana states has slightly exceeded the national decline. For a detailed analysis of official state surveys, see **www.mpp.org/teens**.

No Increase in Marijuana Use in States With Medical Marijuana Laws

"No statistically significant pre-law versus post-law differences were found in any of the ADAM or DAWN sites. Thus, consistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug ....

"Our results indicate that the introduction of medical cannabis laws was not associated with an increase in cannabis use among either arrestees or emergency department patients in cites and metropolitan area located in four states in the USA (California, Colorado, Oregon, and Washington)."

— D.M. Gorman and J.C. Huber, "Do Medical Cannabis Laws Encourage Cannabis Use?," *The International Journal of Drug Policy*, May 2007

No Evidence for the "Wrong Message" Theory

"Use of marijuana by youth, which had been on an upward trend since the early 1990s at all three grade levels, did not intensify as predicted by the 'wrong message' theory. Instead, it leveled off between 1995-96 and the current (1997-98) survey. There is no evidence supporting that the passage of Proposition 215 increased marijuana use during this period."

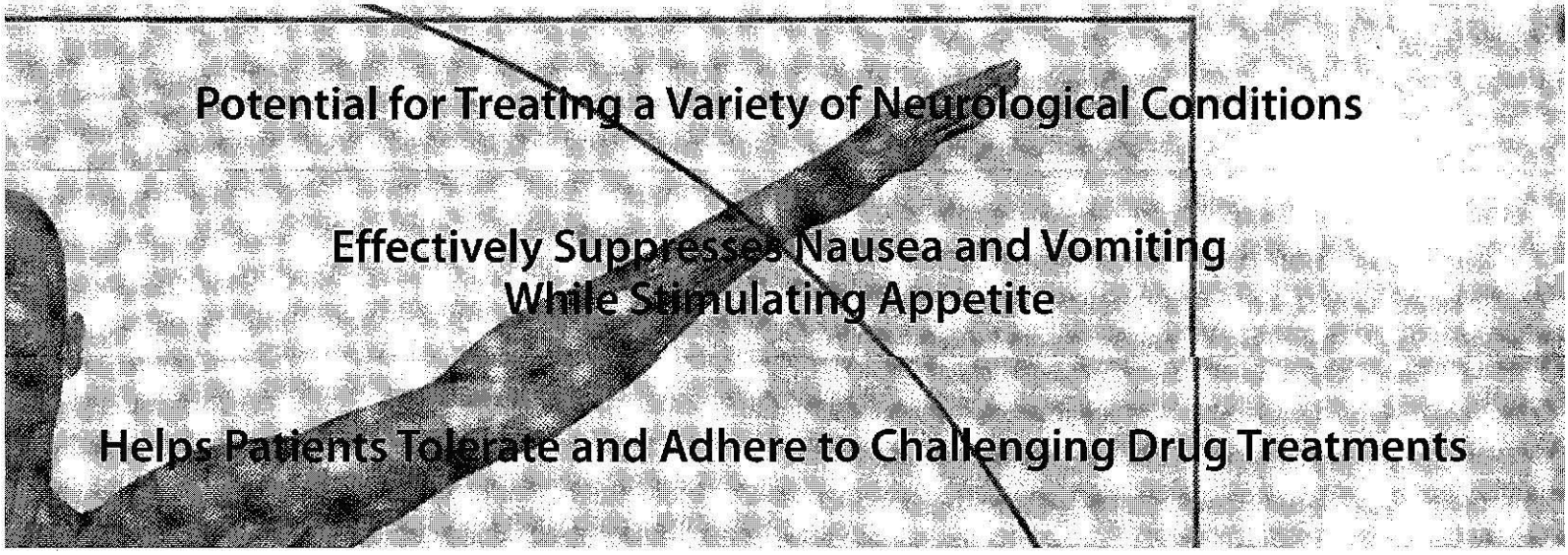
— Rodney Skager, Greg Austin, and Mamie M. Wong, "Marijuana Use and the Response to Proposition 215 Among California Youth, a Special Study From the California Student Substance Use Survey (Grades 7, 9, and 11), 1997-98," p. 7.

Official California Data Show Sharp Decline in Teen Marijuana Use After the State's Medical Marijuana Law Passed in 1996

USE OF MARIJUANA, PAST 6 MONTHS, GRADE 9	PERCENTAGE
1993-94	30.4
1995-96	34.2
1997-98	32.5
1999-00	19.2
2001-02	19.3
2003-04	18.8
2005-06	18.7

USE OF MARIJUANA, PAST 6 MONTHS, GRADE 11	PERCENTAGE
1993-94	40.0
1995-96	42.8
1997-98	41.6
1999-00	34.7
2001-02	34.0
2003-04	30.5
2005-06	29.8

— WestEd. "Report to Attorney General Bill Lockyer: Compendium of Results, 11th Biennial California Student Survey, Grades 7, 9, and 11, 2005-06," October 2006



Potential for Treating a Variety of Neurological Conditions

Effectively Suppresses Nausea and Vomiting While Stimulating Appetite

Helps Patients Tolerate and Adhere to Challenging Drug Treatments

One of the biggest obstacles to successful treatment for long-term illnesses such as HIV/AIDS, hepatitis C, and cancer is the harsh set of side effects caused by medications. Extensive research has documented that these toxicities, including nausea, vomiting, and other debilitating symptoms, are a major reason why patients interrupt or discontinue life-saving treatment. Better medication adherence literally means saved lives, and several studies have now documented that marijuana can help patients stay on life-saving regimens.

Human and animal studies also suggest that use of marijuana and/or cannabinoids may permit reduced use of more toxic or addictive opioid analgesics and other medications.

Adherence to HIV Treatment Regimens

"Excellent adherence to ART [antiretroviral medication to treat HIV] medication (often defined as .95% of medication taken) is related to having a suppressed viral load, increased CD4 response, slower disease progression, lower rates of hospital admission, and prolonged survival."

"Our data do suggest that use of smoked marijuana specifically for amelioration of nausea may be associated with adherence to ART among patients with HIV/AIDS."

— B. DeJong, et al., "Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea," *Journal of Acquired Immune Deficiency Syndromes*, January 2005

Nausea and Vomiting Relief for Cancer and HIV Patients

"Clinical trials have demonstrated that both oral and smoked marijuana stimulate appetite, increase caloric intake and result in weight gain among patients experiencing HIV wasting. Studies of chemotherapy patients with nausea and vomiting found THC to be equivalent or superior to other antiemetics (including prochloperazine or metoclopramide) for symptom reduction. Research has also found that administration of THC along with another antiemetic was more effective that either drug alone, suggesting opportunities for combined therapy"

"THC and other cannabinoids may offer relief not found in other drugs."

— American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana," January 2008

Improved Quality of Life for Patients

"Cannabis smoking, even of a crude, low-grade product, provides effective symptomatic relief of pain, muscle spasms, and intraocular pressure elevations in selected patients failing other modes of treatment. These clinical cannabis patients are able to reduce or eliminate other prescription medicines and their accompanying side effects; Clinical cannabis provides an improved quality of life in these patients."

— Ethan Russo, et al., "Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis," *Journal of Cannabis Therapeutics*, 2002

Improved Success in Hepatitis C Due to Better Treatment Adherence

"The results of this observational study suggest that the use of cannabis during HCV [hepatitis C virus] treatment can improve adherence by increasing the duration of time that patients remain on therapy; this translates to reduced rates of post-treatment virological relapse and improved SVR [sustained virological response]."

"Clinical trials have demonstrated that cannabinoids reduce nausea and improve appetite in humans, and cannabis has shown benefit in modulating the nausea of cancer chemotherapy, multiple sclerosis-related spasticity, and the wasting syndrome of HIV."

"... [O]ur results suggest that moderate cannabis use during HCV treatment may offer significant benefit to certain patients."

[Note: In this study, the rate of treatment success (sustained virological response) for marijuana users was three times that of non-users]

— D. Sylvestre, et al., "Cannabis Use Improves Retention and Virological Outcomes in Patients Treated for Hepatitis C," *European Journal of Gastroenterology & Hepatology*, October 2006

Potential for Treating a Variety of Neurological Conditions

Effectively Suppresses Nausea and Vomiting While Stimulating Appetite

Currently, clinical uses of marijuana and cannabinoids primarily center on symptomatic relief, including relief of nausea, vomiting, and wasting — whether caused by illness or as side effects of medications such as cancer chemotherapy and treatments for HIV and hepatitis C.

Marijuana Stimulates Appetite and Increases Caloric Intake

"Clinical trials have demonstrated that both oral and smoked marijuana stimulate appetite, increase caloric intake and result in weight gain among patients experiencing HIV wasting."

— American College of Physicians, "Supporting Research into the Therapeutic Role of Marijuana," January 2008

American Medical Association Recognizes Marijuana's Antiemetic Properties

"Smoked marijuana was comparable to or more effective than oral THC [Marinol], and considerably more effective than procholorperazine or other previous antiemetics in reducing nausea and emesis."

— American Medical Association, "Council on Scientific Affairs Report 10 — Medical Marijuana," December 9, 1997

Institute of Medicine Recognizes Medical Marijuana for Appetite Loss

"Nausea, appetite loss, pain and anxiety are all afflictions of wasting, and all can be mitigated by marijuana."

"For patients such as those with AIDS or who are undergoing chemotherapy and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad spectrum relief not found in any other single medication."

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

Inhaled Marijuana Effectively Treats Nausea and Vomiting

"Fifty-six patients who had no improvement with standard antiemetic agents were treated and 78% demonstrated a positive response to marijuana … inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."

— Vincent Vinciguerra, et al., "Inhalation Marijuana as an Antiemetic for Cancer Chemotherapy," *New York State Journal of Medicine*, October 1988

Antiemetic Properties for Cancer Patients

"We conclude that THC is an effective antiemetic in many patients who receive chemotherapy for cancer and for whom other antiemetics are ineffective."

— S.E. Sallan, et al., "Antiemetics in Patients Receiving Chemotherapy for Cancer," *New England Journal of Medicine*, 1980

Nausea and Vomiting Relief for Cancer Chemotherapy Patients

"On the basis of these studies, it appears that smoked marijuana can be a very successful treatment for nausea and vomiting following cancer chemotherapy."

— Musty R. E. and Rossi R., "Effects of Smoked Cannabis and Oral Δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials," *Journal of Cannabis Therapeutics*, 2002

Multiple Medical Benefits of Marijuana and THC

"The available pharmacological data have provided evidence that cannabis, and THC in particular, have a potential for clinical use. The accomplishment of a greater number of controlled clinical trials makes it possible to affirm that THC exhibits an interesting therapeutic potential as anti-emetic, appetite stimulant in debilitating diseases (cancer and AIDS), analgesic, as well as in the treatment of multiple sclerosis and Tourette's syndrome."

— Barbara Costra, "On the Pharmacological Properties of Δ9-Tetrahydrocannabinol (THC)," *Chemistry & Biodiversity*, August 2007

Palliative Effects in Cancer Patients

"Cannabinoids — the active components of Cannabis sativa and their derivatives — exert palliative effects in cancer patients by preventing nausea, vomiting and pain and by stimulating appetite."

—Manuel Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews: Cancer*, October 2003

Increased Food Intake, Better Sleep, No Disruption in Functioning

"Thus, these data suggest that for HIV-positive marijuana smokers, dronabinol and marijuana produce comparable increases in food intake and improve mood without producing disruptions in psychomotor functioning; marijuana has the added benefit of improving ratings of sleep."

"It has been reported that among HIV-positive patients who had tried dronabinol and smoked marijuana, 93% reported preferring marijuana."

[Note: in this study it took eight times the standard dose of dronabinol (Marinol) to produce effects roughly equal to low-potency smoked marijuana containing 3.9% THC]

— Margaret Haney, et al., "Dronabinol and Marijuana in HIV-Positive Marijuana Smokers: Caloric Intake, Mood, and Sleep," *Journal of Acquired Immune Deficiency Syndromes*, May 16, 2007

Potential for Treating a Variety of Neurological Conditions

Multiple human and animal studies using a variety of different forms of marijuana and cannabinoids indicate relief of tremor, spasticity, and other neurological symptoms, and potential for treating conditions such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), multiple sclrerosis, epilepsy, and Alzheimer's disease.

Medical Marijuana Controls Clinical Symptoms of ALS

"I have spent my entire career in search of more effective treatments for this awful disease [amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease)]. We have now found that the cannabinoids, the active ingredients in medical marijuana, work remarkably well in controlling the clinical symptoms of ALS. Even more exciting is that we are now discovering that the cannabinoids actually protect nerve cells and may prolong the life of patients with ALS."

— Gregory Carter, M.D., clinical professor of Rehabilitation Medicine, University of Washington School of Medicine, and co-director, Muscular Dystrophy Association (MDA)/ Amyotrophic Lateral Sclerosis (ALS) Center. Testimony submitted to Illinois Senate Public Health Committee, March 2007

Medical Marijuana Benefits Related to ALS

"[M]arijuana has now been shown to have strong antioxidative and neuroprotective effects, which may prolong neuronal cell survival. From a pharmacological perspective, marijuana is safe with minimal possibility of overdose. In states where it is legal to do so, marijuana should be considered in the pharmacological management of ALS."

— Gregory T. Carter and Bill S. Rosen, "Marijuana in the Management of Amyotrophic Lateral Sclerosis, "*American Journal of Hospice and Palliative Care*, July/August 2001

More Reported Medical Marijuana Benefits Related to ALS

"The results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling."

— Dagmar Amtmann, et al., "Survey of Cannabis Use in Patients With Amyotrophic Lateral Sclerosis," *American Journal of Hospice & Palliative Medicine*, March/April 2004

Extended Symptom Relief Without Increased Dosage

"... [P]atients with MS who derive symptom relief from CBM [cannabis-based medicine] in the first 10 weeks, generally maintain that symptom relief over an extended period of treatment without any increase in dose."

— Wade D. T., et al., "Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis," *Multiple Sclerosis*, 2006

Marijuana Component Cannabidiol Has Potential Benefits in Epilepsy

"The anticonvulsant nature of cannabidiol suggests that it has a therapeutic potential in at least three of the four major types of epilepsy: grand mal, cortical focal, and complex partial seizures."

— R. Karler and S.A. Turkanis, "The Cannabinoids as Potential Antiepileptics," *The Journal of Clinical Pharmacology*, August 1981

Prevention of the Neurodegenerative Process of Alzheimer's

"Our results indicate that cannabinoid receptors are important in the pathology of [Alzheimer's Disease] and that cannabinoids succeed in preventing the neurodegenerative process occurring in the disease."

— Belen Ramirez, et al., "Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation," *The Journal of Neuroscience*, February 25, 2005

Relief of Spasticity and Pain in MS With a Cannabis Extract

"There was evidence of a treatment effect on patient-reported spasticity and pain (p=0·003), with improvement in spasticity reported in 61% (n=121, 95% CI 54·6–68·2), 60% (n=108, 52·5–66·8), and 46% (n=91, 39·0–52·9) of participants on cannabis extract, Δ9-THC, and placebo, respectively."

— Zajicek J., et al., "Cannabinoids For Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis (CAMS Study): Multicentre Randomized Placebo-Controlled Trial," *The Lancet*, November 8, 2003

Treatment of Both Symptoms and Disease Progression in Alzheimer's Disease

"AChE inhibitors such as THC and its analogues may provide an improved therapeutic for Alzheimer's disease, augmenting acetylcholine levels by preventing neurotransmitter degradation and reducing Aβ aggregation, thereby simultaneously treating both the symptoms and progression of Alzheimer's disease."

— L. Eubanks, et al., "A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology," *Molecular Pharmaceutics*, June 2006

Marijuana Use Associated with Fewer and Less Severe Seizures Among Epileptics

"Although more data are needed, animal studies and clinical experience suggest that marijuana or its active constituents may have a place in the treatment of partial epilepsy. Here we present the case of a 45-year-old man with cerebral palsy and epilepsy who showed marked improvement with the use of marijuana. This case supports other anecdotal data suggesting that marijuana use may be a beneficial adjunctive treatment in some patients with epilepsy ... In a Canadian telephone survey and chart review of 136 patients older than 18 years, 21% admitted active marijuana use. None felt that marijuana exacerbated seizures, 68% reported improved seizure severity, and 54% reported reduced seizure frequency."

—Katherine Mortati, "Marijuana: An Effective Antiepileptic Treatment in Partial Epilepsy? A Case Report and Review of the Literature," *Reviews in Neurological Diseases*, Spring 2007

Relative Addictiveness of Drugs
By Philip J. Hilts, New York Times, Aug. 2, 1994

Is Nicotine Addictive? It Depends on Whose Criteria You Use. Experts say the definition of addiction is evolving.

WASHINGTON - When heavily dependent users of cocaine are asked to compare the urge to take cocaine with the urge to smoke cigarettes, about 45 percent say the urge to smoke is as strong or stronger than that for cocaine.

Among heroin' addicts, about 3 percent rank the urge to smoke as equal to or stronger than the urge to take heroin. Among those addicted to alcohol, about 50 percent say the urge to smoke is at least as strong as the urge to drink.

Yet seven chief executives of tobacco companies testified under oath before a Congressional subcommittee in April that nicotine was not addictive. Experts in addiction disagree with that assessment, hut they say that the definition of addiction is evolving, and that they can see how such a statement might be made. <3>Hearings on Smoking This week, the Food and Drug Administration is holding hearings to consider whether cigarettes fit in the array of addictive drugs and whether the Government should regulate them.

The standard definition of addiction comes from the American Psychiatric Association and the World Health Organization, which list nine criteria for determining addiction. The two groups, which prefer the term drug dependence, base their definition on research done since the 1960's, which has determined that multiple traits must be considered in determining whether a substance is addictive. Thus although cigarettes do not offer as intense an effect as drugs like heroin and cocaine, they rank higher in a number of other factors. They not only create dependence among users but also elicit a high degree of tolerance, the need for more and more of drug to satisfy a craving. When all the factors are added up, the consensus among scientists is that nicotine is strongly addictive.

In smoking, it is not the nicotine addiction that is most harmful, but other toxic chemicals produced by burning tobacco, which cause most of the 400,000 deaths each year that are attributed to smoking.

Dr. Lynn T. Koslowski, an addiction expert at Pennsylvania State University, said addiction could generally be defined as "the repeated use of a psychoactive drug which is difficult to stop." He added that there might be many explanations for why it was hard to stop, including withdrawal that was too disturbing, or a high that was too enticing.

A diagnosis of mild dependence on a psychoactive drug is determined by meeting three of the nine criteria. Five items show moderate dependence and seven items indicate a strong dependence. (Not all nine items apply to each drug. For example, time and effort spent acquiring a drug are a significant feature of heroin addiction, but have no meaning in nicotine addiction.)

<3>Criteria of Addiction

1. Taking the drug more often or in larger amounts than intended.
2. Unsuccessful attempts to quit; persistent desire, craving.
3. Excessive time spent in drug seeking.
4. Feeling intoxicated at inappropriate times, or feeling withdrawal symptoms from a drug at such times.
5. Giving up other things for it.
6. Continued use, despite knowledge of harm to oneself and others.
7. Marked tolerance in which the amount needed to satisfy increases at first before leveling off.
8. Characteristic withdrawal symptoms for particular drugs.
9. Taking the drug to relieve or avoid withdrawal.

Before applying a test of the nine criteria, the expert first determines if the symptoms have persisted for at least a month or have occurred repeatedly over a longer period of time.

Asked about the tobacco executives' testimony on addiction, Dr. Kozlowski said, "In a way, I can see how they could say that. It has to do with a mistaken image of what addiction is, and I have many well-educated, intelligent people say something like that to me. People often think of a person taking one injection of heroin and becoming hopelessly addicted for the rest of their lives. That is wrong."

In addition, he said, when people tend to think of the high that heroin produces, one that is about as intense as cocaine and alcohol, they cannot believe cigarettes are in the same category. And they are not. Even though in large doses nicotine can cause a strong high and hallucinations, the doses used in cigarettes produce only a very mild high.

But researchers now know, says Dr. Jack Henningfield, chief of clinical pharmacology at the Addiction Research Center of the Government's National Institute on Drug Abuse, that many qualities are related to a drug's addictiveness, and the level of intoxication it produces may be one of the least important.

If one merely asks how much pleasure the drugs produce, as researchers used to do and tobacco companies still do, then heroin or cocaine and nicotine do not seem to be in the same category. Dr. Kozlowki said, "It's not that cigarettes are without pleasure, but the pleasure is not in the same ball park with heroin."

But now, he said, there are more questions to ask. "If the question is How hard is it to stop? then nicotine a very impressive drug," he said. "Its urges are very similar to heroin."

Among the properties of a psychoactive drug - how much craving it can cause, how severe is the withdrawal, how intense a high it brings - each addicting drug has its own profile.

Heroin has a painful. powerful withdrawal, as does alcohol. But cocaine has little or no withdrawal. On the other hand, cocaine is more habit-forming in some respects, it is more

reinforcing in the scientific terminology, meaning that animals and humans will seek to use it frequently in short periods of time, even over food and water.

Drugs rank differently on the scale of how difficult they are to quit as well, with nicotine rated by most experts as the most difficult to quit.

Moreover, it is not merely the drug that determines addiction, says Dr. john R. Hughes, an addiction expert at the University of Vermont. It is also the person, and the circumstances in the person's life. A user may be able to resist dependence at one time and not at another.

A central property of addiction is the user's control over the substance. With all drugs. including heroin, many are occasional users. The addictive property of the substance can be measured by how many users maintain a casual habit and how many are persistent, regular users.

According to large Government surveys of alcohol users, only about 15 percent are regular. dependent drinkers. Among cocaine users, about 8 percent become dependent. For cigarettes, the percentage is reversed. About 90 percent of smokers are persistent daily users, and 55 percent become dependent by official American Psychiatric Association criteria, according to a study by Dr. Naomi Breslau of the Henry Ford Health Sciences Center in Detroit. Only 10 percent are occasional users.

Surveys also indicate that two-thirds to four-fifths of smokers want to quit but cannot, even after a number of attempts. Dr. John Robinson, a psychologist who works for the R. J. Reynolds Tobacco Company, contests the consensus view of nicotine as addictive. Using the current standard definition of addiction, he said at a recent meeting on nicotine addiction, he could not distinguish "crack smoking from coffee drinking, glue sniffing from jogging. heroin from carrots and cocaine from colas."

It is not that Dr. Robinson and other scientists supported by tobacco companies disagree with the main points made by mainstream scientists. but that they define addiction differently. Dr. Robinson says intoxication that is psychologically debilitating is the major defining trait of an addicting substance. It is a feature that was part of standard definitions of the 1950's, and is still linked to popular ideas about addiction, but which experts now say is too simplistic and has been left behind as scientific evidence accumulates.

Experts Rate Problem Substances

* **Dr. Jack E. Henningfield of the National Institute on Drug Abuse and Dr. Neal L. Benowitz of the University of California at San Francisco** ranked six substances based on five problem areas. Withdrawal: Presence and severity of characteristic withdrawal symptoms.

* Reinforcement: A measure of the substance's ability, in human and animal tests, to get users to take it again and again, and in preference to other substances.

* Tolerance: How much of the substance is needed to satisfy increasing cravings for it, and the level of stable need that is eventually reached.

* Dependence: How difficult it is for the user to quit, the relapse rate, the percentage of people who eventually become dependent, the rating users give their own need for the substance and the degree to which the substance will be used in the face of evidence that it causes harm.

* Intoxication: Though not usually counted as a measure of addiction in itself, the level of intoxication is associated with addiction and increases the personal and social damage a substance may do.

1 = Most serious 6 = Least serious

HENNINGFIELD RATINGS

Substance	Withdrawal	Reinforcemt	Tolerance	Dependnce	Intoxictn
Nicotine	3	4	2	1	5
Heroin	2	2	1	2	2
Cocaine	4	1	4	3	3
Alcohol	1	3	3	4	1
Caffeine	5	6	5	5	6
Marijuana	6	5	6	6	4

BENOWITZ RATINGS

Substance	Withdrawal	Reinforcemt	Tolerance	Dependnce	Intoxictn
Nicotine	3*	4	4	1	6
Heroin	2	2	2	2	2
Cocaine	3*	1	1	3	3
Alcohol	1	3	4	4	1
Caffeine	4	5	3	5	5
Marijuana	5	6	5	6	4

*equal ratings

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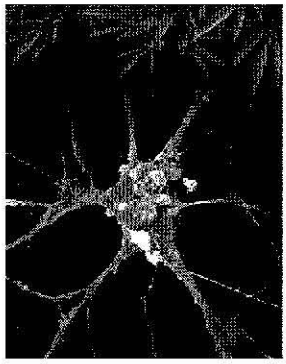
Source: Scientific American
Date: January 2004



The Brain's Own Marijuana

Research into natural chemicals that mimic marijuana's effects in the brain could help to explain - and suggest treatments for - pain, anxiety, eating disorders, phobias and other conditions

By Roger A. Nicoll and Bradley N. Alger

Marijuana is a drug with a mixed history. Mention it to one person, and it will conjure images of potheads lost in a spaced-out stupor. To another, it may represent relaxation, a slowing down of modern madness. To yet another, marijuana means hope for cancer patients suffering from the debilitating nausea of chemotherapy, or it is the promise of relief from chronic pain. The drug is all these things and more, for its history is a long one, spanning millennia and continents. It is also something everyone is familiar with, whether they know it or not. Everyone grows a form of the drug, regardless of their political leanings or recreational proclivities. That is because the brain makes its own marijuana, natural compounds called endocannabinoids (after the plant's formal name, Cannabis sativa).

The study of endocannabinoids in recent years has led to exciting discoveries. By examining these substances, researchers have exposed an entirely new signaling system in the brain: a way that nerve cells communicate that no one anticipated even 15 years ago. Fully understanding this signaling system could have far-reaching implications. The details appear to hold a key to devising treatments for anxiety, pain, nausea, obesity, brain injury and many other medical problems. Ultimately such treatments could be tailored precisely so that they would not initiate the unwanted side effects produced by marijuana itself.

A Checkered Past

Marijuana and its various alter egos, such as bhang and hashish, are among the most widely used psychoactive drugs in the world. How the plant has been used varies by culture. The ancient Chinese knew of marijuana's pain-relieving and mind-altering effects, yet it was not widely employed for its psychoactive properties; instead it was cultivated as hemp for the manufacture of rope and fabric. Likewise, the ancient Greeks and Romans used hemp to make rope and sails. In some other places, however, marijuana's intoxicating properties became important. In India, for example, the plant was incorporated into religious rituals. During the Middle Ages, its use was common in Arab lands; in 15th-century Iraq it was used to treat epilepsy; in Egypt it was primarily consumed as an inebriant. After Napoleon's occupation of Egypt, Europeans began using the drug as an intoxicant. During the slave trade, it was transported from Africa to Mexico, the Caribbean and South America.

Marijuana gained a following in the U.S. only relatively recently. During the second half of the 19th century and the beginning of the 20th, cannabis was freely available without a prescription for a wide range of ailments, including migraine and ulcers. Immigrants from Mexico introduced it as a recreational drug to New Orleans and other large cities, where it became popular among jazz musicians. By the 1930s it had fallen into disrepute, and an intense lobbying campaign demonized "reefer madness." In 1937 the U.S. Congress, against the advice of the American Medical Association, passed the Marijuana Tax Act, effectively banning use of the drug by making it expensive and difficult to obtain. Ever since, marijuana has remained one of the most controversial drugs in American society. Despite efforts to change its status, it remains federally classified as a Schedule 1 drug, along with heroin and LSD, considered dangerous and without utility.

Millions of people smoke or ingest marijuana for its intoxicating effects, which are subjective and often described as resembling an alcoholic "high." It is estimated that approximately 30 percent of the U.S. population older than 12 have tried marijuana, but only about 5 percent are current users. Large doses cause hallucinations in some individuals but simply trigger sleep in others. The weed impairs short-term memory and cognition and adversely affects motor coordination, although these setbacks seem to be reversible once the drug has been purged from the body. Smoking marijuana also poses health risks that resemble those of smoking tobacco.

On the other hand, the drug has clear medicinal benefits. Marijuana alleviates pain and anxiety. It can prevent the death of injured neurons. It suppresses vomiting and enhances appetite--useful features for patients suffering the severe weight loss that can result from chemotherapy.

Finding the Responsible Agent

Figuring out how the drug exerts these myriad effects has taken a long time. In 1964, after nearly a century of work by many individuals, Raphael Mechoulam of the Hebrew University in Jerusalem identified delta-9-tetrahydrocannabinol (THC) as the compound that accounts for virtually all the pharmacological activity of marijuana. The next step was to identify the receptor or receptors to which THC was binding.

Receptors are small proteins embedded in the membranes of all cells, including neurons, and when specific molecules bind to them--fitting like one puzzle piece into another--changes in the cell occur. Some receptors have water-filled pores or channels that permit chemical ions to pass into or out of the cell. These kinds of receptors work by changing the relative voltage inside and outside the cell. Other receptors are not channels but are coupled to specialized proteins called G-proteins. These G-protein-coupled receptors represent a large family that set in motion a variety of biochemical signaling cascades within cells, often resulting in changes in ion channels.

In 1988 Allyn C. Howlett and her colleagues at St. Louis University attached a radioactive tag to a chemical derivative of THC and watched where the compound went in rats' brains. They discovered that it attached itself to what came to be called the cannabinoid receptor, also known as CB1. Based on this finding and on work by Miles Herkenham of the National Institutes of Health, Lisa Matsuda, also at the NIH, cloned the CB1 receptor. The importance of CB1 in the action of THC was proved when two researchers working independently--Catherine Ledent of the Free University of Brussels and Andreas Zimmer of the Laboratory of Molecular Neurobiology at the University of Bonn--bred mice that lacked this receptor. Both investigators found that THC had virtually no effect when administered to such a mouse: the compound had nowhere to bind and hence could not trigger any activity. (Another cannabinoid receptor, CB2, was later discovered; it operates only outside the brain and spinal cord and is involved with the immune system.)

As researchers continued to study CB1, they learned that it was one of the most abundant G-protein coupled receptors in the brain. It has its highest densities in the cerebral cortex, hippocampus, hypothalamus, cerebellum, basal ganglia, brain stem, spinal cord and amygdala. This distribution explains marijuana's diverse effects. Its psychoactive power comes from its action in the cerebral cortex. Memory impairment is rooted in the hippocampus, a structure essential for memory formation. The drug causes motor dysfunction by acting on movement control centers of the brain. In the brain stem and spinal cord, it brings about the reduction of pain; the brain stem also controls the vomiting reflex. The hypothalamus is involved in appetite, the amygdala in emotional responses. Marijuana clearly does so much because it acts everywhere.

Over time, details about CB1's neuronal location emerged as well. Elegant studies by Tamás F. Freund of the Institute of Experimental Medicine at the Hungarian Academy of Sciences in Budapest and Kenneth P. Mackie of the University of Washington revealed that the cannabinoid receptor occurred only on certain neurons and in very specific positions on those neurons. It was densely packed on neurons that released GABA (gamma-aminobutyric acid), which is the brain's main inhibitory neurotransmitter (it tells recipient neurons to stop firing). CB1 also sat near the synapse, the contact point between two neurons. This placement suggested that the cannabinoid receptor was somehow involved with signal transmission across GABA-using synapses. But why would the brain's signaling system include a receptor for something produced by a plant?

The Lesson of Opium

The same question had arisen in the 1970s about morphine, a compound isolated from the poppy and found to bind to so-called opiate receptors in the brain. Scientists finally discovered that people make their own opioids--the enkephalins and endorphins. Morphine simply hijacks the receptors for the brain's opioids.

It seemed likely that something similar was happening with THC and the cannabinoid receptor. In 1992, 28 years after he identified THC, Mechoulam discovered a small fatty acid produced in the brain that binds to CB1 and that mimics all the activities of marijuana. He named it anandamide, after the Sanskrit word ananda, "bliss." Subsequently, Daniele Piomelli and Nephi Stella of the University of California at Irvine discovered that another lipid, 2-arachidonoyl glycerol (2-AG), is even more abundant in certain brain regions than anandamide is. Together the two compounds are considered the major endogenous cannabinoids, or endocannabinoids. (Recently investigators have identified what look like other endogenous cannabinoids, but their roles are uncertain.) The two cannabinoid receptors clearly evolved along with endocannabinoids as part of natural cellular communication systems. Marijuana happens to resemble the endocannabinoids enough to activate cannabinoid receptors.

Conventional neurotransmitters are water-soluble and are stored in high concentrations in little packets, or vesicles, as they wait to be released by a neuron. When a neuron fires, sending an electrical signal down its axon to its tips (presynaptic terminals), neurotransmitters released from vesicles cross a tiny intercellular space (the synaptic cleft) to receptors on the surface of a recipient, or postsynaptic, neuron. In contrast, endocannabinoids are fats and are not stored but rather are rapidly synthesized from components of the cell membrane. They are then released from places all over the cells when levels of calcium rise inside the neuron or when certain G-protein-coupled receptors are activated.

As unconventional neurotransmitters, canna-bin-oids presented a mystery, and for several years no one could figure out what role they played in the brain. Then, in the early 1990s, the answer emerged in a somewhat roundabout fashion. Scientists (including one of us, Alger, and his colleague at the University of Maryland School of Medicine, Thomas A. Pitler) found something unusual when studying pyramidal neurons, the principal cells of the hippocampus. After calcium concentrations inside the cells rose for a short time, incoming inhibitory signals in the form of GABA arriving from other neurons declined.

At the same time, Alain Marty, now at the Laboratory of Brain Physiology at the René Descartes University in Paris, and his colleagues saw the same action in nerve cells from the cerebellum. These were unexpected observations, because they suggested that receiving cells were somehow affecting transmitting cells and, as far as anyone knew, signals in mature brains flowed across synapses in one way only: from the presynaptic cell to the postsynaptic one.

A New Signaling System

it seemed possible that a new kind of neuronal communication had been discovered, and so researchers set out to understand this phenomenon. They dubbed the new activity DSI, for depolarization-induced suppression of inhibition. For DSI to have occurred, some unknown messenger must have traveled from the postsynaptic cell to the presynaptic GABA-releasing one and somehow shut off the neurotransmitter's release.

Such backward, or "retrograde," signaling was known to occur only during the development of the nervous system. If it were also involved in interactions among adult neurons, that would be an intriguing finding--a sign that perhaps other processes in the brain involved retrograde transmission as well. Retrograde signaling might facilitate types of neuronal information processing that were difficult or impossible to accomplish with conventional synaptic transmission. Therefore, it was important to learn the properties of the retrograde signal. Yet its identity remained elusive. Over the years, countless molecules were proposed. None of them worked as predicted.

Then, in 2001, one of us (Nicoll) and his colleague at the University of California at San Francisco, Rachel I. Wilson--and at the same time, but independently, a group led by Masanobu Kano of Kanazawa University in Japan--reported that an endocannabinoid, probably 2-AG, perfectly fit the criteria for the unknown messenger. Both groups found that a drug blocking cannabinoid receptors on presynaptic cells prevents DSI and, conversely, that drugs activating CB1 mimic DSI. They soon showed, as did others, that mice lacking cannabinoid receptors are incapable of generating DSI. The fact that the receptors are located on the presynaptic terminals of GABA neurons now made perfect sense. The receptors were poised to detect and respond to endocannabinoids released from the membranes of nearby postsynaptic cells.

Over time, DSI proved to be an important aspect of brain activity. Temporarily dampening inhibition enhances a form of learning called long-term potentiation--the process by which information is stored through the strengthening of synapses. Such storage and information transfer often involves small groups of neurons rather than large neuronal populations, and endocannabinoids are well suited to acting on these small assemblages. As fat-soluble molecules, they do not diffuse over great distances in the watery extracellular environment of the brain. Avid uptake and degradation mechanisms help to ensure that they act in a confined space for a limited period. Thus, DSI, which is a short-lived local effect, enables individual neurons to disconnect briefly from their neighbors and encode information.

A host of other findings filled in additional gaps in understanding about the cellular function of endocannabinoids. Researchers showed that when these neurotransmitters lock onto CB1 they can in some cases block presynaptic cells from releasing excitatory neurotransmitters. As Wade G. Regehr of Harvard University and Anatol C. Kreitzer, now at Stanford University, found in the cerebellum, endocannabinoids located on excitatory nerve terminals aid in the regulation of the massive numbers of synapses involved in coordinated motor control and sensory integration. This involvement explains, in part, the slight motor dysfunction and altered sensory perceptions often associated with smoking marijuana.

Recent discoveries have also begun to precisely link the neuronal effects of endocannabinoids to their behavioral and physiological effects. Scientists investigating the basis of anxiety commonly begin by training rodents to associate a particular signal with something that frightens them. They often administer a brief mild shock to the feet at the same time that they generate a sound. After a while the animal will freeze in anticipation of the shock if it hears the sound. If the sound is repeatedly played without the shock, however, the animal stops being afraid when it hears the sound--that is, it unlearns the fear conditioning, a process called extinction. In 2003 Giovanni Marsicano of the Max Planck Institute of Psychiatry in Munich and his co-workers showed that mice lacking normal CB1 readily learn to fear the shock-related sound, but in contrast to animals with intact CB1, they fail to lose their fear of the sound when it stops being coupled with the shock.

The results indicate that endocannabinoids are important in extinguishing the bad feelings and pain triggered by reminders of past experiences. The discoveries raise the possibility that abnormally low numbers of cannabinoid receptors or the faulty release of endogenous cannabinoids are involved in post-traumatic stress syndrome, phobias and certain forms of chronic pain. This suggestion fits with the fact that some people smoke marijuana to decrease their anxiety. It is also conceivable, though far from proved, that chemical mimics of these natural substances could allow us to put the past behind us when signals that we have learned to associate with certain dangers no longer have meaning in the real world.

Devising New Therapies

The repertoire of the brain's own marijuana has not been fully revealed, but the insights about endocannabinoids have begun helping researchers design therapies to harness the medicinal properties of the plant. Several synthetic THC analogues are already commercially available, such as nabilone and dronabinol. They combat the nausea brought on by chemotherapy; dronabinol also stimulates appetite in AIDS patients. Other cannabinoids relieve pain in myriad illnesses and disorders. In addition, a CB1 antagonist--a compound that blocks the receptor and renders it impotent--has worked in some clinical trials to treat obesity. But though promising, these drugs all have multiple effects because they are not specific to the region that needs to be targeted. Instead they go everywhere, causing such adverse reactions as dizziness, sleepiness, problems of concentration and thinking abnormalities.

One way around these problems is to enhance the role of the body's own endocannabinoids. If this strategy is successful, endocannabinoids could be called forth only under the circumstances and in the locations in which they are needed, thus avoiding the risks associated with widespread and indiscriminant activation of cannabinoid receptors. To do this, Piomelli and his colleagues are developing drugs that prevent the endocannabinoid anandamide from being degraded after it is released from cells. Because it is no longer broken down quickly, its anxiety-relieving effects last longer.

Anandamide seems to be the most abundant endocannabinoid in some brain regions, whereas 2-AG dominates in others. A better understanding of the chemical pathways that produce each endocannabinoid could lead to drugs that would affect only one or the other. In addition, we know that endocannabinoids are not produced when neurons fire just once but only when they fire five or even 10 times in a row. Drugs could be developed that would alter the firing rate and hence endocannabinoid release. A precedent for this idea is the class of anticonvulsant agents that suppress the neuronal hyperactivity underlying epileptic seizures but do not affect normal activity.

Finally, indirect approaches could target processes that themselves regulate endocannabinoids. Dopamine is well known as the neurotransmitter lost in Parkinson's disease, but it is also a key player in the brain's reward systems. Many pleasurable or addictive drugs, including nicotine and morphine, produce their effects in part by causing dopamine to be released in several brain centers. It turns out that dopamine can cause the release of endocannabinoids, and various research teams have found that two other neurotransmitters, glutamate and acetylcholine, also initiate endocannabinoid synthesis and release. Indeed, endocannabinoids may be a source of effects previously attributed solely to these

neurotransmitters. Rather than targeting the endocannabinoid system directly, drugs could be designed to affect the conventional neurotransmitters. Regional differences in neurotransmitter systems could be exploited to ensure that endocannabinoids would be released only where they were needed and in appropriate amounts.

In a remarkable way, the effects of marijuana have led to the still unfolding story of the endocannabinoids. The receptor CB1 seems to be present in all vertebrate species, suggesting that systems employing the brain's own marijuana have been in existence for about 500 million years. During that time, endocannabinoids have been adapted to serve numerous, often subtle, functions. We have learned that they do not affect the development of fear, but the forgetting of fear; they do not alter the ability to eat, but the desirability of the food, and so on. Their presence in parts of the brain associated with complex motor behavior, cognition, learning and memory implies that much remains to be discovered about the uses to which evolution has put these interesting messengers.

HB 1393: Providing for the medical use of marijuana

Hundreds of Pennsylvania's seriously ill are counting on the legislature to enact HB 1393, sponsored by Rep. Mark Cohen (D–202). This legislation would allow certain seriously ill patients to relieve their debilitating symptoms with marijuana, according to their doctors' advice, without facing arrest.

Marijuana Has Been Proven to Have Medical Value

• Studies show that many patients suffering from AIDS, cancer, multiple sclerosis, epilepsy, and other debilitating illnesses find that marijuana provides relief from their symptoms.

• Available prescription drugs often come with far more serious side effects than marijuana, and many patients who find relief from marijuana simply do not respond to prescription medications.

• In 1999, the prestigious Institute of Medicine reviewed the research on marijuana's medical value and found, "Nausea, appetite loss, pain, and anxiety are all afflictions of wasting and can be mitigated by marijuana," and that "there will likely always be a subpopulation of patients who do not respond well to other medications."

• In 1988, after reviewing volumes of evidence on marijuana's medical value, the DEA's chief administrative law judge, Francis Young, found that maintaining marijuana as a Schedule I drug would be "unreasonable, arbitrary, and capricious" and that "marijuana, in its natural form, is one of the safest therapeutically active substances known to man."

Thirteen States Protect Medical Marijuana Patients; Nine Others Considering Bills

• These 13 states allow the doctor-advised medical use of marijuana: Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Washington, and Vermont.

• These laws are working well, enjoy strong popular support, and are protecting patients. Data have shown that any concerns about these laws increasing youth marijuana use are unfounded: All 11 of the medical marijuana states that have produced before-and-after data have reported overall decreases in teen marijuana use — exceeding 50% in some age groups.

• Nine other state legislatures – Delaware, Illinois, Iowa, Massachusetts, New Jersey, New York, North Carolina, Tennessee, and Wisconsin – are considering enacting medical marijuana laws, and many more are expected to consider medical marijuana during their 2010 sessions. All of these bills but Tennessee's would allow state-licensed entities to dispense medical marijuana to qualifying patients.

Federal Law Does Not Stand In the Way

• Nothing in the Constitution or federal law prohibits states from having penalties that differ from federal law.

• Attorney General Eric Holder, under President Barack Obama's direction, issued a memo directing the U.S. Attorneys in states with medical marijuana programs not to prosecute patients, caregivers, and dispensaries so long as they are in strict compliance with state law.

• A federal appellate court ruled that the federal government cannot punish physicians — or even investigate them — for discussing or recommending the medical use of marijuana with patients.

• Each month, the federal government's Investigational New Drug program ships about 8 ounces of marijuana to four patients. The program was closed to new patients in 1992, depriving other seriously ill patients of this protection and safe access to the medicine their doctors recommend.

There is Strong Popular, Medical, and Religious Support For Allowing Medical Marijuana

• A 2006 Keystone Poll found that 61% of Pennsylvanians support "allowing adults to legally use marijuana for medical purposes if a doctor recommends it." A 2005 national Gallup poll found that 78% of Americans support "making marijuana legally available for doctors to prescribe in order to relieve pain and suffering." A 2004 AARP poll showed that 72% of adults aged 45 and older think patients should be allowed to legally use marijuana for medical purposes if a physician recommends it.

• In November 2008, 63% of Michigan voters approved a medical marijuana initiative. A majority of voters in each of its 83 counties approved the law.

• Support includes the American Bar Association, the American Public Health Association, the American Academy of HIV Medicine, and the Leukemia & Lymphoma Society. Two former U.S. Surgeons General – Joycelyn Elders and Jesse Steinfeld – also recognize marijuana as a legitimate, beneficial medicine.

• Religious support includes the Presbyterian Church (USA), the Union for Reform Judaism, the United Methodist Church, the United Church of Christ, the Episcopal Church, the Unitarian Universalist Association, and the Progressive National Baptist Convention.

HB 1393: Providing for the medical use of marijuana

• HB 1393 includes non-profit dispensaries, similar to those added by over 97% of Rhode Island legislators in June and approved by 59% of Maine voters in November 2009.

• This legislation would make a narrow exception to Pennsylvania's criminal laws to allow seriously ill patients to possess and grow marijuana for the patients' medical use. It would make Pennsylvania the 14th state to allow medical marijuana.

• The Department of Health would issue medical marijuana ID cards, which make it easy for police to verify that a patient is allowed to use medical marijuana. A patient or caregiver with an ID card and no more than one ounce and six plants would not be subject to arrest as long as he or she is in compliance with the law. The ID cards could be revoked for a violation of the law.

• To qualify for an ID card, a patient with a qualifying condition would have to submit to the department a physician's written certification that the potential benefits of the medical use of marijuana would likely outweigh the health risks for the patient. Qualifying conditions are: cancer, glaucoma, HIV/AIDS, or a chronic or debilitating disease or medical condition causing severe pain, severe nausea, cachexia, seizures, or severe and persistent muscle spasms.

• The bill maintains commonsense restrictions, including prohibitions on public use of marijuana and driving under the influence. Employers would not be required to allow patients to be impaired at work or possess marijuana at a workplace.

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Research paper

Do medical cannabis laws encourage cannabis use?

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Abstract

Medical cannabis is a contentious issue in the United States, with many fearing that introduction of state laws will increase use among the general population. The present study examined whether the introduction of such laws affects the level of cannabis use among arrestees and emergency department patients. Using the Arrestee Drug Abuse Monitoring system, data from adult arrestees for the period 1995–2002 were examined in three cities in California (Los Angeles, San Diego, San Jose), one city in Colorado (Denver), and one city in Oregon (Portland). Data were also analysed for juvenile arrestees in two of the California cities and Portland. Data on emergency department patients from the Drug Abuse Warning Network for the period 1994–2002 were examined in three metropolitan areas in California (Los Angeles, San Diego, San Francisco), one in Colorado (Denver), and one in Washington State (Seattle). The analysis followed an interrupted time-series design. No statistically significant pre-law versus post-law differences were found in any of the ADAM or DAWN sites. Thus, consistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug. One reason for this might be that relatively few individuals are registered medical cannabis patients or caregivers. In addition, use of the drug by those already sick might "de-glamorise" it and thereby do little to encourage use among others.

Keywords: Medical cannabis; Arrestee Drug Abuse Monitoring program; Drug Abuse Warning Network; Cannabis use; Drug control policy

Introduction

There are currently 12 states in the USA with laws that remove penalties for the cultivation, possession and use of cannabis for medical reasons (Alaska, California, Colorado, Hawaii, Maine, Maryland, Montana, Nevada, Oregon, Rhode Island, Vermont and Washington) (Drug Policy Alliance, 2006; NORML, 2006). In most cases the law allows a written or oral recommendation by a physician stating that the patient will benefit from use of cannabis to serve as a medical necessity defense should the patient be arrested on charges of cannabis possession. These so-called "effective" laws differ from medical cannabis research laws and "symbolic" laws, such as Arizona's Proposition 200, which do not accord the same legal protection to patients who use cannabis (Pacula, Chriqui, Reichmann & Terry-McElrath, 2002; Schmitz & Thomas, 2004).

Medical use of cannabis has become an increasingly contentious issue as it is the primary arena in which the forces on either side of the prohibition-legalization debate engage one another, with both sides seeing the introduction of state laws as an initial step on the road to decriminalization of the drug (Clark, 2000; Schrag, 2002; Stein, 2002). The federal government vehemently opposes state-level introduction of medical cannabis laws on a number of grounds, including a fear that they have the potential to increase use among the general population (especially young people) through sending the message that cannabis use is acceptable (Clark, 2000; Medical Marijuana ProCon, 2006; Schrag, 2002). Moreover, this "wrong message" argument is not confined to the federal government. The authors of the 1999 Institute of Medicine Report observed that "almost everyone" that spoke to its study team "about the potential harms posed by medical marijuana felt that it would send the wrong message to children and

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teenagers". The Report goes on to state that: "The question here is not whether marijuana can be both harmful and helpful but whether the perception of its benefits will increase its abuse. For now any answer to the question remains conjecture. Because marijuana is not an approved medicine, there is little information about the consequences of its medical use in modern society" (Institute of Medicine, 1999, p. 101).

If the "wrong message" hypothesis is correct, one would anticipate greater use of cannabis and attendant problems to follow the passage of a state's medical cannabis law. We address this issue by examining trends in cannabis use among two high risk subgroups (arrestees and emergency department patients) from the mid-1990s through 2002 in five cities and five metropolitan areas in states that had passed medical cannabis laws in the previous 10 years.

Methods

Study design and data analyses

Data on cannabis use among arrestees were extracted from the Arrestee Drug Abuse Monitoring (ADAM) system which was established (as the Drug Use Forecasting program) by the National Institute of Justice in 1987 and ran until 2003 (National Institute of Justice, 1990, 2004). Twenty-three of the 38 ADAM sites active at the time that the program was discontinued had been in the program long enough to provide a sufficient number of data points to use in time-series analysis. Of these 23 cities, five were in states with effective medical cannabis laws—three in California, one in Oregon and one in Colorado.

Data on cannabis use among emergency department patients were extracted from the Drug Abuse Warning Network (DAWN) for the period 1994–2002. DAWN was established by the Substance Abuse and Mental Health Services Administration (SAMHSA) of the US Department of Health and Human Services in 1972, and substantially revised in 1988 and 2003 (Caulkins, Ebener & McCaffrey, 1995; Harrison, 1992; Substance Abuse and Mental Health Services Administration, 2002). Five of the 21 DAWN metropolitan areas are in states that introduced medical cannabis laws before 2002 (Maryland's law was introduced after this date). Three of these metropolitan areas are in California (Los-Angeles/Long Beach, San Francisco and San Diego), one in Colorado (Denver), and one in Washington State (Seattle). In general, the metropolitan areas included in DAWN are larger than individual cities and include the major city and its surrounding counties or suburbs.

The data analysis followed an interrupted time-series design, in which observations prior to an intervention (in this case, a law) are compared to those that occur afterwards (Cook & Campbell, 1979). This is one of the few designs available to assess full coverage interventions (such as state-wide laws) in which it is difficult to identify suitable units of analysis to act as a comparison condition (Rossi, Freeman & Lipsey, 1999). In the present instance, while there are ADAM and DAWN sites in states without medical cannabis laws, these are not suitable controls for the sites in the medical cannabis states since the dynamics of cannabis use vary even among states within the same region of the country (Golub & Johnson, 2001). Thus, using internal pre-law versus post-law comparisons (as done in a time-series analysis) is more appropriate than making comparisons across cities with very different patterns of drug use over time.

The basic idea that is tested in a time-series analysis is that if the law in question has an impact (either positive or negative) then the series of observations that follow its implementation will have a different slope or trend to those that occurred before (Cook & Campbell, 1979). Specifically, the focus of the present analysis was on the proportion of arrestees or emergency room patients "positive" for cannabis prior to the implementation of the medical cannabis law in each state versus the proportion following its implementation. If the law has the type of negative impact suggested by the "wrong message" argument, one would expect an increase in this proportion to follow the passage of the law.

A logit transformation was used to normalise both the ADAM and DAWN data so that standard ARIMA models could be used. All models were estimated using the ARIMA routines (Chatfield, 2004) available in the Stata statistical package, using lags that were specific to each model (StataCorp, 2005). The portmanteau statistic was used to test for residual autocorrelation (Chatfield, 2004). In the models, the variable "level" is an indicator variable defined as 0 prior to implementation of the law and 1 after the law went into effect. The variable "trend" is an interaction term computed as the product of time and level. All models were adjusted for the natural logarithm of the total number of arrestees from quarter to quarter.

Details of each state's medical cannabis laws are presented in Table 1, along with the names of the ADAM cities and DAWN metropolitan areas and the number of pre-law and post-law quarterly data points used in the time-series analysis in each state.

ADAM and DAWN datasets

As their titles imply, one of the primary purposes of developing the ADAM and DAWN programs was to use data to forecast, monitor and warn of trends in drug use. As stated on its website, "DAWN is an indicator system" and the data it contains, when used in conjunction with other indicators, "can help identify emerging trends in drug abuse at the local and national level" (Drug Abuse Warning Network, 2002). Likewise, one of the primary purposes of developing the ADAM program was to use data to forecast trends in drug use, not only in the criminal population, but also in the general population (Mieczkowski, 1996; National Institute of Justice, 1993; Wish & Gropper, 1990). This forecasting function is

Table 1
State medical cannabis laws in sites included in the ADAM program and DAWN

State	Legislation/initiative	Date effective	DAWN metropolitan areas	ADAM cities	Pre-laws data points[a]			Post-law data points		
					D	A-A	A-J	D	A-A	A-J
California	Proposition 215	6 November 1996	Los Angeles/Long Beach	Los Angeles	12	7	7	24	25	23
			San Diego	San Diego	12	7	7	24	25	23
			San Francisco	–	12	–	–	24	–	–
			–	San Jose	–	7	–	–	25	–
Colorado	Amendment 20	30 June 2001	Denver	Denver	30	26	–	5[b]	6	–
Washington	Initiative measure 692	3 November 1998	Seattle	–	20	–	–	16	–	–
Oregon	Ballot measure 67	3 December 1998	–	Portland	–	16	16	–	16	11

[a] D, DAWN dataset; A-A, ADAM adult dataset; A-J, ADAM juvenile dataset.
[b] The Colorado DAWN dataset ended at the third quarter of 2002 not the fourth quarter.

premised on the idea that trends in drug use among high-risk sub-groups can function as a leading indicator for future use among the general population (Mieczkowski, 1996; Wish & Gropper, 1990). It is reasoned that as a drug becomes more physically, socially and/or economically available those who are most "at-risk" will be first to initiate use; the use of the drug will then filter out to the general population.

The ADAM program collects data on a quarterly basis through urinalysis and self-reports in order to assess recent drug use among arrestees. At each ADAM site, trained interviewers conduct voluntary and anonymous interviews and collect urine specimens. Arrestees are approached within 48 h of their arrest and asked to participate in the study. Over the years, more than 80% of those approached each quarter in most sites agreed to the interview and, of those, about 80% agreed to give a urine specimen (National Institute of Justice, 2003a, p. 15). The analysis presented in this study was based on the urine test data, with the threshold for a positive urine analysis set at 50 ng per deciliter. All five of the cities included in the analysis provided data on adult arrestees (aged 18 years and above), and three included data from juvenile arrestees (aged 10–18 years). Juvenile data were never collected at the San Jose ADAM site, while the Colorado dataset contained only one post-law data point (making it insufficient for time-series analysis).

The ADAM dataset was obtained from the National Archive of Criminal Justice Data, which is maintained by the University of Michigan's Inter-university Consortium for Political and Social Research. The analysis was restricted to the data from 1995 to 2002, since the threshold for a positive cannabis test changed in 1995 from 100 to 50 ng per deciliter (Golub & Johnson, 2001, pp. 4–5) and the 2002 dataset was the most recent available at the time that we began the analysis. In Oregon, one data-point in the adult time-series and two in the juvenile time-series had to be imputed as raw data were missing. As shown in Table 1, there were fewer post-law data points in the juvenile dataset for both California and Oregon since the time-series ended at the second quarter of 2002 for the former and the third quarter of 2001 for the latter.

The DAWN program monitors the number of drug-related episodes by retrospectively examining records in a sample of non-Federal, short-stay general medical and surgical hospitals that operate emergency departments that are open 24 hours a day, 7 days a week (Substance Abuse and Mental Health Services Administration, 2003). The data collection procedure entails a review of medical records, not direct interviewing of patients. In each participating facility, a designated DAWN reporter reviews all available medical records to identify emergency room visits that were caused by or related to drug use. DAWN data are publicly available as half year estimates, but we used quarterly data for the period 1994–2002 obtained directly from the Substance Abuse and Mental Health Services Administration's Office of Applied Studies. The advantage of this dataset over the publicly available one was that it doubled the number of data points for the

time-series analysis; the disadvantage was that it did not break down drug mentions by age groups, meaning that we could not examine the effects of the law among younger patients. We ended the data series in 2002 since DAWN underwent a fundamental redesign in 2003 (Substance Abuse and Mental Health Services Administration, 2002).

Results

ADAM data

The average number of adult arrestees per quarter who provided urine samples was 328 in Denver (range 180–696), 285 in Portland (range 0–754), and 885 in the three California cities combined (range 382–2152). The wide range across quarters in California was due to the fact that Los Angeles contributed very little or no data to the quarterly counts for the period 2000 through 2002. While this would not affect the results for the immediate post-law period in California (1997–1999), it could influence the analysis of the longer term effects of the law. In light of this, we conducted the time-series analysis for California both with and without the data from Los Angeles. Since the results were essentially the same, the table and figure below present the analysis for all three cities. For juvenile arrestees, the average number of urine samples per quarter was 81 in Portland (range 0–260), and 255 in the two combined California ADAM sites (Los Angeles and San Diego) that included juveniles (range 74–724). As noted above, the missing values in the Portland datasets were imputed.

Fig. 1 shows the proportion of urine tests that were positive for cannabis among adult arrestees for each quarter from 1995 through 2002 for the three cities in California, as well as for Portland (Oregon) and Denver (Colorado). Following Golub and Johnson (2001), we present the data for all adult arrestees as well as "youthful" arrestees (i.e., those aged 18–20 years). There appears to be no noticeable increase in the trend following introduction of law in any of the three states, either for all adult arrestees or the youthful arrestees. This is especially noticeable in the lowess line, which uses a local regression technique to smooth the time series (Agresti, 2002).

Fig. 2 presents the same data for the juvenile arrestees in the two California cities and in Oregon. While there is a steep increase in the proportion testing positive for cannabis among Oregon juveniles in the early part of the data series, this levels off about 2 years before the introduction of the law and remains essentially flat thereafter.

To formally assess whether any change could be detected in the ADAM cannabis urine analysis data that coincided with the introduction of the medical cannabis laws, we examined the pre-law versus post-law proportion of positive tests using a series of ARIMA models. The results of these analyses are presented in Table 2. The parameter estimates for both the level and trend are shown in column 3, followed by the standard error of the coefficient, the statistical significance of

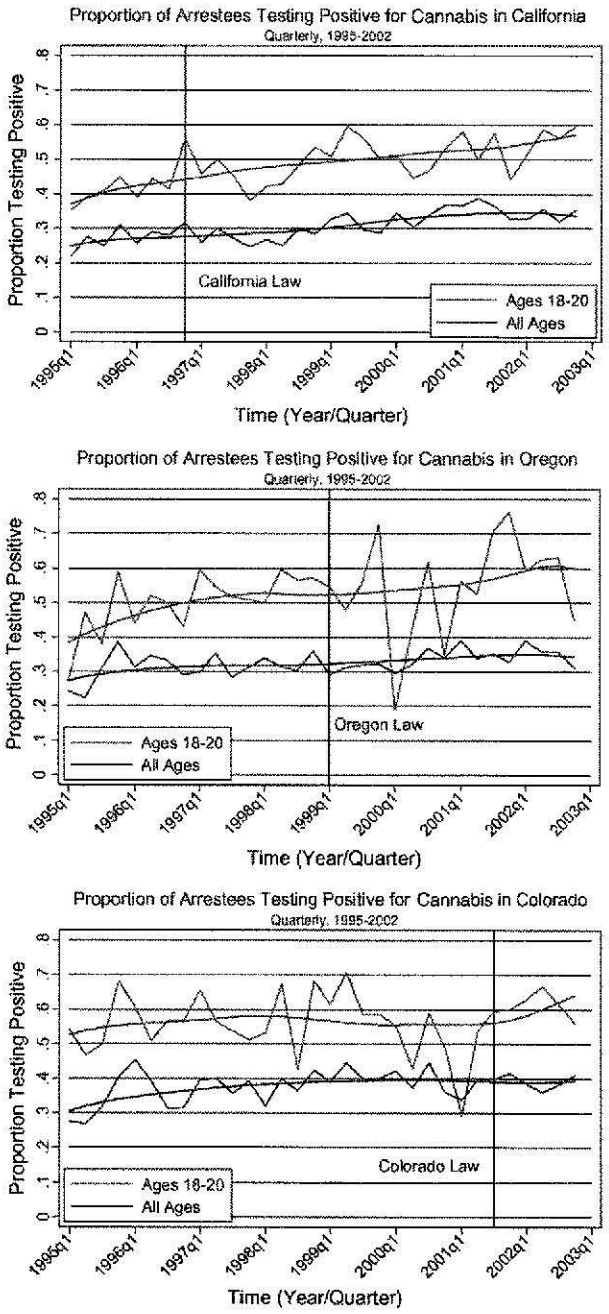

Fig. 1. Proportion of urine tests positive for cannabis among adult arrestees, 1995–2002: California, Oregon and Colorado.

the estimate, and the upper and lower boundaries of the 95% confidence interval. It can be seen that none of the parameter estimates even approached statistical significance. This was true of both the estimates of change in trend and change in level. It was also the case for the total adult sample and the youthful adult arrestees in all three states, and for the juvenile arrestees in California and Oregon. The non-significant χ^2 for the portmanteau test[19] reported in the final two columns of the table indicate that the models were successful in removing residual autocorrelation.

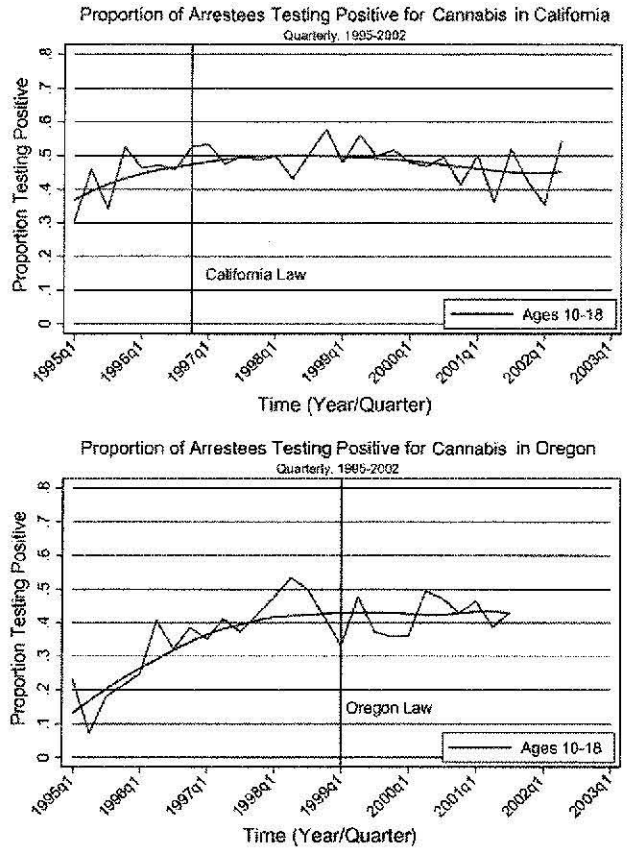

Fig. 2. Proportion of urine tests positive for cannabis among juvenile arrestees, 1995–2002: California and Oregon.

DAWN data

The samples obtained in the DAWN program were much larger than those for ADAM. The average number of emergency department visits per quarter was 121,833 in Denver (range 102,000–158,000), 155,666 in Seattle (range 132,000–197,000), and 873,750 in the three California cities combined (range 771,000–1,015,000). The outcome variable for the DAWN data was the proportion of emergency department visits in which cannabis was mentioned. Since the resulting proportions were very small, they were multiplied by 100 for all graphs as well as descriptive and inferential statistics. The inferential statistics were computed on both the proportions and the proportions multiplied by 100 and the conclusions drawn from each of these models were the same.

Fig. 3 shows the proportion multiplied by 100 of emergency department visit in which cannabis was mentioned for each quarter from 1994 through 2002 for the three cities in California, for Portland (Oregon), and for Seattle (Washington). The results of the ARIMA analysis of these trends are presented in Table 3. As with the ADAM data, none of the parameter estimates of change in trend or change in level are statistically significance.

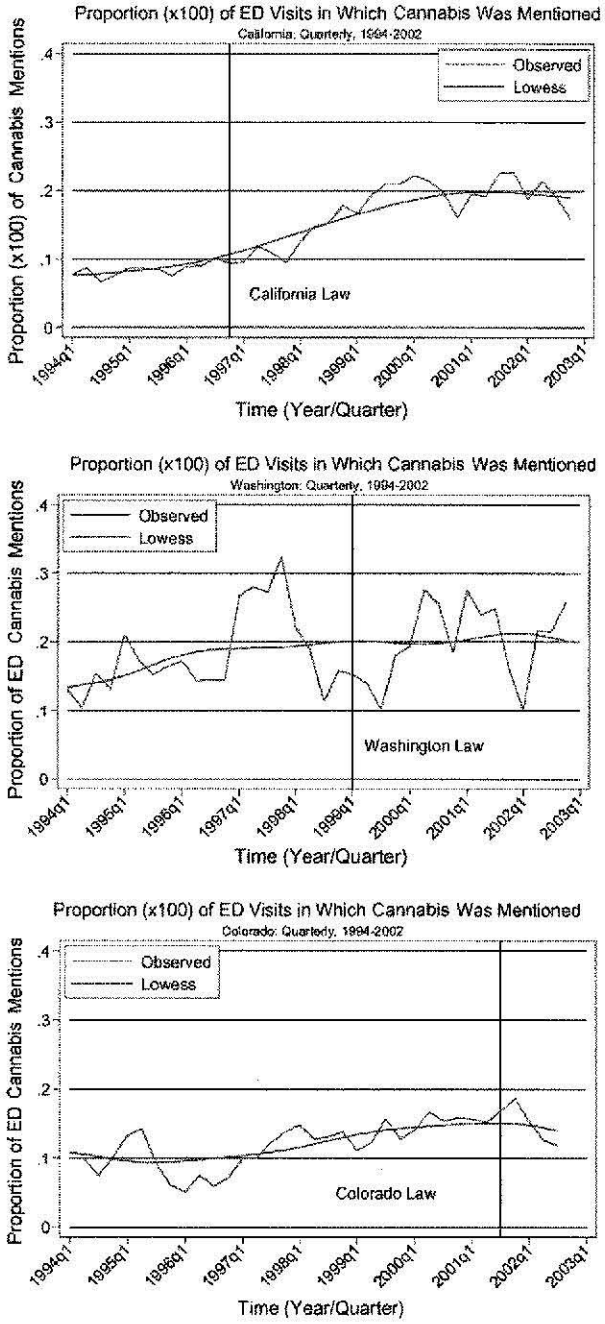

Fig. 3. Proportion of urine tests positive for cannabis among adult arrestees, 1995–2002: California, Oregon and Colorado.

Discussion

Our results indicate that the introduction of medical cannabis laws was not associated with an increase in cannabis use among either arrestees or emergency department patients in cities and metropolitan areas located in four states in the USA (California, Colorado, Oregon and Washington). For the arrestee data, the results are most persuasive for California and Oregon since the post-law time-series in these states were

Table 2
Time-series (ARIMA) models of the proportion of urine tests positive for cannabis in ADAM sites, 1995–2002

State (age group)	Coefficient	Standard error	p-Value	95% confidence interval		White noise test	
				Lower	Upper	χ^2	p-Value
California (all adults)							
Level	−3.32	5.07	0.51	−13.25	6.61	12.14	0.52
Trend	0.02	0.04	0.52	−0.05	0.09		
California (adults18–20)							
Level	−5.30	33.63	0.88	−71.22	60.62	15.68	0.27
Trend	0.04	0.23	0.88	−0.42	0.49		
California (juveniles)							
Level	−9.26	22.43	0.68	−53.22	34.70	19.31	0.08
Trend	0.06	0.16	0.68	−0.24	0.37		
Oregon (all adults)							
Level	−1.53	3.20	0.63	−7.79	4.73	18.85	0.09
Trend	0.01	0.02	0.63	−0.03	0.05		
Oregon (adults 18–20)							
Level	−0.39	2.99	0.90	−6.24	5.47	8.11	0.84
Trend	0.00	0.02	0.92	−0.04	0.04		
Oregon (juveniles)							
Level	−10.18	14.56	0.49	−38.73	18.36	8.89	0.54
Trend	0.06	0.09	0.50	−0.12	0.24		
Colorado (all adults)							
Level	−2.80	29.10	0.92	−59.84	54.24	14.76	0.32
Trend	0.02	0.17	0.92	−0.32	0.36		
Colorado (adults 18–20)							
Level	26.09	20.31	0.20	−13.71	65.90	19.09	0.12
Trend	−0.15	0.12	0.20	−0.39	0.08		

fairly long. This is also true of the DAWN analysis of the California and Washington State time-series. Since we have only a short time-series for both the ADAM and DAWN Colorado dataset it is possible that the law could have a delayed effect that we are unable to identify (although neither ADAM or DAWN data can be used to assess this since the former was discontinued in 2003 and the latter substantially revised in 2003).

The fact that we observed the same pattern of results in two different datasets increases confidence in the findings presented. However, before interpreting these findings and discussing their implications, the limitations of the study (which emanate from the shortcomings of the ADAM and DAWN datasets) should first be noted. The main problem in using the ADAM dataset to test the hypothesis that medical cannabis laws encourage use of the drug is that it is limited to large metropolitan areas and to a subgroup of the population of these cities (i.e., arrestees) that most represents the socioeconomically disadvantaged and those involved in multiple problem behaviors. In addition, most crimes do not result in arrest, and arrest is most likely to occur in the case of serious crime (e.g., robbery, assault and burglary) and when a criminal is a frequent drug user (Chaiken & Chaiken, 1996). Thus, the ADAM data may not even be generalizable to all types

Table 3
Time-series (ARIMA) models of the proportion of emergency department visits in which cannabis was mentioned in California, Washington State, and Colorado DAWN sites, 1994–2002

State (age group)	Coefficient	Standard error	p-Value	95% confidence interval		White noise test	
				Lower	Upper	χ^2	p-Value
California							
Level	1.57	1.98	0.43	−2.30	5.45	17.97	0.26
Trend	−0.01	0.01	0.47	−0.04	.02		
Washington							
Level	−1.76	3.38	0.60	−8.38	4.85	13.64	0.87
	0.01	0.02	0.57	−0.03	0.05		
Colorado							
Level	12.65	29.47	0.67	−45.11	70.42	9.15	0.92
Trend	−0.08	0.18	0.67	−0.42	0.27		

of criminals, let alone non-criminals. Thus, it is possible that cannabis use increased in Oregon, Colorado and California following the passage of medical cannabis laws but that this occurred among subgroups other than arrestees and/or was concentrated in geographic areas not included in the ADAM program.

In addition, due to various sampling quotas and the fact that only booked arrestees in the facility at the time of data collection were sampled, ADAM data were not representative of all arrestees in the participating sites from 1995 through 1999 (Caulkins, 2000). Probability-based sampling was introduced for male arrestees in 2000, thereby reducing comparability with earlier years (National Institute of Justice, 2003b). Given that the medical cannabis law in Oregon was introduced in December of 1998 and the law in Colorado in June of 2000, this change in the ADAM system could affect the results presented herein for these two states.

The DAWN dataset has similar limitations that affect its generalizabilty, as well displaying inconsistencies in the application of drug definitions (Caulkins, 2000). Like ADAM, it focuses on an urban high-risk subgroup, although emergency department patients are probably more representative of the general population than arrestees. DAWN also does not collect data from all of the emergency departments in the metropolitan areas involved in the program, but rather is based on a statistical sample of these. Moreover, since it is a voluntary system, selected emergency rooms can decline to participate. Finally, in the present analysis, we were unable to examine the DAWN data for specific age subgroups, thereby preventing analysis of the effects of the law on juveniles and young adults who are most likely to initiate cannabis use.

Having stated these limitations, it should be noted that both datasets have been successfully used in describing trends in drug use across different geographic locations (Caulkins, 2001; Golub & Johnson, 2001; Harrison, 1992; Martin, Maxwell, White & Zhang, 2004), and DAWN has been previously used to assess the effects of changes in state cannabis laws (Model, 1993). Thus, while caution should be exercised when it comes to interpreting the findings from arrestees and emergency department patients, it is reasonable to assume that the ADAM and DAWN datasets can be used to assess the effects of changes in cannabis policies, at least among these high-risk subgroups of a state's population.

Given the paucity of research into the effects of changes in drug policy (including medical cannabis laws) and the reluctance of the US government to fund evaluations of such policies, the datasets used in virtually every evaluation of liberalization of cannabis laws have limitations. Thus, like any other single study in this area, the findings of the current research are most appropriately considered within the context of the broader body of research into the effects of changes in cannabis laws (MacCoun & Reuter, 1997). The US research that is available pertains almost exclusively to the decriminalization reforms of 1970s and, like our study, shows that changes in laws have little effect on cannabis use (Maloff, 1981; Single, Christie & Ali, 2000). Likewise, studies from countries other than the US suggest that liberalization of laws alone have at most a modest influence on cannabis use (Donnelly, Hall & Christie, 1995; MacCoun & Reuter, 1997).

There are at least two reasons why one might expect medical cannabis laws to have even less influence on use of the drug than decriminalization laws. First, the number of people affected by the laws is relatively small. While California has only recently introduced a voluntary registration system, both Colorado and Oregon have operated mandatory systems since the implementation of their medical cannabis laws, thereby allowing some assessment of the number of people directly affected. In Colorado, which had a 2000 population of about 4.3 million, the total number of patients in possession of a valid registration card in May of 2006 was just 780 (Colorado Department of Public Health and Environment, 2006). In Oregon, where the 2000 population was 3.4 million, 10,775 patients and 5119 caregivers held medical cannabis identification cards as of 1 April 2006 (Oregon Department of Human Services, 2006). If it is the visibility of medical cannabis users or the potential that they present to increase the availability of the drug that matters when it comes to promoting use in the general population (rather than simply the equivocal message that medical cannabis laws send), then it is unlikely that use would go up in Colorado where there is fewer than one registered user for every 5000 people. Even in Oregon there are less than five cardholders per 1000 population, so their ability to convert non-users either as role models or as a source of the drug is also probably very limited.

Second, it may be that even if the number of medical cannabis users was greater in these states this would still not have a strong influence on the decision of others to use the drug. As Bruce Mirkin of the Marijuana Policy Project observed: "Frankly, it never made any sense that kids would think a drug 'cool' because cancer or AIDS patients use it to keep from vomiting" (Marijuana Policy Project, 2004). Indeed, it might be argued that such patients "de-glamorised" the drug and thus have a negative impact on use, especially among youth. According to Musto (1993), one of the reasons that drug epidemics eventually die out is that the casualties of the early wave act as a deterrent on initiation—they become essentially a bad advertisement for the drug. Cannabis use by already sick individuals might have a similar deterrent effect, especially if an outside observer is unable to discern the nature of the relationship between use of the drug and the individual's disease (as might be the case with young people).

As noted above, the recent Institute of Medicine (1999) report observed that there is little information about the consequences of the medical use of cannabis in modern society, and therefore one can only speculate as to whether the introduction of medical cannabis laws increases use of the drug. It is hoped that the results presented herein go some way towards moving the debate beyond such speculation and conjecture. Consistent with other studies of the liberalization of cannabis laws, they indicate that medical cannabis laws do not increase use of the drug. However, our study is far

from the final word on this issue, and the effects of medical cannabis laws must be further examined with populations other than arrestees and in geographic sites other than the large metropolitan areas included in the ADAM and DAWN programs.

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Medical Marijuana Research

The model medical marijuana bill allows patients to obtain a medical marijuana card if they have a qualifying medical condition and a licensed physician believes they are likely to receive therapeutic or palliative benefit from the use of medical marijuana. The qualifying medical conditions listed in the bill are as follows (the state department of health can add others):

1. Cancer, glaucoma, positive status for human immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, nail patella, or the treatment of these conditions.

2. A chronic or debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia or wasting syndrome; severe and chronic pain; severe nausea; seizures, including but not limited to those characteristic of epilepsy; or severe and persistent muscle spasms, including but not limited to those characteristic of multiple sclerosis.

Key medical references addressing marijuana's ability to alleviate these conditions are below, with related items/ subjects grouped together.

Nausea, Vomiting, Appetite Loss, Cachexia

In its 1999 report "Marijuana and Medicine: Assessing the Science Base," the Institute of Medicine concluded, "Nausea, appetite loss, pain and anxiety are all afflictions of wasting, and all can be mitigated by marijuana." Marijuana's active components (cannabinoids) can both stimulate appetite and reduce the nausea, vomiting, and weight loss experienced by patients in many circumstances, including the side effects of drug therapies given for cancer, HIV infection, and hepatitis C. Observational studies suggest this may improve treatment adherence among patients experiencing gastrointestinal toxicity from drug therapy.

Cancer References

1) Vincent Vinciguerra et al., "Inhalation Marijuana as an Antiemetic for Cancer Chemotherapy," *New York State Journal of Medicine* (October 1988).

In this clinical trial sponsored by the state of New York, "Fifty-six patients who had no improvement with standard antiemetic agents were treated and 78% demonstrated a positive response to marijuana ... inhalation marijuana is an effective therapy for the treatment of nausea and vomiting due to cancer chemotherapy."

2) Richard Musty and Rita Rossi, "Effects of Smoked Cannabis and Oral Δ9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy: A Review of State Clinical Trials," *Journal of Cannabis Therapeutics* 1, no. 1 (2001): 43-56.

Musty and Rossi reviewed data from a series of state-sponsored clinical trials of marijuana for relief of nausea and vomiting caused by cancer chemotherapy conducted in the 1970s and 1980s, concluding, "Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief."

(3) Manuel Guzman, "Cannabinoids: Potential Anticancer Agents," *Nature Reviews* 3 (2003): 745-766.

In this review article, Dr. Guzman, a leading cancer researcher, examined the data regarding use of marijuana and cannabinoids in cancer treatment. He concluded that marijuana/cannabinoids can be useful in preventing or treating "chemotherapy-induced nausea and vomiting." He also noted that cannabinoids have potential as antitumor agents: "Regarding effectiveness, cannabinoids exert a notable antitumour activity... Regarding toxicity, cannabinoids not only show a good safety profile but also have palliative effects in patients with cancer, indicating that clinical trials with cannabinoids in cancer therapy are feasible."

(4) K. Nelson et al., "A Phase II Study of Delta-9-Tetrahydrocannabinol for Appetite Stimulation in Cancer-Associated Anorexia," *Journal of Palliative Care* 10, no. 1 (1994): 14-8.

In this study of patients with anorexia due to advanced cancer, the researchers concluded, "THC is an effective appetite stimulant in patients with advanced cancer. It is well tolerated at low doses."

HIV/AIDS References

1) Donald Abrams et al., "Short-Term Effects of Cannabinoids on Patients With HIV-1 Infection: A Randomized, Placebo-Controlled Clinical Trial," *Annals of Internal Medicine* 139, no. 4 (2003): 258-266.

This preliminary, short-term clinical trial, conducted over 21 days using 62 HIV-infected patients, was designed to examine the short-term safety of smoked marijuana and oral THC on HIV-infected patients, including potential interactions with HIV protease inhibitors, viral load, and CD4 and CD8 counts. Secondary endpoints included weight, caloric intake, and appetite. No safety concerns emerged with either treatment, and the authors concluded, "Our short-duration clinical trial suggests acceptable safety in a vulnerable immune-compromised patient population." Both the marijuana and oral THC groups gained significantly more weight than the placebo group.

2) B.D. de Jong et al., "Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea," *Journal of Acquired Immune Deficiency Syndromes* 38, no. 1 (2005): 43-6.

Use of illicit drugs is typically associated with poor adherence to medication regimens. This observational study sought to determine whether this common assumption applies to HIV/AIDS on antiretroviral therapy (ART). Marijuana-using patients who suffered moderate to severe nausea were far more likely to be adherent to ART than those suffering nausea who did not use marijuana (OR = 3.3). The authors concluded, "These data suggest that medicinal use of marijuana may facilitate, rather than impede, ART adherence for patients with nausea, in contrast of other illicit substances," particularly in the case of "use of smoked marijuana specifically for amelioration of nausea."

3) M. Haney, et al., "Dronabinol and Marijuana in HIV-Positive Marijuana Smokers. Caloric Intake, Mood, and Sleep," *Journal of Acquired Immune Deficiency Syndromes* 45, no. 5 (2007): 545-54.

In this controlled clinical trial, both marijuana and oral THC (dronabinol) use resulted in increased caloric intake and body weight. Strikingly, a dronabinol dose "eight times current recommendations" was required to approximate the effect of relatively low-potency (3.9% THC) marijuana, and only the marijuana improved ratings of sleep. While both drugs produced some intoxication, researchers reported "little evidence of discomfort and no impairment of cognitive performance."

(See the section on chronic pain below for studies of marijuana for HIV-associated peripheral neuropathy.)

Hepatitis C References

1) D.L. Sylvestre, B.J. Clements, and Y. Malibu, "Cannabis Use Improves Retention and Virological Outcomes in Patients Treated For Hepatitis C," *European Journal of Gastroenterology and Hepatology* 18 (2006): 1057-63.

A prospective observational study was conducted on 71 patients to define the impact of cannabis use during interferon/ribavirin treatment for the hepatitis C virus. Compared to non-users, marijuana users had three times the rate of sustained virological response, apparently due to better treatment adherence. The researchers stated, "[T] he use of cannabis during HCV treatment can improve adherence by increasing the duration of time that patients remain on therapy; this translates to reduced rates of post-treatment virological relapse."

2) B. Fischer, et al., "Treatment For Hepatitis C Virus and Cannabis use in Illicit Drug User Patients: Implications and Questions," *European Journal of Gastroenterology and Hepatology* 18 (2006):1039-42.

This commentary, published alongside the above study, placed the results in context, explaining how marijuana "may help address key challenges faced by drug users in HCV treatment (e.g. nausea, depression)."

Other References

1) Richard W. Foltin, Marian W. Fischman, and Maryanne F. Byrne, "Effects of Smoked Marijuana on Food Intake and Body Weight of Humans Living in a Residential Laboratory," *Appetite* 11 (1988):1-14.

This study, involving healthy volunteers living in a residential laboratory, documented marijuana's efficacy as an appetite stimulant. Compared to placebo, relatively weak marijuana cigarettes (2.3% THC) smoked at scheduled intervals resulted in a 40% increase in daily caloric intake.

(2) R. Layeeque, et al., "Prevention of Nausea and Vomiting Following Breast Surgery," *American Journal of Surgery* 191, no. 6 (2006): 767-72.

This retrospective review found that a prophylactic regimen combining oral THC with rectal prochlorperazine "significantly reduced the number and severity of episodes" of post-operative nausea and vomiting in breast surgical patients.

Severe or Chronic Pain

Studies have shown that marijuana is especially effective in treating neuropathic pain, commonly seen in multiple sclerosis, HIV/AIDS, and other ailments, and notoriously resistant to treatment with conventional pain drugs, including opiates. Preclinical research as well as case series and anecdotal reports suggest that marijuana use may allow reduced opioid doses when given in combination.

References

(1) Donald Abrams, et al., "Cannabis in Painful HIV-Associated Sensory Neuropathy: a Randomized Placebo-Controlled Trial," *Neurology* 68, no. 7 (2007): 515-21.

This clinical trial involved HIV/AIDS patients suffering from HIV-associated sensory neuropathy, a painful condition estimated to eventually afflict up to one third of HIV-infected persons. There are presently no FDA-approved treatments for this indication. Donald Abrams and his colleagues tested the efficacy of smoked marijuana on both HIV neuropathy and a type of laboratory-induced pain. Smoked marijuana produced an average 34% reduction in pain and was well tolerated.

(2) R.J. Ellis, et al., "Smoked Medicinal Cannabis For Neuropathic Pain in HIV: a Randomized, Crossover Clinical Trial," *Neuropsychopharmacology* 34, no. 3 (2009): 672-80.

This trial focused on patients with HIV-associated neuropathy refractory to at least two previous analgesic classes. Ellis and colleagues reported, "In the present experiment, cannabis reduced pain intensity and unpleasantness equally. Thus, as with opioids, cannabis does not rely on a relaxing or tranquilizing effect, (e.g. anxiolysis) but rather reduces both the core component of nociception and the emotional aspect of the pain experience to an equal degree. ... In general, side effects and changes in mood were inconsequential."

(3) B. Wilsey, et al., "A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain," *Journal of Pain* 9, no. 6 (2008):506-21.

This study investigated the efficacy of smoked marijuana in patients suffering from neuropathic pain related to a variety of conditions, including multiple sclerosis, spinal cord injury, diabetes, and complex regional pain syndrome. Wilsey and colleagues concluded, "This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs."

(4) David Baker, et al., "The Therapeutic Potential of Cannabis," *The Lancet Neurology* 2, no. 5 (2003): 291-8.

This review, written prior to publication of the clinical trials described above, discussed in detail the biochemical basis for marijuana's analgesic effects. It also discussed the drawbacks of oral dosing, explaining that "oral administration is probably the least satisfactory route for cannabis owing to sequestration of cannabinoids into fat from which there is slow and variable release into plasma. In addition, significant first-pass metabolism in the liver, which degrades THC, contributes to the variability of circulating concentrations of orally administered cannabinoids, which makes dose titration more difficult and therefore increases the potential for adverse psychoactive effects. Smoking has been the route of choice for many cannabis users because it delivers a more rapid 'hit' and allows more accurate dose-titration."

(5) M.E. Lynch, J. Young, A.J. Clark, "A Case Series of Patients Using Medicinal Marihuana for Management of Chronic Pain Under the Canadian Marihuana Medical Access Regulations," *Journal of Pain and Symptom Management* 32, no. 5 (2006): 497-501.

This case series is based on 30 patients qualified to use medical marijuana under Canadian regulations, seen at a pain management center in Nova Scotia. All suffered from chronic, severe pain that had not responded to conventional approaches. On an 11-point scale, 93% reported pain relief equal to 6 or greater, and many reported relief of other symptoms such as spasticity, poor sleep, nausea, and vomiting. 70% reported being "able to decrease use of other medications that had been causing side effects (e.g., NSAIDs, opioids, and antidepressants)."

Glaucoma

Glaucoma is a leading cause of blindness, damaging the optic nerve, which is responsible for carrying images from the eye to the brain. High pressure within the eye is one of the main risk factors for this optic nerve damage. There currently is no cure for glaucoma. Marijuana helps relieve the pressure within the eye, thus preventing damage.

Although other drugs are considered first-line glaucoma treatments, some patients and physicians have found marijuana useful when conventional drugs fail. One of the three patients who still receive medical marijuana from the federal government – Elvy Musikka – is a glaucoma patient, who also successfully argued in a Florida court case that marijuana was medically necessary to maintaining her vision.

(1) J.E. Joy, S.J. Watson, J.A. and Benson, *Marijuana and Medicine: Assessing the Science Base* (National Academy Press, 1999).

"In a number of studies of healthy adults and glaucoma pressure, IOP (intra-ocular pressure) was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC -- a reduction as good as that observed with most other medications available today."

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord, progressively reducing the ability of the brain to initiate and control muscle movement. Some research has shown that cannabinoids can delay the progression of ALS. Some ALS patients have indicated that medical marijuana has helped alleviate their symptoms, such as pain, appetite loss, depression, and drooling.

References

(1) Gregory T. Carter and Bill S. Rosen, "Marijuana in the Management of Amyotrophic Lateral Sclerosis," *American Journal of Hospice and Palliative Care* 18, no. 4 (2001): 264-69.

This review article, co-authored by a leading ALS and palliative medicine researcher from the University of Washington, concluded that marijuana may help with many symptoms of ALS, including pain, spasticity, drooling, dysautonomia, and wasting. The authors also discussed how marijuana's antioxidative and neuroprotective effects may prolong neuronal cell survival, and concluded, "In areas where it is legal to do so, marijuana should be considered in the pharmacological management of ALS."

(2) E. de Lago, J. Fernández-Ruiz, "Cannabinoids and Neuroprotection in Motor-Related Disorders," *CNS and Neurological Disorders — Drug Targets* 6, no. 6 (2007): 377-87.

This review explored in detail the mechanisms of cannabinoid neuroprotection related to a variety of disorders, including ALS.

(3) Dagmar Amtmann et al., "Survey of Cannabis Use in Patients With Amyotrophic Lateral Sclerosis," *American Journal of Hospice and Palliative Medicine*, March-April 2004.

This anonymous survey of 131 people with ALS found that 10 percent had reported using marijuana in the past year, reporting relief of multiple symptoms. The authors concluded, "...results indicate that cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling."

Crohn's disease

Crohn's disease is marked by inflammation of the digestive tract, most commonly the lower part of the small intestine. It can cause severe abdominal pain, nausea, and weight loss – all symptoms that marijuana can help mitigate, as noted in other sections of this document. Preclinical research has demonstrated the role of the endocannabinoid system, the body's natural, marijuana-like chemicals, in protecting the GI tract, providing support for anecdotal reports of relief.

References

(1) J.E. Joy, S.J. Watson, and J.A. Benson, *Marijuana and Medicine: Assessing the Science Base* (National Academy Press, 1999).

"For patients ... who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

(2) F. Massa, M. Storr, and B. Lutz, "The Endocannabinoid System in the Physiology and Pathophysiology of the Gastrointestinal Tract," *Journal of Molecular Medicine* 83, no. 12 (2005): 944-54.

This review article noted, "Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Such protective activities are largely in agreement with anecdotal reports from folk medicine on the use of Cannabis sativa extracts by subjects suffering from various GI disorders."

Agitation of Alzheimer's disease

In preliminary research, THC has been shown to reduce agitation in severely demented Alzheimer's patients. Preclinical research also suggests that marijuana components may help retard the progression of Alzheimer's disease.

References

(1) S. Walther et al., "Delta-9-Tetrahydrocannabinol for Nighttime Agitation in Severe Dementia," *Psychopharmacology* (Berl) 185, no. 4 (2006): 524-8.

This open-label pilot study reported, "Compared to baseline, dronabinol led to a reduction in nocturnal motor activity (P=0.028). These findings were corroborated by improvements in Neuropsychiatric Inventory total score (P=0.027) as well as in subscores for agitation, aberrant motor, and nighttime behaviors (P<0.05). No side effects were observed."

(2) G. Esposito et al., "The Marijuana Component Cannabidiol Inhibits Beta-Amyloid-Induced Tau Protein Hyperphosphorylation Through Wnt/beta-catenin Pathway Rescue in PC12 Cells," *Journal of Molecular Medicine* 84, no. 3 (2006): 253-8.

"Here, we report that cannabidiol inhibits hyperphosphorylation of tau protein in Abeta-stimulated PC12 neuronal cells, which is one of the most representative hallmarks in AD. ... These results provide new molecular insight regarding the neuroprotective effect of cannabidiol and suggest its possible role in the pharmacological management of AD, especially in view of its low toxicity in humans."

Multiple sclerosis, seizures, muscle spasms

There is a shortage of formal research on whole marijuana for treatment of MS, but a number of studies have been conducted with various marijuana extracts, which have reported relief of both pain and spasticity.

Considerable data from animal models as well as some human clinical evidence suggest a role for marijuana in the treatment of seizure disorders such as epilepsy.

Multiple Sclerosis References

(1) J. Zajicek et al., "Cannabinoids for Treatment of Spasticity and Other Symptoms Related to Multiple Sclerosis (CAMS Study): Multicentre Randomised Placebo-Controlled Trial," *The Lancet* 362 (2003): 1517-26.

This trial, using an oral cannabis extract, reported "evidence of a treatment effect on patient-reported spasticity and pain (p=0·003), with improvement in spasticity reported in 61% (n=121, 95% CI 54·6–68·2), 60% (n=108, 52·5–66·8), and 46% (n=91, 39·0–52·9) of participants on cannabis extract, 9-THC, and placebo, respectively."

(2) D.T. Wade et al., "Long-Term Use of a Cannabis-Based Medicine in the Treatment of Spasticity and Other Symptoms in Multiple Sclerosis" *Multiple Sclerosis* 12 (2006): 639-45.

In this long-term follow-up of a clinical trial of a marijuana-based oral spray, patients were followed for as much as 82 weeks. The marijuana spray demonstrated long-term relief of spasticity, pain, and bladder issues related to MS, "without unacceptable adverse effects."

Epilepsy and Other References

(1) Alsasua del Valle, "Implication of Cannabinoids in Neurological Diseases," *Cellular and Molecular Neurobiology* 26, no. 4-6 (2006): 579-91

This wide-ranging review of the neurobiology of marijuana and its constituents in relation to neuroprotection and neurological disease noted, "It has been known for centuries that exogenous cannabinoids have anti-convulsant activity."

(2) K. Mortati, B. Dworetzky, and O. Devinsky, "Marijuana: an Effective Antiepileptic Treatment in Partial Epilepsy? A Case Report and Review of the Literature," *Reviews in Neurological Diseases* 4, no. 2 (2007): 103-6.

Mortati and colleagues reported the case of a 45-year-old male with cerebral palsy and epilepsy "who showed marked improvement with the use of marijuana." The authors reviewed the current literature and concluded, "Although more data are needed, animal studies and clinical experience suggest that marijuana or its active constituents may have a place in the treatment of partial epilepsy."

(3) D.W. Gross et al., "Marijuana Use and Epilepsy: Prevalence in Patients of a Tertiary Care Epilepsy Center," *Neurology* 62, no. 11 (2004): 2095-7.

In this patient survey, of 28 epileptic patients who actively used marijuana, 68% reported that it improved severity of seizures and 54% reported improvement of seizure frequency. None reported that it worsened these symptoms.

Nail-Patella Syndrome

Nail-patella syndrome is a rare genetic disorder involving the bones, joints, and connective tissue. Patients may have problems due to limitation of joint mobility, dislocation or both, especially at the elbow and knee where osteoarthritis may eventually occur. Nail-patella patients are also at increased risk for glaucoma and kidney problems. While there is a lack of controlled research on marijuana and nail-patella, one of the three patients who still receive medical marijuana from the federal government – George McMahon – suffers from the condition, and his case is described in the one study of these patients that has been published. This article notes: "On May 10, 2000, a letter to FDA noted the patient continued to do well on the therapy, smoking 8-10 cigarettes per day without other medication. He continued to function well using a cane and occasionally a wheelchair when bothered by spasms and nausea. At present, he utilizes about 7 grams a day or 1/4 ounce of NIDA material that is 3.75% THC ... He indicates that he has been short on his supply 3 times in 10 years, generally for 1-2 weeks, secondary to lack of supply or paperwork problems. When this occurs he suffers more nausea and muscle spasms and is less active as a consequence."

References

(1) E. Russo et al., "Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis," *Journal of Cannabis Therapeutics* 2, no. 1 (2002): 3-57.

Vaporization as an Alternative to Smoking

One often-mentioned objection to medical use of marijuana is the respiratory risk associated with smoking. For this reason, the Institute of Medicine urged development of a "nonsmoked, rapid-onset cannabinoid delivery system." Published research suggests that vaporization — in which marijuana is heated to the point where cannabinoid vapors are released, but not to the point of combustion — represents a viable solution to this problem.

References

(1) A. Hazekamp et al., "Evaluation of a Vaporizing Device (Volcano) for the Pulmonary Administration of Tetrahydrocannabinol," *Journal of Pharmaceutical Sciences* 95, no. 6 (2006): 1308-17.

This laboratory test of a commercially available vaporizer known as the Volcano used language striking similar to that of the Institute of Medicine, concluding, "Our results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients."

(2) D.I. Abrams et al., "Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study," *Clinical Pharmacology and Therapeutics* 282, no. 5 (2007): 572-8.

In this clinical trial, again using the Volcano vaporizer, volunteers were randomly assigned to either smoke or vaporize marijuana of three different strengths. Vaporization was comparable to smoking in terms of THC delivery, but dramatically reduced the amount of carbon monoxide, indicating "little or no exposure to gaseous combustion toxins." The researchers concluded that vaporization "therefore is expected to be much safer than smoking marijuana cigarettes."

(3) M. Earleywine and S.S. Barnwell, "Decreased Respiratory Symptoms in Cannabis Users Who Vaporize," *Harm Reduction Journal* 4, no. 11 (2007).

This Internet sample of nearly 7,000 participants compared self-reported respiratory symptoms among marijuana users whose primary method was smoking with those whose primary method was vaporization, reporting, "use of a vaporizer predicted fewer respiratory symptoms even when age, sex, cigarette smoking, and amount of cannabis used were taken into account."

From: <ethicsnj@nyms.net>
To: <mbaker@pahousegop.com>
Date: 12/1/2009 2:35 PM
Subject: Smoking A Joint Doesn't Make Marijuana Medicinal

Smoking A Joint Doesn't Make Marijuana Medicinal- It Does However Diminsh Medical Science and Scientific Certainty. Said differently, the next time you're in a drug store - look around at the safe, accurate, valid and reliable F.D.A. approved medicines, both prescription and over the counter, covering a wide range of illnesses. Then ask yourself a question - do you want emotional anedotal, preclinical evidence (Ephedirin is a good example) offered by political interest groups or the dispassionate scientific certainty associated with the expert scientific process devoid of political considerations to be the standard for determining both the medications and amounts of medications the public uses?

SUMMARY: (URL's Updated 12-01-09 2:15 P.M. EDT. If link is gone use Google.com (not google.com/news))

The issue of whether marijuana has a medicinal use is a question for science to be answered with scientific certainty and not a popularity contest resulting from the political promotions of special interests or a tool of litigation public relations. If the interest in marijuana is indeed medicinal then its time to walk the talk by deferring any pending legislation until scientific inquiry (such as with Sativex) demonstrates its use is safe, valid, accurate and reliable as well as administratively manageable. In short, the dispassionate process of scientific certainty is in the interest of those who truly suffer while preventing those with less altruistic motives from using people with severe illnesses as human shields.

"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 PSCYHOACTIVE SUBSTANCES."(emphasis added). American Medical Association, Report 3 of the Council on Science and Public Health (I-09) (SEE Last page of www DOT ama-assn DOT org /ama1 /pub /upload /mm /interim-2009 /i-09-council-reports DOT pdf).

1. The American Medical Association, LA Times & Washington Post are calling for extensive federal research of marijuana's medicinal purpose(s). The A.M.A. House of Delegates has called "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. The November 21, 2009 LA Times Editorial "The AMA's reversal on marijuana" specifically notes: For all the debate over whether marijuana has medicinal value, arguments that the drug has significant palliative properties or that it has none suffer from the same flaw: There's little scientific proof either way." [www DOT latimes DOT com /news /opinion /la-ed-ama21-2009nov21,0,406900 DOT story]

3. At the same time, the AMA specifically refused to endorse state-based medical marijuana programs & the Washington Post editorial (Oct 25 "Questions About Pot") called for a moratorium on new state programs.

4. Moreover, the same Washington Post article also recognizes the medical marijuana controversy may be moot in the near future as a number of extensive FDA supervised clinical trials of a drug known as Sativex (cancer & MS) have ended or are near an end. [www DOT gwpharm DOT com /product-pipeline DOT aspx]

DETAIL ((URL's Updated 12-01-09 2:15 P.M. EDT. If link is gone use Google.com (not google.com/news))

The Washington Post's Editors write in "Questions About Pot?"
(www DOT washingtonpost DOT com /wp-dyn /content /article /2009 /10 /25 /AR2009102502293 DOT html)
"More information -- good old-fashioned scientific information -- is needed before the federal government or more states formally endorse marijuana smoking for medicinal use. The Institute of Medicine, an arm of the National Academy of Sciences, in 1999 published what is widely considered to be the most comprehensive study; it was decidedly mixed, listing the many possible drawbacks of smoking marijuana, including respiratory problems, while noting that such use seemed to provide some patients with relief not obtained from pills containing marijuana's active ingredients.

More recently, Dr. Peter J. Cohen, an adjunct professor at the Georgetown University Law Center, noted in a 2009 law review article that reputable studies released in the past few years showed that patients with AIDS and hepatitis C experienced reduced pain and nausea and were better able to tolerate traditional treatment as a result of smoking marijuana. Yet these preliminary results -- as Dr. Cohen points out -- have not been subjected to rigorous testing by the Food and Drug Administration. The reason: A manufacturer must submit the drug for review before the FDA will tackle the assignment. So far, no such "manufacturer" has come forward.

The medical marijuana controversy may be moot in the near future because of a drug known as Sativex, a spray mist approved for conditional use in Canada and the United Kingdom that delivers the active ingredients found in marijuana. If cleared by the FDA, patients will have some confidence that it is safe and effective. Patients have the right to know if the same can be said about smoked marijuana."

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It should be said upfront that we strongly disagree with "Executive Branch nullification (as opposed to prosecutorial discretion)" of Constitutional legislation and Supreme Court review because it embodies the essence of "arbitrary government." It not only ignores the Constutional seperation of powers between the Executive and Congress and the Court, it shreds "our Federalsim", i.e. the Constitutional relationship between the Federal and State Governments. That said, however, and for the reasons set forth below, the Post's focus on science over interest group politics is compelling.

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Scientific Certainty of F.D.A. Sativex Trials Moots NJ's Compassionate Medical Marijuana Act

If any decision concerning the medicinal use of marijuana is as simple as some suggest one must ask why the U.S. & U.K. National MS Societies & the American Cancer Society question its use and continue to withhold their approval. In reality there are many obstacles. For example, "Marijuana Smokers Face Rapid Lung Destruction -- As Much As 20 Years Ahead Of Tobacco Smokers." January 2008 Respirology. And, as the Center for Disease Control points out in its 09-04-09 MMWR weekly, eating marijuana gives rise to a seperate set of problems - including efficacy, doseage, duration, etc. Finally, people with MS have higher rates of depression and suicide compared to the general population. â€œSince marijuana can induce psychosis and anxiety in healthy people ... it was especially important to look at its effects on people with MS ... February 13, 2008, online edition of Neurology, the medical journal of the American Academy of Neurology.

George Washington University Constitutional law Professor Turley has commented the partisan political interests involved in the issue of marijuana for medicinal purposes has resulted in the major political party's acting in a manner that is completely at odds with their traditional view of the Constitution and the prevailing status of the defined Constitutional relationship between Federal and state governments.(1). So too,Georgetown University adjunct law professor Peter J. Cohen, an apparent advocate for marijuana, provides a substantive confirmation of the problem in his Utah Law Review article "Medical Marijuana: The conflict Between Scientific Evidence and Political Ideology.(2). In effect, Cohen agures any medicinal use must be determined soley by science while any recreational use is a political question.

According to Cohen "... advocacy is a poor substitute for dispassionate analysis [and] popular votes should not be allowed to trump scientific evidence in deciding whether or not marijuana is an appropriate pharmaceutical agent to use in modern medical practice. ... scientific evidence devoid of political considerations should be allowed to guide future decisions regarding the status of Cannabis sativa when used for medical purposes." Cohen, p.41-42.

To make a scientific decision requires help. It enhances public trust and confidence in the legislature when it recognizes it lacks the expertise, resources and organization to make such a decision. Such decisions are first the provence of a peer review of the testimony and studies of pharmacologists, epidemiologists,and psychologists. For example, the Iowa legislature is currently faced with a similar question. Unlike NJ, however, the Iowa Pharmacy Board is engaged in hearings that will lead to a recommendation to Iowa legislature as to what, if any, use of marjiuna should be permitted.(3). The Board consists of five licensed pharmacists and two public members. Four are Democrats, two are republicans and one is an independent.(4). Even with their expertise the Iowa Board has a Herculean task. The Iowa Pharmacy Board's actions to determine if there is any appropriate medicinal use for marijuana, including any recommendations concerning production, distribution and consumption
, will quite rightly be compared (5) to the standards and process by which the U.S. Food and Drug Administration approves any drug for human use. (6) (7).

There are many criteria that must be met. Unless a state governmentâ€™s expertise,resources and organization are at least equal to that of the F.D.A. it is questionable any state can reinvent the wheel (the next time youâ€™re in a drug store look around at the over-the-counter and prescription medicines). Scientific certainty, while not absolute certainty, seems precise. Scientific testing is not a hodge podge of studies based on too few few participants or a collection of personal testimonials. While those studies and antedotes may be relevant and may inform an F.D.A. review, the F.D.A. requires several phases of testing that generally includes the monitoring of several thousand participants. Indeed, the Iowa Globe-Gazzette's 10-07-09 report (8) on yesterday's Iowa Board hearing notes an apparent consensus that while marijuana may relieve pain, more testing is necessary. The Iowa Globe's observation is important because it is exactly the same conclusion reaced by the IOM stu
dy relied on in the NJ legislation.(9).

It now appears the F.D.A. is close to resolving many of the outstanding issues. In 2006 GW Pharmaceuticals (gwpharm DOT com) began clinical trials of "Sativex" under the supervision & in accord with F.D.A. guidelines. Sativex meets a diverse range of criteria by delivering the cannabis product via an inhaler and thus allows a user to function "normally" because it relieves [1] the pain [2] without the "high" and [3] prevents the rapid deterioration to lung function associated with smoking marijuana.(10).

Clinical trials are presently in or at the end of their phase II or III level. These trials provide a clear meaning to the "scientific certainty" required for approval by measuring both its purported benefits while seeking to mitigate its potential harms. In short the tests address the foreseeable consequences of the drugs use in order to insure its application is not only accurate, valid and reliable, but its harm is insignificant and the potential for abuse minimized. Specifically, the Sativex trials for MS, cancer and other disorders demonstrate how science must be applied to discern if there is any benefit to patients without damage from ingestion and discouraging recreational use.

In sum, the F.D.A. will soon settle the issue as to whether and under what cirumstances marijuana has any medical value.

NOTES :

(1) www DOT jonathanturley DOT org /2008 /02 /01 /1053 /

(2) www DOT epubs DOT utah DOT edu /index DOT php /ulr /article /viewFile /143 /125 (note: slow to load)

www DOT epubs DOT utah DOT edu /index DOT php /ulr /article /viewFile /143 / (note: slow to load)

(3) www DOT iowa DOT gov / ibpe /marijuana_hearings DOT html

(4) www DOT iowa DOT gov / ibpe /marijuana_hearings DOT html

(5) Cohen, Peter, Medical Marijuana: The conflict Between Scientific Evidence and Political Ideology, Utah Law Review, p. 42.

(6) www DOT fda DOT gov /Drugs /ResourcesForYou /Consumers /ucm143534 DOT htm

(7) www DOT fda DOT gov /NewsEvents /Testimony /ucm161673 DOT htm

(8) medicalmarijuana DOT procon DOT org /sourcefiles /IOM_Report DOT pdf (no www prefix)

(9) "Consensus: Medical marijuana helps pain, needs more research"

http :// www DOT globegazette DOT com /articles /2009/10/07 /news/latest/ doc4acd1e63a01f3201012168 DOT txt

(10) According to the previous 2008-09 GW pharmaceuticals web site:

(i) "GW intends to seek marketing approval for "Sativex" by means of the conventional FDA regulatory process. As GW moves through that process, we will naturally follow the FDA's guidance â€|"

(ii) "It is important to understand that the medical benefits of cannabis-based medicines are separate and distinct from the â€œhighâ€ associated with cannabis. Evidence from GW's clinical trials shows that the majority of patients can obtain the medical benefits of cannabis before any feeling of a "high". Patients emphasize that they seek to obtain the medical benefits and do not wish to experience intoxication. This is similar to the reports of patients who use self-administered morphine for pain control. Patients control or â €œtitrateâ€ the dose that they need to relieve their pain while minimizing unwanted side effects such as intoxication."

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* URL's Updated 12-01-09 2:15 P.M. EDT. If link is gone use Google.com (not google.com/news)

Respectfully submitted,
ethicsnj.blogspot.com
ethicsnj@nyms.net

Disclaimer: No person or blogger at this site has any interest, financial or otherwise, or personal relationship, financial or otherwise, with any entity or person mentioned in this article.

This is an ever-growing list of organizations that have taken action to formally support patient access to therapeutic cannabis. Healthcare professionals are strongly encouraged to take action within their specialty organizations by urging and assisting them in formally supporting patient access to cannabis through a resolution or position paper. Please contact Patients Out of Time for assistance if needed and notify us of any organization that passes a supportive paper. As the list continues to grow, politicians and policy makers will have the necessary support to change the laws and end the cannabis prohibition.

Organizations Supporting Access to Therapeutic Cannabis

As Compiled by Patients Out of Time

Addiction Science Forum - 2009

AIDS Action Council - 1996

*Alaska Nurses Association - 1998

Alaska Voters - 1998

Alliance for Cannabis Therapeutics – 1981

+American Academy of Family Physicians – 1989, 1995

American Academy of HIV Medicine - 2003

American Anthropological Association - 2003

American Civil Liberties Union (ACLU)

American College of Physicians – 2008

American Federation of State, County and Municipal Emplyees - 2006

American Medical Association's Council on Scientific Affairs – 2001

American Medical Association's Medical Student Section – 2008

American Medical Association's Pacific Rim Caucus – 2008

Alaska Medical Association

Hawaii Medical Association

Guam Medical Association

American Medical Students Association – 1993

+*American Nurses Association - 2003

*American Preventive Medical Association – 1997

+*American Public Health Association (APHA) – 1995

Ann Arbor, MI - 2004

Arizona Voters - 1996 & 1998

+Association of Nurses in AIDS Care - 1999

Berkeley, CA - 1979

Breckenridge, CO - 1994

Burlington, VT – 1994 & 2004

California Academy of Family Physicians - 1996

California Democratic Party - 1993

California Legislative Council for Older Americans - 1993

+California Medical Association - 1994

California Nurses Association - 1995

California-Pacific Annual Conference of the United Methodist Church - 1996

California Pharmacists Association - 1997

California Voters - 1996

Cannabis Freedom Fund – 1996

Coalition for Rescheduling Cannabis - 2002

Colorado Voters - 2000

*Colorado Nurses Association – 1995

Columbia, MO - 2004

*+Connecticut Nurses Association - 2004

Contigo-Conmigo - 1997

Consumer Reports Magazine - 1997

Crescent Alliance Self Help for Sickle Cell - 1999

Cure AIDS now – 1991

Detroit, MI - 2004

District of Columbia Voters - 1999

+Episcopal Church of the U.S. - 1982

Farmacy - 1999

Federation of American Scientists – 1994

Ferndale, MI - 2004

Florida Governor's Red Ribbon Panel on AIDS - 1993

Florida Medical Association - 1997

Frisco, CO – 1994

Green Party – 1998

Hailey, ID - 2007

Hawaii Kokua Council of Senior Citizens - 2000

*Hawaii Legislature - 2000

*Hawaii Nurses Association – 1999

+HIV Medicine Association - 2006

Idaho Disabled American Veterans - 2004

*Illinois Nurses Association - 2004

Institute of Medicine - 1982 & 1999

International Cannabis Alliance of Researchers and Educators (I-CARE) - 1992

Iowa Civil Liberties Union

Iowa Democratic Party - 1994 & 2000 & 2004

Kaiser Permanente – 1997

Lancet - 1997

Life Extension Foundation - 1997

Libertarian Party – 1999

Los Angeles County AIDS Commission - 1996

Lymphoma Foundation of America - 1997

Madison, WI – 1993, 2004

Maine AIDS Alliance - 1997

Maine Voters - 1999

Marin County, CA – 1993

+Medical Society of the State of New York – 2004

Michigan Democratic Party – 2008

Michigan Voters - 2008

Minnesota Democratic Farm-Labor Party - 1992

*Mississippi Nurses Association – 1995

Molaki Advertiser-News Editorial Staff – 1999

Montana Voters - 2006

Mothers Against Misuse and Abuse (MAMA) -1992

Multiple Sclerosis California Action Network (MS-CAN) - 1996

National Association for Public Health Policy - 1998

National Association of Attorneys General - 1983

National Association of Criminal Defense Lawyers (NACDL)

National Association of People with AIDS - 1992

*National Nurses Society on Addictions (NNSA) - 1995

Nevada Voters - 1998

New England Journal of Medicine – 1997

New Hampshire Medical Association - 2003

New Jersey Nurses Association – 2002

New Mexico Legislature - 2007

New Mexico Medical Society - 2001

*New Mexico Nurses Association – 1997

*New York State Nurses Association – 1995

New York State Association of County Health Officials - 2003

*North Carolina Nurses Association – 1996

Oak Creek, CO - 2005

Oakland, California – 1998

Ohio Patient Network - 2001

Oregon Voters – 1998

Oregon Green Party - 2001

Oregon Democratic Party - 1998

Patients Out of Time - 1995

Physicians Association for AIDS Care

Physicians for Social Responsibility (Oregon) – 1998

Presbyterian Church (USA), General Assembly - 2006

Progressive National Baptist Convention - 2004

Republican Liberty Caucus National Committee – 1999

Rhode Island Legislature – 2006

Rhode Island Medical Society – 2004

Rhode Island Nurses Association – 2004

Rhode Island Patient Advocacy coalition - 2003

San Diego, CA - 1994

San Francisco, CA - 1992

San Francisco Medical Society - 1996

Santa Cruz County, CA – 1993

+Texas Democratic Convention – 2004

Texas Nurses Association -2005

The American Federation of State, County and Municipal Employees (AFSCME) - 2006

Traverse City, MI - 2004

Unitarian Universalist Association - 2004

United Methodist Church – 2004

+Union for Reform Judaism – 2003

Vermont Legislature – 2007

Veterans for Medical Marijuana Access - 2007

*Virginia Nurses Association – 1994, 2004

*Virginia Nurses Society on Addictions - 1993

*Washington Hemp Education Network - 1999

Washington Democratic Party - 1998 & 2000

Washington Medical Association - 2008

Washington Voters - 1998

Wisconsin Democratic Party – 1997& 2002

Wisconsin Public Health Association - 1999

Wisconsin Nurses Association - 1999

Supporting Research

American Academy of Addiction Psychiatry - 2000

+American Academy of Family Physicians - 1977

American Cancer Society – 1997

+*American Nurses Association - 2003

*American Nurses Association, Congress of Nursing Practice - 1996

American Society of Addiction Medicine – 2000

+Association of Nurses in AIDS Care - 1999

+California Medical Association – 1997 & 2006

California Society of Addiction Medicine – 1997

+*Connecticut Nurses Association - 2004

+Council of Health Organizations - 1971

Federation of American Scientists – 1995

+HIV Medicine Association - 2006

+Medical Society of the State of New York - 2004

National Institute of Health Workshop on the Medical Utility of Marijuana -1997

+Northern New England Psychiatric Society

+Texas Democratic Convention – 2004

Texas Medical Association - 2003

+Union for Reform Judaism - 2003

Wisconsin State Medical Society – 1998

Women of Reform Judaism - 2000

No Criminal Penalty

Amherst, MA - 2000

Alaska Medical Association - 1972

+American Academy of Family Physicians - 1977

American Bar Association - 1977

American Medical Association – 1977

+*American Nurses Association - 2003

+American Public Health Association - 1971

American Social Health Association – 1974

+Association of Nurses in AIDS Care - 1999

+Berkeley, CA – 1972

Billy Graham Ministries - 1998

B'nai B'rith Women – 1974

+California Medical Association - 2006

Central Conference of American Rabbis – 1973

+*Connecticut Nurses Association - 2004

+Council of Health Organizations - 1971

District of Columbia Medical Society - 1973

+Episcopal Church of the US - 1973

Episcopal Diocese of New York - 1975

Gray Panthers - 1975

Illinois Bar Association - 1974

Lutheran Student Movement - 1975

Massachusetts Bar Association - 1974

National Association for Mental Health - 1972

National Association of Social Workers – 1975

National Council of Churches - 1973

National Education Association - 1978

New York Bar Association - 1974

+Northern New England Psychiatric Society

Progressive National Baptist Convention - 2004

Southern California Psychiatric Society – 1979

+Texas Democratic Convention – 2004

United Church of Christ - 2002

United Methodists - 1976

+Unitarian Universalist Association – 1970, 2002, 2004

Vermont Bar Association - 1974

+Washington Democratic Party - 2000

Non-U.S. Organizations

Arachnoiditis Trust, UK - 2000

Australian National Task Force on Cannabis – 1994

Australian Medical Association (New South Wales) Limited – 1999

British Columbia, Canada, Green party - 2004

British Medical Association - 1997

Bundesverband Poliomyelitis (Federal Union for Polio),

Germany – 1998

Canadian AIDS Society - 2004

Canadian Association of Chiefs of Police - 2001

Canadian Medical Association – 2001

Canadian Medical Association Journal - 2001

Canadian Medical Journal - 2001

Deutsche AIDS-Hilfe (German AIDS Support Organization) - 1998

Deutsche Epilepsievereinigung (German Association for Epilepsy) -1998

Deutsche Gesellschaft für Algesiologie (German Society for Algesiology) -1998

Deutsche Gesellschaft für Drogen-und Suchtmedizin

(German Society for Drug and Addiction Medicine) -1998

Deutsche Gesellschaft niedergelassener Ärzte zur

Versorgung HIV – 1998

French Ministry of Health - 1997

Health Canada - 1997

House of Lords (UK) Select Committee on Science and Technology – 1999

International Association for Cannabis as Medicine - 2000

Infizierter (German Working Group for Therapists of the HIV infected) –1999

International Association for Cannabis as Medicine - 2000

Legalise Cannabis Alliance - 2000

New South Wales (Australia) Parliamentary Working Party on the Use of Cannabis for Medical Purposes – 2000

New Zealand Health Select Committee - 2003

Lancet (UK) – 1995, 1998

Medical Association of Jamaica - 2001

Medical Cannabis Research Foundation (UK) – 2000

National Commission on Ganja, Jamaica - 2001

National Council on Drug Abuse, Jamaica - 2001

Preventive Medical Center, Netherlands - 1993

Schmerztherapeutisches Kolloquium (Society for Pain Therapists) Germany - 1998

Stichting Institute of Medical Marijuana, Netherlands - 1993

United Church of Jamaica and Cayman Islands – 2000

+ Denotes listing in multiple categories 11/2009

ORIGINAL ARTICLE

Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future directions

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ABSTRACT

Cannabis (marijuana) has been used for medicinal purposes for millennia, said to be first noted by the Chinese in c. 2737 BCE. Medicinal cannabis arrived in the United States much later, burdened with a remarkably checkered, yet colorful, history. Despite early robust use, after the advent of opioids and aspirin, medicinal cannabis use faded. Cannabis was criminalized in the United States in 1937, against the advice of the American Medical Association submitted on record to Congress. The past few decades have seen renewed interest in medicinal cannabis, with the National Institutes of Health, the Institute of Medicine, and the American College of Physicians, all issuing statements of support for further research and development. The recently discovered endocannabinoid system has greatly increased our understanding of the actions of exogenous cannabis. Endocannabinoids appear to control pain, muscle tone, mood state, appetite, and inflammation, among other effects. Cannabis contains more than 100 different cannabinoids and has the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms. This article reviews the current and emerging research on the physiological mechanisms of cannabinoids and their applications in managing chronic pain, muscle spasticity, cachexia, and other debilitating problems.

Key words: cannabinoids, cannabis, marijuana, chronic pain, opioids, opiates, botanical medicine

INTRODUCTION: AN OVERVIEW OF CANNABINOID MEDICINE IN THE UNITED STATES

Though disrupted by a post-1937 *Cannabis sativa* L. prohibition, the emerging field of cannabinoid medicine is growing in the United States (see Figure 1) as ever greater numbers of healthcare providers become educated about the physiologic importance of the endogenous cannabinoid system[1-3] and about the wide safety margins[4] and broad clinical efficacies[5-8] of cannabinoid drugs. Cannabinoid medicines are available in both purely botanical and purely chemical varieties and are useful for managing pain and other conditions in the growing chronically and critically ill patient population.[9] This article provides a current and historical perspective of the use of cannabinoid therapies in the United States.

The following is a brief overview of the various cannabinoid medicines currently utilized in the American healthcare sector. They fall into three categories: single molecule pharmaceuticals, cannabis-based liquid extracts, and phytocannabinoid-dense botanicals—the main focus of this article (Figure 2). The first category includes US Food and Drug Administration (FDA)-approved synthetic or semi-synthetic single molecule cannabinoid pharmaceuticals available by prescription. Currently, these are dronabinol, a Schedule III drug and nabilone, a Schedule II drug. Though both are also used off-label, dronabinol, a (-)*trans*-Δ9-tetrahydrocannabinol (THC) isomer found in natural cannabis, has been approved for two uses since 1985 and 1992,

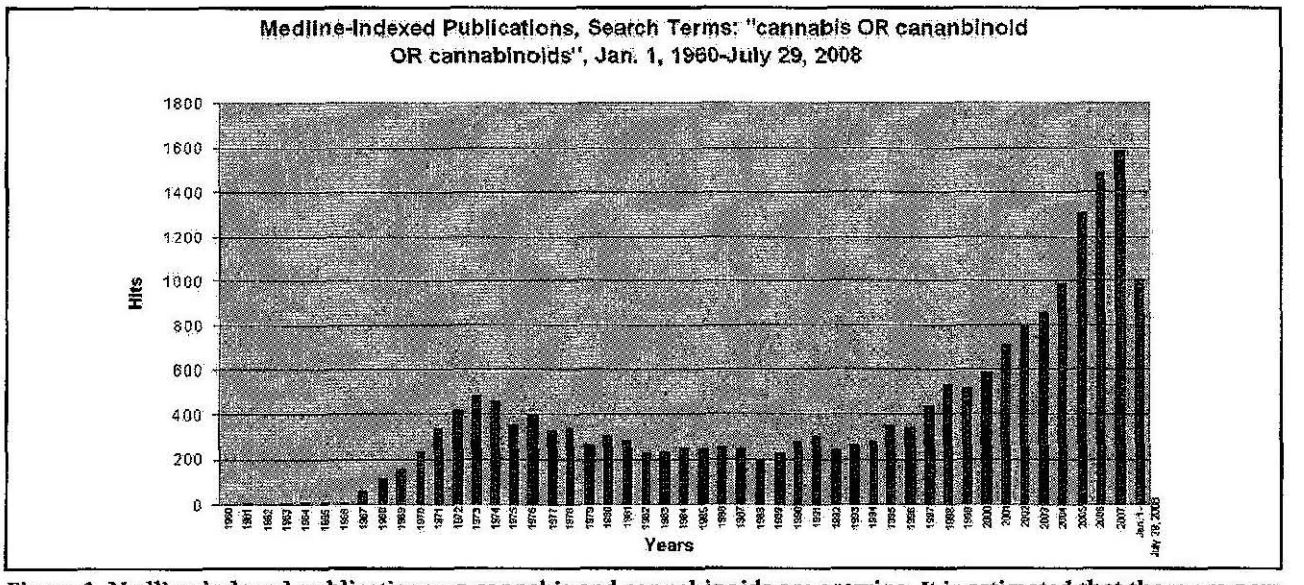

Figure 1. Medline-indexed publications on cannabis and cannabinoids are growing. It is estimated that there are now more than 15,000 articles on the chemistry and pharmacology of cannabis and cannabinoids and more than 2,000 articles on the endocannabinoids in the scientific literature.[1]

respectively: the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments and the treatment of anorexia associated with weight loss in patients with AIDS.[10,11] Nabilone, a synthetic molecule shaped similarly to THC, has also been approved since 1985 for use in the treatment of nausea and vomiting associated with cancer chemotherapy.[12,13]

The second category of cannabinoid medicines being used in the United States includes a line of cannabis-based medicinal extracts developed by several companies. The industry leader is GW Pharmaceuticals, a UK-based biopharmaceutical company whose lead product is currently undergoing FDA-approved, multisite Phase IIb clinical trials for the treatment of opioid-refractory cancer pain in the United States[14] and has received prior approval for Phase III clinical trials in the United States. This botanical drug extract which goes by the nonproprietary name nabiximols has already secured approval in Canada for use in the treatment of central neuropathic pain in multiple sclerosis (in 2005) and in the treatment of intractable cancer pain (in 2007).[15] It is also available on a named patient basis in the United Kingdom and Catalonia,[16,17] a scheme which allows a doctor to prescribe an unlicensed drug to a particular "named patient," and has been exported to 22 countries to date. This phytocannabinoid natural product preparation, produced with permission from the British government, is made by formulating cold organic solvent ($CO_{2(l)}$) extracts of two strains of herbal *Cannabis sativa*—cultivated and ground-up in-house at an undisclosed location in the southern English countryside—into an oromucosal spray.

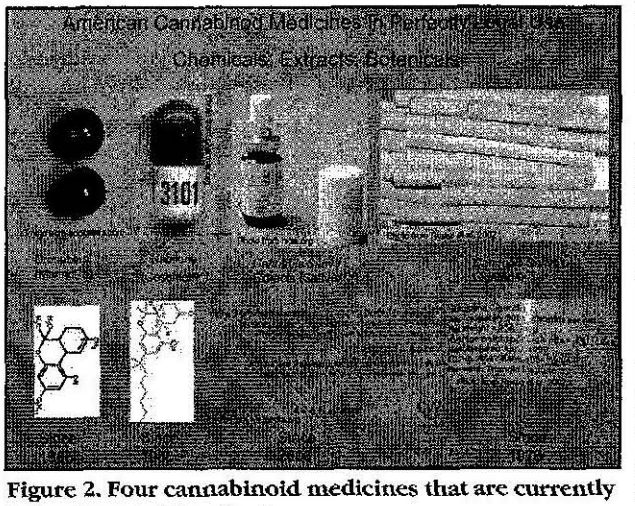

Figure 2. Four cannabinoid medicines that are currently in legal use in US patients.

The third category of cannabinoid medicines currently being used in the United States includes the Schedule I medicinal plant *Cannabis sativa* L. itself, which, while currently unavailable for general prescription use in the United States, is in use in the context of two active controlled clinical trials,[18,19] 33 completed controlled clinical trials,[20-52] and one on-going,

yet essentially defunct, three-decade investigational clinical study.[53,54] The few patients enrolled in American cannabis clinical studies are prescribed a cannabis strain or blend cultivated under contract at the federal research farm at the University of Mississippi at Oxford. The analytical chemist in charge of the farm (whom author SKA met at the 2005 International Cannabinoid Research society meeting) holds the patent on a rectal suppository formulation of dronabinol. This drug has heretofore been produced by total synthesis, but recently it and other cannabinoid formulations were approved for commercial extraction as natural products directly from the cannabinoid botanical supply grown in Oxford, Mississippi.[55] Since cultivation began, the federal cannabis herbal product has been inaccessible for general medical use, and since 1970, federal agencies have maintained the ideological hardliner position that cannabis, pejoratively termed "mari(h/j)uana" during the early 1900s, has "no currently accepted medical use in treatment in the United States."[56]

As the focus of this article is on cannabinoid botanicals, this overview of cannabinoid medicines in use in the United States would be incomplete without a brief overview of the clinical evidence base for their use. The contemporary era of American cannabinoid botanical medicine clinical research began in May 1998 when the first FDA-approved clinical study of cannabis use in a patient population in 15 years enrolled its first subject.[30,57] Overall, the 33 completed and published American controlled clinical trials with cannabis have studied its safety, routes of administration, and use in comparison with placebos, standard drugs, and in some cases dronabinol, in: appetite stimulation in healthy volunteers, the treatment of HIV neuropathy and other types of chronic and neuropathic pain, both pathological and experimentally induced, spasticity in multiple sclerosis, weight loss in wasting syndromes, intraocular pressure in glaucoma, dyspnea in asthma, both pathological and experimentally induced, and emesis, both secondary to cancer chemotherapy and experimentally induced. There has been only one long-term, prospective, federally funded cannabis clinical study that was jointly administered by National Institute on Drug Abuse (NIDA) and FDA. This technically is a study in name only as no clinical response data in the patient cohort have ever been systematically collected or disseminated. The study has been running for more than three decades without any documented follow-up aside from one independent comprehensive health assessment of four of the then seven enrolled patients in 2001 which showed no demonstrable adverse outcomes related to their chronic medicinal cannabis use.[54] Because of attrition, the program now has only these four chronically ill patients enrolled in total (three of whom author SKA has met). It was abruptly closed to new enrollees in 1992 with the explanation from the US Public Health Service that the program was undermining negative public perceptions about cannabis needed to sustain its illegality for the general population.[58]

Four reviews of modern human clinical studies with cannabis and cannabinoids in the United States and elsewhere have recently been published in the peer-reviewed literature.[5-8] Musty et al.'s[8] "Effects of smoked cannabis and oral Δ9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: A review of state clinical trials" reviewed seven state health department-sponsored clinical trials with data from a total of 748 patients who received smoked cannabis and 345 patients who received oral THC for the treatment of nausea and vomiting following cancer chemotherapy in Tennessee (1983), Michigan (1982), Georgia (1983), New Mexico (1983 and 1984), California (1989), and New York (1990). To assess the evidence from these clinical trials, the authors systematically performed a meta-analysis of the individual studies, to assess possible beneficial effects. These trials were randomized, although it is not clear that they were truly blind. The authors found that patients who received smoked cannabis experienced 70-100 percent relief from nausea and vomiting, while those who used oral THC experienced 76-88 percent relief. Even judged in the bright light of modern day evidence-based medicine criteria, the evidence is fully convincing that cannabis does relieve nausea and vomiting in this setting.

Bagshaw et al.'s[7] "Medical efficacy of cannabinoids and marijuana: A comprehensive review of the literature" reviewed 80 human studies of cannabis and cannabinoids, including 10 case reports, and found a preponderance of evidence in support of their use in the treatment of refractory nausea, refractory pain, and appetite loss. It is not possible to tell from this review or even from examining a sampling of the original studies exactly how well the individual studies were controlled, randomized, or blinded. Case reports can only be considered as anecdotal evidence. However, this review of

the literature does a good job at describing the pharmacology, therapeutics, adverse effects, and societal implications of the medical use of marijuana within the context of the data available in these trials and case reports. Safety is one key conclusion that can be derived from this summary. The most prominent effects of marijuana are mediated by receptors in the brain and acute intoxication is characterized by euphoria, transient short-term memory interruption, and stimulation of the senses. Actual intoxication is not a commonly seen effect in clinical trials since the doses are tightly controlled. Thus, outright adverse side effects such as depersonalization, panic attacks, and increased heart rate are rarely reported. Moreover, none of these studies noted any significant withdrawal symptoms. Thus one can conclude, on the basis of these studies, that cannabis shows clinical efficacy for the treatment of refractory nausea, pain, and appetite loss (cachexia).

Ben Amar's[6] "Cannabinoids in medicine: A review of their therapeutic potential" identified 72 controlled studies of the therapeutic effects of cannabis and cannabinoids. In this review, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included reports and reviews published in English, French, and Spanish. For the final selection, the authors only included properly controlled clinical trials. Open-label studies were excluded. Seventy-two controlled studies evaluating the therapeutic effects of cannabis and cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy, and adverse effects are described. The authors concluded that on the basis of the reviewed studies, cannabinoids present an "interesting" therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy, and glaucoma.

Rocha et al.'s[5] "Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: Systematic review and meta-analysis" identified 30 randomized, controlled clinical trials that evaluated the antiemetic efficacy of cannabinoids in comparison with conventional drugs and placebo. A Cochrane-style meta-analysis of 18 studies, including 13 randomized, controlled clinical trials comparing cannabis to standard antiemetics for treatment of nausea and vomiting in cancer patients receiving chemotherapy, revealed a statistically significant patient preference for cannabis or its components versus a control drug, the latter being either placebo or an antiemetic drug such as prochlorperazine, domperidone, or alizapride ($n = 1138$; RR = 0.33; CI = 0.24-0.44; $p < 0.00001$; NNT = 1.8).

Although the aforementioned reviews and meta-analyses draw from both American and internationally conducted research, current and past clinical trials of cannabis—not cannabinoids—occurring specifically in the United States deserve some separate considerations due to historical and political reasons. Seven randomized, placebo-controlled or dronabinol-controlled clinical trials of cannabis from 2005 to 2008 conducted in patient populations in the United States—published after Ben Amar's[6] review cut-off date—which investigated indications such as HIV-related and other forms of painful neuropathy, spasticity in multiple sclerosis, and appetite stimulation in HIV patients, have consistently shown statistically significant improvements in pain relief, spasticity, and appetite in the cannabis-using groups compared with controls.[20-23,25-27] In fact, nearly all of the 33 published controlled clinical trials with cannabis conducted in the United States have shown significant and measurable benefits in subjects receiving the treatment, though it is important to note that there is a potential for a bias toward publication of positive results. Four notable negative results are from Chang et al.'s[42] randomized, placebo-controlled study involving eight patients receiving cancer chemotherapy which reported that smoked cannabis or oral THC had no antiemetic effect compared with placebo; the California state health department-sponsored study[34] in which smoked cannabis given to 98 patients was found to be inferior to oral THC given to 2,000 patients for nausea and vomiting associated with cancer chemotherapy; Greenberg et al.'s[32] randomized placebo-controlled trial in 10 patients with spastic multiple sclerosis and 10 healthy controls which showed a subjective feeling of clinical improvement in some patients, but greater impairment of posture and balance in the patient group; and Hill et al.'s[48] placebo-controlled study of cannabis in the treatment of electrically

induced experimental pain in 26 healthy male volunteers, six of whom received placebo and 20 of whom received cannabis, which showed decreased pain tolerance and increased sensitivity to pain in the cannabis using group.

In assessing the past literature *en bloc*, the primary limitations are the relatively small size of many of the trials, as well as the unclear degree to which some of the earlier studies were blinded. Indeed, as the clinical effects of cannabinoids are usually quite apparent, true blinding would be difficult under any circumstance. Further, given the variability in methodologies among the studies, it is not possible to combine all of the data and attempt to do a valid, statistical analysis comparing cannabis with placebo. Despite these limitations, it is our opinion that the majority of American cannabis clinical trials provide empirical evidence supporting the medical efficacy of cannabis.

CONTESTING CANNABIS AS MEDICINE

The rising prominence of phytocannabinoid-rich botanicals in healthcare is actually a rediscovery and not a novel medical practice since the medicinal use of the dried flowers of cannabis has an extensive ancient history cross-culturally, with the oldest documented references known today in the Chinese pharmacopoeia of Emperor Shen-Nung dated to 2737 BCE in the oral tradition, but written down in the first century CE.[59,60] The medical use of cannabis in the modern period was common in the United States from the mid-1850s to the early 1940s due to its introduction into Western medicine as "Indian Hemp" by Calcutta Medical College cofounder and professor, Dr. W.B. O'Shaughnessy (1809-1889), in a landmark 1839 journal article.[61]

Today, nearly one and three-quarter centuries later, the medical science of cannabinoid botanicals has greatly advanced due in large part to the elucidation of *in vivo* cannabinergic structure and function. The cannabinoid system helps regulate the function of major systems in the body, making it an integral part of the central homeostatic modulatory system—the check-and-balance molecular signaling network that keeps the human body at a healthy "98.6," as illustrated by the title of the May 2008 theme issue[2] of the *Journal of Neuroendocrinology*: "Here, there and everywhere: The endocannabinoid system." The discovery and elucidation of the endogenous cannabinoid signaling system with widespread cannabinoid receptors and ligands in human brain and peripheral tissues, and its known involvement in normal human physiology, specifically in the regulation of movement, pain, appetite, memory, immunity, mood, blood pressure, bone density, reproduction, and inflammation, among other actions, has led to the progression of our understanding of the therapeutic actions of cannabinoid botanical medicines from folklore to valid science.[3,53]

Cannabinoids, which are classically 21-carbon terpenophenolics, of which cannabis contains 108,[1] along with other bioactive compounds, have many distinct pharmacologic properties, including analgesic, antiemetic, antispasmodic, antioxidative, neuroprotective, antidepressant, anxiolytic, and anti-inflammatory properties, as well as the capacity for glial cell modulation and tumor growth regulation. Their application in pain management is especially promising as cannabinoids inhibit pain in "virtually every experimental pain paradigm" in supraspinal, spinal, and peripheral regions[62] and have no risk of accidental lethal overdose.

However, these properties are medically underutilized and scarcely recognized by regulatory bodies as a large translational gap currently exists in the field of cannabinoid medicine between research-driven scientific knowledge and patient-centered medicine. This translational gap is a legacy of the historical and on-going suppression and misrepresentation of the scientific data by the opponents of medicinal cannabis. Although allowing patients' access to medical cannabis use consistently enjoys widespread support in all public polling, physicians' knowledge base of this medicine lags behind the public's comfortability with its use. In our opinion, there is significant evidence indicating that the major reason for this translational gap is due to lack of knowledge on the part of medical practitioners. This continues to be perpetuated by intentionally misleading practitioners about the scientific basis of cannabinoid medicines and omitting education about cannabinoid medicines in medical schools, residencies, and postgraduate and continuing medical education, in general.

There remains a near complete absence of education about cannabinoid medicine in any level of medical training. This is certainly true at our institution, the University of Washington. This occurs despite the fact that the Institute of Medicine concluded after reviewing relevant scientific literature, including dozens of works documenting marijuana's therapeutic value, that "nausea, appetite loss, pain,

and anxiety are all afflictions of wasting, and all can be mitigated by marijuana."[63] Further, legal access to marijuana for specific medical purposes continues to be supported by numerous national and state medical organizations including the American College of Physicians, which has historically been quite conservative. Other major players on this list include the American Academy of Family Physicians, the American Psychiatric Association Assembly, the American Academy of Addiction Psychiatry, the Washington State Medical Association, the California Medical Association, the Medical Society of the State of New York, the Rhode Island Medical Society, the American Academy of HIV Medicine, the HIV Medicine Association, the Canadian Medical Association, the British Medical Association, and the Leukemia and Lymphoma Society, among others.[64,65] The American Medical Association (AMA)-Medical Student Section has already adopted a favorable position statement which the House of Delegates of the AMA is currently studying and considering for adoption. At the most recent AMA meeting (November 2008), support for this position was expressed by the Pacific Rim Caucus of state medical associations, which includes California, Hawaii, Alaska, and Guam. The House of Delegates opted to commission a study by the AMA's Council on Science and Public Health on whether the accumulated evidence supports the position that marijuana should be reclassified from a Schedule I controlled substance into a more appropriate schedule and on whether medical ethics demands that the AMA call for protection of both doctors and patients who act in accordance with state medical marijuana laws. The report is slated for release later this year.

Clearly, there is a growing acceptability of the therapeutic practice of medicinal cannabis use amongst organized medicine groups, yet it is still classified as a Schedule I drug in the United States. Federal agencies such as the Drug Enforcement Administration (DEA) and the Department of Health and Human Services (HHS) are required by law to make drug reclassifications based on scientific and medical considerations. However, federal agencies continue to insist[66] that marijuana "has no currently accepted medical use in treatment in the United States" and that "there is a lack of accepted safety for the use of" marijuana "under medical supervision"[56] as grounds for maintaining its prohibition. In supporting these positions which are neither based on thorough scientific review nor any cogent line of logical reasoning (eg, given the fact that the most psychoactive constituent of cannabis, THC, is available as a Schedule III drug), federal and state agencies could be accused, based on the international bill of rights, of shrinking their specific legal "obligation to refrain from prohibiting or impeding traditional preventive care, healing practices and medicines," engaging in the "deliberate withholding or misrepresentation of information vital to health protection or treatment," and aiming for "the suspension of legislation or the adoption of laws or policies that interfere with the enjoyment of any of the components of the right to health." These are all specifically enumerated violations of governmental obligations to respect the human right to health in international law.[67]

GEOGRAPHIC AND LEGAL ISSUES IN THE ACCESS AND DELIVERY OF MEDICINAL CANNABIS IN THE UNITED STATES

In moving toward the protection and fulfillment of the right to health, 13 American states—Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, Washington—containing approximately 23.5 percent of the national population and representing 41.5 percent of the total geographic area of United States—have passed laws granting physicians the authority to approve or recommend use of cannabinoid botanicals based on medical evaluation to qualifying chronically or critically ill patients, thereby freeing such patients from state-level prosecution and the worst consequences of the ongoing denial of cannabis's medical utility in federal law. A medical marijuana authorization is the means by which patients receive *access* to this healthcare resource. Although not a true prescription, it is a legally recognized doctor–patient clinical discussion viewed as protected speech according to a ruling by the Ninth US Circuit Court of Appeals that the Supreme Court of the United States let stand.[68] Estimates indicate that in 2008, approximately 7,000 American physicians have made such authorizations for a total of approximately 400,000 patients.*

*Currently available figures indicate that more than 1,500 physicians have recommended medical marijuana use for 350,000 patients in California,[69,70] 182 physicians for 2,051 patients in Colorado,[71] 124 physicians for 4,047 patients in Hawaii,[72] 145 physicians for 634 patients in Montana,[73] 145 physicians for 900 patients in Nevada,[74] 2,970 physicians for 19,646 patients in Oregon,[75] 149 physicians for 302 patients in Rhode Island,[76] and 2,000 physicians[53] for 25,000 patients in Washington.[77]

After receiving medical marijuana authorizations, patients procure cannabinoid botanical medicinal products, or medical cannabis, for their self-administered use under medical supervision from in-state channels and hence *delivery* of the treatment is effectuated—actions which continue to be harshly criminally sanctioned under federal law.[78,79] In such a sociopolitical environment, major medicine access and delivery problems certainly do remain for patients. Patients often depend on the knowledge base of their healthcare providers when exploring treatment options. Access to knowledgeable physicians who feel comfortable recommending medical cannabis is a challenge for patients. Following such recommendations and receiving a safe and adequate supply is a major hardship because of the lack of comprehensive laws at the state level.

Work in the field of medical geography which has a specialization in assessing spatial perspectives on healthcare access and delivery systems focuses on the key question: what is the impact of geographic factors on the acquisition of various medical services? Given the current state of conflicting policies that regulate cannabinoid botanical medical systems in the United States, federal courts have mandated that the medical geography of cannabinoid botanicals access and delivery be necessarily bipolar, with patients receiving *access to* treatment at one set of locations and *delivery of* treatments at other locations. Note that the terms *access* and *delivery* here carry specific meanings with respect to cannabinoid botanical medical systems in the United States; they should not be thought of in terms of their general usages in the field of medical geography.

Generally speaking, according to key experts in the field,

> access to healthcare, is the product of four sets of variables: the availability of services, the possession of the means of access (money or insurance, transportation), the nondiscriminatory attitudes of health care providers, and the failure of the ill themselves to cope with their situation, such as their ability to recognize symptoms, communicate with health professionals, and navigate the health care system.
>
> Meade and Earickson[80(p 381)]

For accessing healthcare with cannabinoid botanicals, the critical variable is availability of the service. This is contingent on the legality of the practice in a given region and its acceptability within the medical profession. In this healthcare delivery system, the authorizing physician "acts as a gatekeeper for the individual entering the formal health care delivery system."[81(p 182)] For Joseph and Phillips,[82] people's "socio-economic accessibility" of a healthcare service includes consideration of "whether they are permitted to use it (organizational and institutional restrictions on accessibility)"(p. 2). However, proof of access or accessibility is not simply the mere presence or legality of a service or practitioner who provides it. It is only through *utilization* of healthcare resources that accessibility is revealed. The medical cannabis healthcare system, which is now functionally available in 13 states, is most certainly under-utilized due in large part to a lack of understanding about the workings of such programs on the part of clinicians and patients alike and to a lack of basic knowledge on the science underpinning cannabinoid therapeutics on the part of clinicians who often operate as if cannabinoid medicines or the cannabinoid signaling system simply do not exist or are of only minor and insignificant importance. In addition, lingering social stigmas such as the flippant connotations which cannabis use often carries likely create aversion to its use on behalf of doctors and patients alike.

ONE STATE'S EXPERIENCE: AUTHORIZING THE MEDICAL USE OF CANNABIS IN WASHINGTON STATE

Washington State voters originally passed the Medical Use of Marijuana Act in 1998 as a ballot initiative (I-692). The Washington State Legislature subsequently amended the Act in 2007 with Engrossed Senate Substitute Bill 6032. In early 2008, the Washington Department of Health further clarified the law by adopting a rule defining a "60-day supply" of medical marijuana. Two of the authors of this article (SKA, GTC) lobbied against these revisions on a number of grounds, not the least of which was that the supply limitations are not based on the known pharmacology of cannabis. Rather, these were amounts arrived at through an arbitrary, nonscientific process. The entire act can be found on-line (*www.doh.wa.gov/hsqa/medical-marijuana/*), codified in Chapter 69.51A of the Revised Code of Washington and at Chapter 246-275 of the Washington Administrative Code. A readable guide to the law created by the American Civil Liberties Union of Washington State, from which some

detailed legal information in the following sections is freely drawn, can be found on-line as well (*www.aclu-wa.org/detail.cfm?id = 182*).

The University of Washington School of Medicine, which is the only medical school in a five-state region (Washington, Alaska, Idaho, Wyoming, Montana) subsequently adopted policy guidelines for physicians regarding medical marijuana in March 2002.[83] The medical marijuana law amendment process, which occurred primarily in the 2007 state Legislative session[84] was allotted $94,000. This money was allocated to the Washington State Department of Health (WA DOH) to formally study medical marijuana dosing and supply needs. Despite this, WA DOH summarily ignored the only peer-reviewed studies done on the actual dosing of medicinal cannabis,[33,53] and chose instead to listen extensively to law enforcement representatives who presented their own anecdotal opinions on what they believed would be appropriate amounts of cannabis to be allowed for medical uses. Ultimately the WA DOH defined a 60-day supply of medical marijuana as not more than 24 ounces of usable marijuana and not more than 15 cannabis plants. Usable marijuana is defined as "the dried leaves and flowers of the Cannabis plant Moraceae[sic]" and does not include "stems, stalks, seeds and roots" (WAC 246-75-010 (2)(d)). A plant is defined as "any marijuana plant in any stage of growth" (WAC 246-75-010 (2)(b)). Patients maintain the right to present evidence in court that their necessary medical use exceeds the presumptive amount (WAC 246-75-010 (3)(c)). Patients who possess not more than this amount will be presumed to be in compliance with the law, whereas patients who require more than this amount still maintain the right to present evidence of their personal, actual medical need in court.

As of February 2009, valid documentation for medical marijuana has been provided to an estimated 25,000 qualifying patients by approximately 1,000-2,000 Washington-licensed physicians across the state.[53,77] The list of state-approved qualifying conditions includes cancer, human immunodeficiency virus (HIV), multiple sclerosis, epilepsy or other seizure disorder, spasticity disorders; intractable pain, defined as pain unrelieved by standard medical treatments and medications; glaucoma, either acute or chronic, limited to mean increased intraocular pressure unrelieved by standard treatments and medications; Crohn's Disease with debilitating symptoms unrelieved by standard treatments or medications; Hepatitis C with debilitating nausea and/or intractable pain unrelieved by standard treatments or medication; or any disease, including anorexia, which results in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, and/or spasticity, when these symptoms are unrelieved by standard treatments or medications. A process exists whereby additional conditions may be added to this list.

As with any state law, Washington's law does not change federal marijuana laws. Therefore, anybody who manufactures, distributes, dispenses, or possesses marijuana for any purpose still may be prosecuted under federal law (Title 21, Chapter 13, sections 841 and 844 of the United States Code). Fortunately, due to more pressing criminal justice priorities, very few medical marijuana patients or providers have warranted the attention of Washington's federal law enforcement agents and US Attorneys. The Medical Use of Marijuana Act does not legalize marijuana for recreational or any other use that is not specifically covered by the law. The law applies to only the medical conditions listed in the statute and others that may be approved by the Washington State Medical Quality Assurance Commission and Board of Osteopathic Medicine and Surgery. All other uses of marijuana remain illegal. Originally, the law protected qualifying patients and their designated providers from conviction by allowing them a medical marijuana "affirmative defense" but did not technically protect them from arrest or prosecution. In 2007, the Legislature added the following language which outlines an encounter process that law enforcement officers *may* choose to follow, but are technically not legally obligated to carry out: "If a law enforcement officer determines that marijuana is being possessed lawfully under the medical marijuana law, the officer may document the amount of marijuana, take a representative sample that is large enough to test, but not seize the marijuana."

ASSESSING A PATIENT FOR THE MEDICINAL USE OF CANNABIS

Who is a protected "qualifying patient" and how does a physician assess this patient for appropriateness? Washington's law protects patients suffering from specified terminal or debilitating medical conditions who have been diagnosed by, and received a qualifying statement from, a Washington state physician licensed under RCW 18.71 (M.D.) or RCW 18.57 (osteopath). The patient must be a resident of

Washington State at the time he or she is diagnosed by that physician with a covered illness, and he or she must be advised by the physician (1) about the "risks and benefits" of medical marijuana and (2) that he or she "may benefit from the medical use of marijuana." The Washington State Medical Association has developed a standard form for physicians to use. Interestingly, there is no specification as to how often the patient needs to be seen or exactly for how long the authorization is good.

For medical cannabis recommendations to be considered a standard, quality medical treatment, they should be accompanied by health information regarding cannabis usage, including patient education about auto-titration dosing schedules and harm reduction approaches that emphasize the least hazardous means of pharmacological delivery of cannabinoid botanicals (such as vaporization and oral administration). Patients should be provided treatment management over time, if feasible, and their authorizing physicians should be willing to submit medical testimony should patients encounter legal or administrative problems related to their possession or use of the botanical medicine. Patients should also be counseled that they do not necessarily have to be "high" to obtain a medical effect from the treatment. The American Academy of Cannabinoid Medicine, of which two coauthors (SKA, GTC) are founding members, is in the process of formation and intends to accredit physicians in this area of medicine and provide much-needed practice standards, ethics, and continuing medical education.

Oddly, the medical marijuana law of Washington State does not cover all terminal or debilitating medical conditions—only those illnesses and categories of illnesses currently listed in the statute or subsequently approved by the Medical Quality Assurance Commission (MQAC) and Board of Osteopathic Medicine and Surgery. However, the law does allow for anyone to petition the MQAC and the Board of Osteopathic Medicine and Surgery to add other terminal or debilitating conditions to the list. Qualifying patients must carry their "valid documentation" with them whenever they possess or use medical marijuana. Valid documentation consists of two items: (1) their physician's authorization and (2) proof of their identity, such as a Washington State driver's license or identity card. A qualifying patient must present both of these items to any law enforcement officer who questions the patient regarding his or her use of medical marijuana.

WHO IS A PROTECTED "DESIGNATED PROVIDER"?

Some qualifying patients need help growing, obtaining, storing, or using medical marijuana, so the law allows them to appoint a "designated provider" who will also be protected under the Medical Use of Marijuana Act. A designated provider is defined as a person who: (a) is 18 years of age or older; (b) has been designated in writing by a patient to serve as a designated provider; (c) is prohibited from consuming marijuana obtained for the personal, medical use of the patient for whom the individual is acting as a designated provider (though this does not preclude a designated provider from her/himself being a qualifying patient); and (d) is the designated provider to only one patient at any one time. This wording effectively eliminates medicinal cannabis cooperatives; however, the leaders of individual counties such as King County, the most populous county in Washington, have adopted written policies expressing their wish to not prosecute medical marijuana cooperatives whose patient-members are individually acting in accordance with state law.

Many patients using medicinal cannabis in Washington State are severely disabled and would not be able to physically perform the tasks necessary to cultivate cannabis, nor would they necessarily have access to just one individual to assign as their cannabis provider. Many have long argued that the WA DOH could certify growers through a formal licensure program that would also allow for state taxation of the produced cannabis. The DOH was amendable to this initially but could not do this due to a conflict with the federal laws. Nevertheless, a formal licensure process has begun in other regions such as New Mexico and numerous California municipalities. The qualifying patient must designate the provider in writing before the provider assumes responsibility for the patient's medical marijuana, and the designated provider must carry (1) a copy of the patient's designation, (2) a copy of the patient's physician authorization, and (3) proof of identity whenever he or she is growing, obtaining, or in possession of medical marijuana, to be presented to law enforcement on request.

DO STATE MEDICAL MARIJUANA LAWS PROTECT PHYSICIANS?

Our Washington law states specifically that licensed physicians "shall not be penalized in any

manner, or denied any right or privilege" for: (1) Advising patients about the risks and benefits of medical marijuana; or (2) Providing a qualifying patient with valid documentation that the medical use of marijuana may benefit that particular patient. Physicians and their prescription licenses are also protected under federal law. In *Conant v Walters*,[68] a ruling that the US Supreme Court has let stand, the Ninth Circuit Court of Appeals ruled that threats from the federal government to revoke physicians' DEA registrations or initiate investigations based solely on physicians' recommendations of medical marijuana to their patients violated the core privacy and First Amendment rights contained in the doctor-patient relationship.[85] It is important to note that physicians still cannot formally prescribe or provide marijuana to their patients as that would violate federal laws banning generalized prescription of schedule I drugs. Only patients and their designated providers may possess marijuana for the patient's medical use. In our experience, patients will often ask where they can obtain marijuana for medical use. Even though a physician can certainly tell a patient where to obtain prescribed drugs, it is technically illegal for a physician to instruct a patient on where to obtain cannabinoid botanicals that they have been medically authorized to use. However, the WA state law also states: "no one can be punished solely for being in the presence or vicinity of medical marijuana or its use" (RCW 69.51A.050). As long as they are not in actual possession of the patient's medical marijuana or actively participating in the growing, obtaining, delivering, or administering of the patient's medical marijuana, then family members, friends, roommates, healthcare providers, social workers, and anyone else may be around medical marijuana users and their designated providers without fear of prosecution under the state law. Additional stipulations in the law include: (1) No health insurer can be required to pay for the medical use of marijuana and (2) Places of employment, school buses, school grounds, youth centers, and correctional facilities are not required to accommodate the on-site use of medical marijuana. This definitely puts constraints on the use of medicinal cannabis since dosages for adequate pain relief can be quite costly. The WA State Department of Corrections (DOC) specifically prohibits the use of medicinal cannabis by anyone who is incarcerated, no matter what the diagnosis or how well-documented the medical need is.

CLINICAL APPLICATIONS: USING CANNABIS FOR PAIN MANAGEMENT

With regards to the medical use of cannabinoid botanicals specifically for pain management, several considerations should be noted in the risk-benefit ratio. In general, the three properties that make cannabinoids well-suited for analgesia are their established safety, remarkably low toxicity, and documented efficacy for relieving a wide range of pain states, from neuropathic pain to myofascial pain, to migrainous pain. Botanical cannabinoid medicines, with their 108 cannabinoids, have these three properties. With other natural and synthetic single-molecule cannabinoid therapeutic options, such as dronabinol, nabilone, and experimentally-used cannabinoid drugs such as levonantradol, and ajumelic acid, these properties of safety, low toxicity, and efficacy also apply. However, intolerable side effects such as drowsiness, dysphoria, and increased toxicity are occasionally reported in preclinical and clinical data with these compounds.[33,86] A recent review of 31 clinical studies on the adverse effects of medical cannabinoids by Wang et al.[4] showed that the vast majority of adverse events reported were not serious (96.6 percent). With respect to the "164 serious adverse events" that did occur, the authors reported that "there was no evidence of a higher incidence of serious adverse events following medical cannabis use compared with control [drugs] (rate ratio [RR] 1.04, 95% CI 0.78-1.39)."[4(p 1672)] The same held true for medical cannabinoids usage generally.[4(p 1676)] In addition, serious adverse events were not evenly reported in the literature. The authors note: "The fact that 99 percent of the serious adverse events from randomized controlled trials were reported in only two trials suggests that more studies with long-term exposure are required to further characterize safety issues."[4(p 1676)]

SAFETY PROFILE OF CANNABIS

In its 4,000+ years of documented use, there is no report of death from overdose with cannabis. In contrast, as little as 2 grams of dried opium poppy sap can be a lethal dose in humans as a result of severe respiratory depression. This fact about opium is borne out today in the unintentional deaths from prescribed opioids that continue to escalate.[87] If a very large dose of cannabis is consumed ("over dose"), which typically occurs via oral ingestion of a concentrated preparation of cannabis

flowers' resin (eg, in the form of an alcohol tincture or lipophillic extract), agitation and confusion, progressing to sedation, is generally the result.[88] This is time limited and disappears entirely once the cannabis and its psychoactive components are fully metabolized and excreted. This usually occurs within 3-4 hours, although oral ingestion may prolong the duration of these effects.[33] Some have even called this an "acute cannabis psychosis," and this exacerbates fears that cannabis consumption, in the long-term, might lead to schizotypy such as chronic, debilitating psychosis. Review of the current epidemiological data shows that such fears are unfounded.[89-92] No studies have established that cannabis contributes to psychosis. After careful and extensive consideration of the published data, the United Kingdom's Advisory Council on the Misuse of Drugs made these comments:

> In the last year, over three million people appear to have used cannabis but very few will ever develop this distressing and disabling condition. And many people who develop schizophrenia have never consumed cannabis. Based on the available data the use of cannabis makes (at worst) only a small contribution to an individual's risk for developing schizophrenia.[93(p 15)]

> For individuals, the current evidence suggests, at worst, that using cannabis increases the lifetime risk of developing schizophrenia by 1%.[93(p 11)]

The ACMD is a statutory and nonexecutive, nondepartmental, independent public body of experts that advises the UK government on drug-related issues. The ACMD revisited the issue in 2008, and after another thorough review that incorporated data that had been published since its prior review, they concluded:

> since the Council's previous review the evidence has become more, rather than less, confused. Although there is a consistent (though weak) association, from longitudinal studies, between cannabis use and the development of psychotic illness, this is not reflected in the available evidence on the incidence of psychotic conditions. The most likely (but not the only) explanation is that cannabis – in the population as a whole – plays only a modest role in the development of these conditions. The possibility that the greater use of cannabis preparations with a higher THC content might increase the harmfulness of cannabis to mental health cannot be denied; but the behaviour of cannabis users, in the face of stronger products – as well as the magnitude of a causal association with psychotic illnesses – is uncertain.[94(p 33)]

There is some documentation of a syndrome of acute schizoprhreniform reactions to cannabis that may occur in young adults who are under stress and have other vulnerabilities to schizophreniform illness. However, there are no evidence-based studies demonstrating that chronic cannabis use can cause or exacerbate schizophrenia or bipolar disorder. Nonetheless, medicinal cannabis use should be closely monitored in early teens or preteens who have preexisting symptoms of mental illness.

It should also be noted that cannabis use, when delivered via combustion-and-inhalation, does not have similar health hazards to nicotine-rich tobacco smoking, aside from the potential for bronchial irritation and bronchitis. A recent large, population-based retrospective case-control study involving 1,212 incident cancer cases and 1,040 cancer-free controls in the Los Angeles area matched to cases by age and gender demonstrated significant, strongly positive, dose dependant associations between tobacco smoking and the incidence of head, neck, and lung cancers but failed to demonstrate any significant positive associations or dose dependence with cannabis smoking and the incidence of those same cancers. In fact, a significant, albeit small, protective effect was demonstrated in one group of combusted cannabis consumers.[95] Other reviews, such as Melamede's,[96] offer physiological and pharmacological evidence to account for these significant differences between cannabis and tobacco smoke.

It is clear that, as an analgesic, cannabis is extremely safe with minimal toxicity. Unlike opioids, cannabinoid medicines do not promote appetite loss, wasting, and constipation, but instead can be used therapeutically to treat these symptoms. The synergistic effect of administering multiple active plant constituents and an entourage effect involving endocannabinoid signaling molecules and cannabinioid receptors CB1 and CB2 probably results in the superior analgesia of whole plant cannabis. Carter et al.[97] summarize this as follows: "Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a

manner similar—but pharmacologically distinct from—that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids...."[97(p 949)] Second, terpenoids, flavonoids, and essential oils present in cannabinoid botanical preparations have been shown to have therapeutic effects on mood, inflammation, and pain.[86,98-102] Third, cannabinoids are known to have antinociceptive effects in descending pain pathways, such as those mediated by the periaqueductal gray. Finally, cannabinoid-rich cannabis has anti-inflammatory properties (acting through prostaglandin synthesis inhibition and other cytokine-mediated mechanisms) and via retrograde signaling can presynaptically modulate the release of dopamine, serotonin, and glutamate—neurotransmitters involved in migraine, nausea, and many other noxious symptomatologies.

FUTURE TRENDS AND CONCLUSIONS

The future will likely see an ever-growing number of strategies for separating sought after therapeutic effects of cannabinoid receptor agonists from any potential unwanted effects. However, further progress in the clinical development of selective agonists and antagonists for CB1 and CB2 receptors may prove difficult. Progress in producing selective medications could be hindered by the fact that natural cannabis appears to work best when all of the naturally occurring cannabinoids as found in the plant, which have a multiplicity of empirically demonstrated medicinal properties, are allowed to work in concert with each other and with the other compounds in cannabis. This "orchestration" of effects, which has been best characterized in the case of the added anxiolytic effect of combining cannabidiol (CBD) with Δ9-THC versus THC alone,[98,103] appears to improve the efficacy and safety of the whole cannabis plant for medicinal use. This orchestration of effects is also reflective of the differing medicinal properties of various strains of the cannabis plant. Even among the same genotypic plants (ie, strains) there may be considerable differences in medicinal effect, as clinical effects are dependent not only on the genetic strain of the plant but also the conditions under which it was cultivated. These factors will ultimately determine the percentages of the various cannabinoids. A future promising area of research will be the identification and development of cannabis strains that are better suited to particular therapeutic ends. Although refinement of cannabinoids with high therapeutic potential may facilitate the production of cleaner, maximally therapeutic drugs, there may also be unwanted consequences.[100] For example, patients with amyotrophic lateral sclerosis (ALS) report that dronabinol, which is nearly 100 percent THC by weight, is too sedating and does not alleviate symptoms as well as natural cannabis.[101,102]

Effective delivery systems are also needed and will continue to be developed. Because the cannabinoids are volatile, they will vaporize at a temperature much lower than actual combustion of plant matter. Thus, heated air can be drawn through marijuana and the active compounds will vaporize into a fine mist, which can then be dosed and inhaled without the generation of smoke.[24,104] As noted previously, pharmacologically active, aerosolized and sublingual forms of cannabinoid-based medicinal extracts have recently been developed[15] and marketed, but these approvals should not be allowed to exclude or impede medicinal access to the class of organic botanicals from which such preparations are derived.

Arguably cannabis is neither a miracle compound nor the answer to everyone's ills. Yet it is not a plant that deserves the tremendous legal and societal commotion that has occurred over it. Over the past 30 years, the United States has spent hundreds of billions in an effort to stem the use of illicit drugs, including cannabis, with limited success. Because of this climate, unfortunately some very ill people have had to fight and, in many cases, lose long court battles to defend themselves for the use of a medicinal preparation that has helped them. Nonetheless, the purpose of this article is not to discuss the pros and cons of medicinal versus recreational marijuana use. That is a totally separate and altogether different issue. Yet, at the very least, it should be noted that there is no evidence that recreational cannabis use is any higher in states that allow for its medicinal use. Gorman et al. examined whether the introduction of laws allowing for the medical use of cannabis affected the level of cannabis use among arrestees and emergency department patients.[105] Using the Arrestee Drug Abuse Monitoring (ADAM) system, data from adult arrestees for the period 1995-2002 were examined in three cities in California (Los Angeles, San Diego, San Jose), one city in Colorado (Denver), and one city in Oregon (Portland). Data were also analyzed for juvenile arrestees in two of the California cities and Portland. Data on emergency

department patients from the Drug Abuse Warning Network (DAWN) for the period 1994-2002 were examined in three metropolitan areas in California (Los Angeles, San Diego, San Francisco), one in Colorado (Denver), and one in Washington State (Seattle). The analysis followed an interrupted time-series design. There was no statistically significant pre-medical marijuana law versus post-medical marijuana law differences found in any of the ADAM or DAWN sites. Thus, consistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug. The authors theorized that the use of medical cannabis by "sick" patients might "de-glamorize" its use and thereby actually discourage use among others.

The scientific process continues to evaluate the therapeutic effects of marijuana through ongoing research and assessment of available data. With regard to the medicinal use of marijuana, our legal system should take a similar approach, using amassed scientific evidence and logic as the basis of policy-making rather than political views and societal trends that are more reflective of the ongoing debate over any potential harmful effects of recreational marijuana use. At the same time, physicians and medical students should make extra efforts to fill in the gaps in their training and knowledge base by educating themselves in the art and science of cannabinoid medicine.

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