ARTHRITIS AND MEDICAL CANNABIS



A Note from Americans for Safe Access

We are committed to ensuring safe, legal availability of marijuana for medical uses. Today over one million Americans are legally using medical marijuana—or "cannabis," as it is more properly called—under the care of their medical professional, and nearly half the country lives in a state where this treatment is an option. This publication series is intended to help medical professionals, patients and policymakers better understand how cannabis may be used safely and effectively as a treatment for many medical conditions. You will find information on:

Why Cannabis is Legal to Recommend	3
Overview of the Scientific Research on Medical Cannabis	4
Research on Cannabis and Arthritis	6
Comparison of Medications: Efficacy and Side-Effects	8
Why Cannabis is Safe to Recommend	.10
Testimonials of Patients and Doctors	.13
History of Cannabis as Medicine	.19
Scientific and Legal References	.22

While the federal prohibition of cannabis has limited modern clinical research and resulted in considerable misinformation, a scientific consensus on its therapeutic value has emerged, based on a growing body of successful clinical trials and preclinical research. The experience of patients, medical professionals and research has revealed that cannabis can safely treat a remarkably broad range of medical conditions, often more effectively than conventional pharmaceutical drugs. For some of the most difficult to treat conditions, such as multiple sclerosis and neuropathic pain, cannabis often works when nothing else does.

Many of its therapeutic uses are well known and documented, and medical researchers are learning more each day. Cannabis and its constituent components show potential to fight tumors, autoimmune disorders, and serious neurological conditions for which treatment options are limited. As of July 2015, 23 states and the District of Columbia have laws allowing its use under a doctor's supervision, and cannabis or a dose-controlled whole-plant extract of it is available by prescription in 11 countries and approved for 13 more.

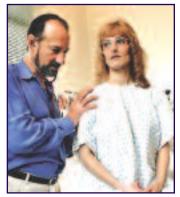
This publication is only a starting point for the consideration of applying cannabis therapies to specific conditions; it is not intended to replace the training and expertise of medical professionals with regard to medicine, or attorneys with regard to the law. But as advocates for the hundreds of thousands of patients who have found relief with cannabis, we know there are millions more for whom it may be the best medicine. For more information, see **AmericansForSafeAccess.org** or call **1-888-929-4367**.

Why Cannabis is Legal to Recommend

Medical professionals have a legal right to recommend cannabis as a treatment in any state, as protected by the First Amendment. That was established by a 2004 United States Supreme Court decision to uphold earlier federal court rulings that doctors and their patients have a fundamental Constitutional right to freely discuss treatment options. State rules for quali-

fying an individual patient for legal protections when using medical cannabis differ as to who may make the recommendation and for what conditions, as well as how that recommendation is communicated to state authorities. Medical professionals and patients should familiarize themselves with the laws and regulations in their state. ASA provides state-by-state resources at: AmericansForSafeAccess.org/state_by_state_recommending_cannabis.

Under federal law, cannabis may not be prescribed, but its therapeutic use can be recommended without any legal jeopardy. The court rulings that protect medical professionals stem



Angel Raich & Dr. Frank Lucido

from a lawsuit brought by a group of doctors and patients led by AIDS specialist Dr. Marcus Conant. The suit was filed in response to federal officials who, within weeks of California voters legalizing medical cannabis in 1996, had threatened to revoke the prescribing privileges of any physicians who recommended cannabis to their patients for medical use.¹ Dr. Conant contended that such a policy would violate the First Amendment, and the federal courts agreed.²³

What doctors may and may not do. In Conant v. Walters,⁴ the Ninth Circuit Court of Appeals held that the federal government could neither punish nor threaten a doctor merely for recommending the use of cannabis to a patient.⁵ But it remains illegal for a doctor to "aid and abet" a patient in obtaining cannabis.⁶ This means physicians and other medical professionals may discuss the pros and cons of medical cannabis with any patient, and recommend its use whenever appropriate. They may put that in writing or otherwise participate in state medical cannabis programs without fear of legal reprisal.⁷ This is true even when the recommending medical professional knows the patient will use the recommendation to obtain cannabis through a state program.⁸ What physicians may not do is prescribe or provide cannabis directly to a patient⁹ or say where or how to obtain it.¹⁰

Patients protected under state law, not federal. As of July 2015, 23 states and the District of Columbia provide legal protections for qualified individuals participating in their state medical cannabis program. However, all use of cannabis remains illegal under federal law, and in June 2005, the U.S. Supreme Court in *Gonzales v. Raich* ruled that state medical cannabis laws do not provide protections for patients and providers from federal pros-

ecution.¹¹ Under the Obama Administration, the Department of Justice has issued three memos providing guidance to federal prosecutors, each indicating that individual patients and caregivers should not be federal enforcement priorities. The latest memo indicates enforcement should be left to states so long as they have effective regulations in place for use and distribution. An analysis by ASA of existing state laws and local regulations found that all reflect the same general enforcement priorities as the 2013 federal guidelines.¹²

For assistance with determining how best to write or obtain a legal recommendation for cannabis, please contact ASA at 1-888-929-4367.

Medical Professionals Say Cannabis is Medicine

Thousands of studies published in peer-reviewed journals indicate cannabis has medical value in treating patients with such serious conditions as AIDS, glaucoma, cancer, epilepsy, and chronic pain, as well as a variety of such neu-

INSTITUTE OF MEDICINE

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

Marijuana and Medicine: Assessing the Science Base, 1999 rological disorders as multiple sclerosis, Parkinsonism, and ALS.

A 2013 poll conducted by the New England Journal of Medicine found that three out of four clinicians would recommend the use of medical cannabis for a hypothetical cancer patient.¹³ The use of medical cannabis has been endorsed by numerous professional organizations, including the American Academy of Family Physicians, the American Public Health Association, and the American Nurses Association. Its

use is supported by such leading medical publications as *The New England Journal of Medicine* and *The Lancet*. The International Cannabinoid Research Society was formally incorporated as a scientific research organization in 1991 with 50 members; as of 2014, there are nearly 500 around the world. The International Association for Cannabinoid Medicines (IACM), founded in 2000, publishes a bi-weekly bulletin and holds international symposia to highlight emerging research in cannabis therapeutics.

The safety and efficacy of cannabis has been attested to by numerous government studies and reports issued over the past 70 years. These include the 1944 LaGuardia Report, the Schafer Commission Report in 1972, a review commissioned by the British House of Lords in 1997, the Institutes of Medicine report of 1999, research sponsored by Health Canada, and numerous studies conducted in the Netherlands, where cannabis has been quasi-legal since 1976 and is currently available from pharmacies by prescription.

Scientific Research Advances

While modern research has until recently been sharply limited by federal prohibition, the last few decades have seen rapid change. More than 15,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of cannabis and cannabinoids have been published, as well as more than 2,000 articles on the body's natural cannabinoids and the receptors they attach to. 14 The discovery of the endocannabinoid system (ECS) opened a door to new understandings of how the body regulates internal systems and how the phytocannabinoids found in the cannabis plant interact with it. Endocannabinoids are crucial to bioregulation, and evidence suggests they play a role in inflammation, insulin sensitivity, and fat and energy metabolism, as well as chronic neurologic and immune conditions. The cannabinoid receptors CB1 and CB2 are identified targets for treating a remarkable variety of serious medical conditions. 15-18

A 2009 review of controlled clinical studies with medical cannabis conducted over a 38-year period found that "nearly all of the 33 published controlled clinical trials conducted in the United States have shown significant and measurable benefits in subjects receiving the treatment." The review's authors note that the more than 100 different cannabinoids in cannabis have the capacity for analgesia through neuromodulation in ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms. Research into the therapeutic potential of cannabis and cannabinoids has expanded considerably in the past decade. As of May 2014, the Center for Medicinal Cannabis Research, a state-funded \$8.7-million research effort at University of California campuses, had completed 13 approved studies. Of those, seven published double-blind, placebo-controlled studies examined pain relief, and each showed cannabis to be effective.²⁰

No adverse health effects related to medical cannabis use have been reported, even among the most seriously ill and immune-compromised patients. Research on CD4 immunity in AIDS patients found no negative effects to the immune systems of patients undergoing cannabis therapy in clinical trials.²¹ A complete health assessment in 2002 of four of the patients enrolled in the

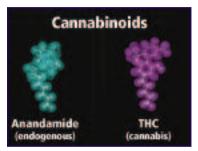


T cells

U.S. Investigational New Drug program who had used cannabis daily for between 11 and 27 years found cannabis to be clinically effective for each with no negative health consequences.²²

In the United Kingdom, GW Pharmaceuticals has been conducting clinical trials for more than a decade with its cannabis medicine, Sativex® Oromucosal Spray, a controlled-dose whole-plant extract. GW's Phase II and Phase III trials show positive results for the relief of neurological pain related to: multiple sclerosis (MS), spinal cord injury, peripheral nerve injury (including peripheral neuropathy secondary to diabetes mellitus or AIDS), central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident, and spina bifida. They have also shown cannabinoids to be effective in clinical tri-

als for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury.²³⁻²⁶



Sativex® was approved in Canada for symptomatic relief of neuropathic pain in 2005, in 2007 for patients with advanced cancer whose pain is not fully alleviated by opiates, and in 2010 for spasticity related to multiple sclerosis. As of 2014, Sativex has been made available or approved for named patient prescription use in 24 countries, including the UK, Spain, Italy and Germany.

In the US, GW was granted an import license for Sativex® by the DEA following meetings in 2005 with the FDA, DEA, the Office for National Drug Control Policy, and the National Institute for Drug Abuse. Sativex® is currently an investigational drug in FDA-approved clinical trials as an adjunctive analgesic treatment for patients with advanced cancer whose pain is not relieved by opioids. In 2013, GW Pharmaceuticals received FDA approval to test a highly purified cannabinoid extract (cannabidiol or CBD) named Epidiolex® on a limited number of US children with seizure disorders. As of January 2014, seven US pediatric epilepsy specialists have been approved to treat 125 children with Dravet syndrome, Lennox-Gastaut syndrome, and other pediatric epilepsy syndromes.

CANNABIS AND ARTHRITIS

More than 31 million Americans suffer from arthritis. There are two main types of arthritis: rheumatoid arthritis and osteoarthritis. Both affect the joints, causing pain and swelling, and limiting movement.

Rheumatoid arthritis (RA) is caused by a malfunction of the immune system. Instead of fighting off intruders such as bacteria or viruses, the body attacks the synovial membranes, which facilitate the movement of joints, eventually destroying cartilage and eroding bones. Rheumatoid arthritis is most common among the aged, whose immune systems are no longer as robust or efficient as they were when younger.

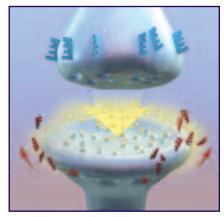
Osteoarthritis (OA), or arthritis of the bones, is also found primarily among the elderly, where cartilage has been worn away through many years of use. Arthritis may also manifest as chronic inflammation of the joints as the result of injuries. OA is the most common form of arthritis, affecting more than 10 million people worldwide. Currently, no drugs are available to treat or modify this disease, and treatment is primarily focused around the use of pain killers, which often have limited benefits and hazardous side effects.

An important aspect of arthritis pathology relates to maintaining healthy

bone. As people age, bones undergo extensive remodeling, which can lead to destruction or functional degradation of synovial joints. Drugs which can not only modulate pain from arthritis but also protect bones are of great importance. Cannabis and cannabinoids represent a promising treatment which can reduce arthritic pain and inflammation and positively modulate bone growth and maintenance. It has already been demonstrated that cannabinoids can effectively treat some types of arthritic pain, but recent evidence

suggests that the cannabinoids are also important for bone growth and maintenance throughout life.²⁷⁻³²

The importance of cannabinoids in bone health has been established in transgenic mice that are missing either the CB1 or CB2 receptor. These mice develop osteoporosis much more quickly than normal or wild mice. Research has recently shown that mice missing both cannabinoid receptors have extremely weak bones, a condition that underlies osteoporosis and osteoarthritis pathology.³³⁻³⁵



CB1 receptor

Based on genetic screening techniques, a correlation between cannabinoids and

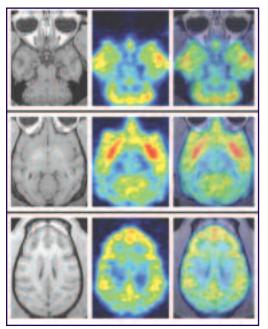
bone is emerging in humans as well. Three studies in three distinct ethnic groups have demonstrated that mutations in the type 2 cannabinoid receptor correlate to bone diseases. One study even showed that hand bone strength weakness is very well correlated with dysfunctional/mutant CB2 receptors.

Arthritis of any type can be an extremely painful and debilitating condition that presents challenges for pain management. The use of cannabis as a treatment for musclo-skeletal pain in western medicine dates to the 1700s. 36-37 Evidence from recent research suggests that cannabis-based therapies are effective in the treatment of arthritis and the other rheumatic and degenerative hip, joint and connective tissue disorders. Since these are frequently extremely painful conditions, the well-documented analgesic properties of cannabis make it useful in treating the pain associated with arthritis, both on its own and as an adjunct therapy that substantially enhances the efficacy of opioid painkillers.

Cannabis has also been shown to have powerful immune-modulation and anti-inflammatory properties,³⁸⁻⁴¹ suggesting that it could play a role not just in symptom management but treatment of arthritis. In fact, one of the earliest records of medical use of cannabis, a Chinese text dating from ca. 2000 BC, notes that cannabis "undoes rheumatism," suggesting its anti-inflammatory and immune modulating effects were known even then.²⁷

Modern research on cannabidiol (CBD), one of the non-psychoactive cannabinoid components of cannabis, has found that it suppresses the immune response in mice and rats that is responsible for a disease resembling arthritis, protecting them from severe damage to their joints and markedly improving their condition.⁴²⁻⁴⁴

Human studies have repeatedly shown cannabis to be an effective treatment for rheumatoid arthritis, and it is one of the enumerated conditions for which many states allow legal medical use. Cannabis has a demonstrated ability to



Cannabinoid receptors in the brain

improve mobility and reduce morning stiffness and inflammation. Research has also shown that patients are able to reduce their usage of potentially harmful Non-Steroidal Anti-Inflammatory drugs (NSAIDs) when using cannabis as an adjunct therapy. 45.46

Medical researchers at Hebrew University in Jerusalem found that when cannabidiol is metabolized, one result is the creation of a compound with potent anti-inflammatory action comparable to the drug indomethacin, but without the considerable gastrointestinal side effects associated with that drug.⁴⁷

In addition, when the body metabolizes tetrahydrocannabinol (THC), one of the primary cannabinoid components of

cannabis, it produces a number of related chemicals. At least one of these metabolites has anti-inflammatory and pain-relieving effects. By modifying this metabolite, researchers have produced a synthetic carboxylic acid known as CT-3 (also called dimethylheptyl-THC-11 oic acid or DMH-11C), which is more powerful than the natural metabolite itself, and thus can be given in smaller doses. Animal tests found CT-3 effective against both chronic and acute inflammation, and it also prevented destruction of joint tissue from chronic inflammation.

The remarkable 5,000-year safety record of cannabis—there has never been a recorded death from an overdose—and the fact that a metabolite with the desired anti-inflammatory effect is produced in the body when cannabis is used, indicates that the development of targeted, safe, and effective anti-inflammatory drugs in this class are possible.⁴⁸ CT3 has also demonstrated con-

siderable analgesic effects in animals. In some cases, the dose-dependent effect of THC was equivalent to morphine, but with a much greater duration of action and far less toxicity. 49,50

In contrast to the NSAIDs commonly prescribed arthritis sufferers, CT3 did not cause ulcers at therapeutically effective doses. Moreover, it does not depress respiration, produce dependence, induce body weight loss, or cause mutations, as many commonly prescribed drugs do. Studies on its mechanism of action are currently underway, with cytokine synthesis one of the pathways being studied.⁵¹

Cannabis may also help combat rheumatoid arthritis through its well-recognized immune-modulation properties.⁵² Rheumatoid arthritis is characterized by dysregulation of the immune system in response to an initial infection or trauma. Over-activity of the immune system's B-cells causes antibodies to attack and destroy the synovial tissues located in the joint.

The immuno-modulatory properties of a group of fats found in cannabis, known as sterols and sterolins, have been used as natural alternatives to con-

ventional rheumatoid arthritis treatments that employ highly toxic drugs to either suppress the entire immune response of the body or to palliate pain and the inflammatory process without correcting the underlying immune dysfunction.

Cytokines play a role in either fuelling or suppressing the inflammation that causes damage in rheumatoid arthritis and some other diseases. The release of select-

ed cytokines is impaired by cannabis, but the findings differ by cell type, experimental conditions, and especially the concentration of the cannabinoids examined.⁵³⁻⁵⁶ A sterol/sterolin combination has been experimentally demonstrated to reduce the secretion of the pro-inflammatory cytokines controlled by the TH2 helper cells and to increase the number of TH helper cells that regulate the secretion of antibodies from the B cells. This selective activation and inhibition of the immune system results is an effective control of the dysfunctional auto-immune response.

Similarly, ajulemic acid (another non-psychoactive cannabinoid) has been found to reduce joint tissue damage in rats with adjuvant arthritis.⁵⁷ Tests on human tissue done in vitro showed a 50% suppression of one of the body's chemicals (interleukin-1beta) central to the progression of inflammation and joint tissue injury in patients with rheumatoid arthritis.⁵⁸

Conventional Arthritis Medications

Over 100 medications are listed by the Arthritis Foundation website for use with arthritis or other related conditions, such as fibromyalgia, psoriasis,

osteoporosis and gout. These medicines include aspirin, ibuprofen and other oral and topical analgesics that dull pain. The most commonly used analgesic, **acetaminophen** (aspirin-free Anacin, Excedrin, Panadol, Tylenol) is usually not associated with side effects, though long-term use of acetaminophen is thought to be one of the common causes of end-stage renal disease.. To effectively control arthritis, **aspirin** must be taken in large, continuous doses (1000-5400 mg daily), which can cause stomach pain or damage; it is believed

FEDERATION OF AMERICAN SCIENTISTS

"Based on much evidence, from patients and doctors alike, on the superior effectiveness and safety of whole cannabis compared to other medications,... the President should instruct the NIH and the FDA to make efforts to enroll seriously ill patients whose physicians believe that whole cannabis would be helpful to their conditions in clinical trials"

FAS Petition on Medical Marijuana, 1994

to cause more than 1,000 deaths annually in the United States. For that reason, some doctors prescribe one of several chemical variations referred to as **nonacetylated salicylates**, such as CMT, Tricosal, and Trilisate, which can cause deafness or ringing in the ears in large doses.

Much stronger analgesics are also prescribed for arthritis, sometimes along with acetaminophen. These are: **codeine**

(Dolacet, Hydrocet, Lorcet, Lortab); morphine (Avinza, Oramorph); **oxycodone** (Vicodin, Oxycontin, Roxicodone); **propoxyphene** (Percocet, Darvon, Darvocet) and **tramadol** (Ultram, Ultracet). These medicines can cause psychological and physical dependence, as well as constipation, dizziness, lightheadedness, mood changes, nausea, sedation, shortness of breath and vomiting. Taking high doses or mixing with alcohol can slow down breathing, a potentially fatal condition.

Analgesics don't treat the inflammation that can cause severe arthritis pain. For inflammation, steroids, NSAIDs and newer COX-2 inhibitors are prescribed. **Corticosteroids** (Cortisone), **prednisone** and related medications can cause bruising, cataracts, elevated blood sugar, hypertension, increased appetite, indigestion, insomnia, mood swings, muscle weakness, nervousness or restlessness, osteoporosis, susceptibility to infection and thin skin.

Twenty NSAIDs are available with a doctor's prescription, with three of those also available over the counter. They are **diclofenac** (Arthrotec, Cataflam, Voltaren); **diflunisal** (Dolobid); **etodolac** (Lodine); **fenoprofen calcium** (Nalfon); **flurbiprofen** (Ansaid); **ibuprofen** (Advil, Motrin IB, Nuprin); **indomethacin** (Indocin); **ketoprofen** (Orudis); **meclofenamate sodium** (Meclomen); **mefenamic acid** (Ponstel); **meloxicam** (Mobic); **nabumetone** (Relafen); **naproxen** (Naprosyn, Naprelan); **naproxen sodium** (Anaprox, Aleve); **oxaprozin** (Daypro); **piroxicam** (Feldene); **sulindac** (Clinoril); and **olmetin sodium** (Tolectin).

Side effects of NSAIDs include abdominal or stomach cramps, edema (swelling of the feet), pain or discomfort, diarrhea, dizziness, drowsiness or lightheadedness, headache, heartburn or indigestion, nausea or vomiting, gastric ulcers, stomach irritation, bleeding, fluid retention, and decreased kidney function. This is because NSAIDs act on arthritis by inhibiting prostaglandins, which protect the stomach lining, promote clotting of the blood, regulate salt and fluid balance, and maintain blood flow to the kidneys. The gastrointestinal complications of NSAIDS are the most commonly reported serious adverse drug reaction, though NSAIDs are reported to cause more than 10,000 deaths and 100,000 hospitalizations annually.

The newer group of arthritis drugs is known as cyclo-oxygenase-2 inhibitors (COX-2), which include **Celebrex**, **Bextra** and **Vioxx**. These medications have the same side effects as NSAIDS, except they are less likely to cause bleeding stomach ulcers and increase susceptibility to bruising or bleeding.

Non-selective NSAIDS have been associated with an increased risk of congestive heart failure. Less is known or has been concluded about the cardiovascular effects of COX-2 inhibitors, though a retrospective analysis of the risk of hospital admission for heart failure done by the Institute for Clinical Evaluative Sciences in Toronto, Canada suggests some may have serious side effects. The study of 130,000 older patients found that those using Vioxx had an 80% increased risk of hospital admission for congestive heart failure. Those using non-selective NSAIDS had a 40% increased risk, and those using Celebrex had the same rate of heart failure as people who had never used NSAIDS.

Antipyretic and anti-inflammatory effects of NSAIDs can mask the signs and symptoms of infection. Their use can interfere with the pharmacologic control of hypertension and cardiac failure in patients who take beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, or diuretics. Long-term use may damage chondrocyte (cartilage) function.

About 60% of patients will respond to any single NSAID. Approximately 10% of rheumatoid arthritis patients will not respond to any NSAID. Biologic response modifiers such as **adalimumab** (Humira); **etanercept** (Enbrel); **infliximab** (Remicade), and **anakinra** (Kineret)) are prescribed to either inhibit or the supplement the immune system components called cytokines. Rare reports of lupus (with such symptoms as rash, fever and pleurisy) have been linked to treatment with adalimumab, etanercept and infliximab. Lupus symptoms resolve when the medication is stopped. Multiple sclerosis has rarely developed in patients receiving biologic response modifiers. Seizures have been reported with etanercept.

Cannabis: By comparison, the side effects associated with cannabis are typically mild and are classified as "low risk." Euphoric mood changes are among the most frequent side effects. Cannabinoids can exacerbate schizophrenic

psychosis in predisposed persons. Cannabinoids impede cognitive and psychomotor performance, resulting in temporary impairment. Chronic use can lead to the development of tolerance. Tachycardia and hypotension are frequently documented as adverse events in the cardiovascular system. A few cases of myocardial ischemia have been reported in young and previously healthy patients. Inhaling the smoke of cannabis cigarettes induces side effects on the respiratory system. Cannabinoids are contraindicated for patients with a history of cardiac ischemia. In summary, a low risk profile is evident from the literature available. Serious complications are very rare and are not usually reported during the use of cannabinoids for medical indications.

Is cannabis safe to recommend?

"The smoking of cannabis, even long term, is not harmful to health...." So began a 1995 editorial statement of Great Britain's leading medical journal, The Lancet. The long history of human use of cannabis also attests to its safety—nearly 5,000 years of documented use without a single death. In the same year as the Lancet editorial, Dr. Lester Grinspoon, a professor emeritus at Harvard Medical School who has published many influential books and articles on medical use of cannabis, had this to say in an article in the *Journal of the American Medical Association* (1995):

One of marihuana's greatest advantages as a medicine is its remarkable safety. It has little effect on major physiological functions. There is no known case of a lethal overdose; on the basis of animal models, the ratio of lethal to effective dose is estimated as 40,000 to 1. By comparison, the ratio is between 3 and 50 to 1 for secobarbital and between 4 and 10 to 1 for ethanol. Marihuana is also far less addictive and far less subject to abuse than many drugs now used as muscle relaxants, hypnotics, and analgesics. The chief legitimate concern is the effect of smoking on the lungs. Cannabis smoke carries even more tars and other particulate matter than tobacco smoke. But the amount smoked is much less, especially in medical use, and once marihuana is an openly recognized medicine, solutions may be found; ultimately a technology for the inhalation of cannabinoid vapors could be developed.

The technology Dr. Grinspoon imagined in 1995 now exists in the form of "vaporizers," (which are widely available through stores and by mail-order) and recent research attests to their efficacy and safety. ⁵⁹ Additionally, pharmaceutical companies have developed sublingual sprays and tablet forms of the drug. Patients and doctors have found other ways to avoid the potential problems associated with smoking, though long-term studies of even the heaviest users in Jamaica, Turkey and the U.S. have not found increased incidence of lung disease or other respiratory problems. A decade-long study of 65,000 Kaiser-Permanente patients comparing cancer rates among non-smokers, tobacco smokers, and cannabis smokers found that those who used only cannabis had a slightly lower risk of lung and other cancers as compared to

12 Americans for Safe Access

non-smokers.⁶⁰ Similarly, a study comparing 1,200 patients with lung, head and neck cancers to a matched group with no cancer found that even those cannabis smokers who had consumed in excess of 20,000 joints had no increased risk of cancer.⁶¹

As Dr. Grinspoon notes, "the greatest danger in medical use of marihuana is its illegality, which imposes much anxiety and expense on suffering peo-



Angel Raich using a vaporizer in the hospital

ple, forces them to bargain with illicit drug dealers, and exposes them to the threat of criminal prosecution." This was the conclusion reached by the House of Lords, which recommended rescheduling and decriminalization.

Cannabis or Marinol?

Those committed to the prohibition on cannabis frequently cite Marinol, a Schedule III drug, as the legal means to obtain the benefits of cannabis. However, Marinol, which is a synthetic form of THC, does not deliver the same therapeutic benefits as the natural herb, which contains at least another 100 cannabinoids in addition to THC. Recent research conducted by GW Pharmaceuticals in Great Britain has shown that Marinol is simply not as effective for pain management as the whole plant; a balance of cannabinoids, specifically CBC and CBD with THC, is what helps patients most. In fact, Marinol is not labeled for pain, only appetite stimulation and nausea control. But studies have found that many severely nauseated patients experience difficulty in getting and keeping a pill down, a problem avoided by use of inhaled cannabis.

Clinical research on Marinol vs. cannabis has been limited by federal restrictions, but a review of state clinical trials conducted in the 70's and 80's published in 2001 reports that "...the data reviewed here suggested that the inhalation of THC appears to be more effective than the oral route... Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used THC capsules experienced 76-88% relief."62 Additionally, patients frequently have difficulty getting the right dose with Marinol, while inhaled cannabis allows for easier titration and avoids the negative side effects many report with Marinol. As the U.K. House of Lords report states, "Some users of both find cannabis itself more effective."

THE EXPERIENCE OF PATIENTS

Dorothy Gibbs

In 1911, at the age of one, I contracted the polio virus.... The early onset of polio caused permanent damage in my legs, spine, and back, resulting in significant weakness and atrophy in my legs. As a result, I have never been able to walk without the assistance of crutches and braces or a wheelchair. Approximately 30 years ago, my condition began to deteriorate. I began to suffer from increasing levels of pain and weakness in my legs and back as well as severe osteoarthritis in my hands, arms, and joints. Over time, my deteriorating medical condition has been exacerbated by my pain, leaving me increasingly immobilized....

By May, 1996, my physician [Dr. Arnold Leff, M.D.] had tried various prescription medications to relieve my pain, including: Tylenol #3, Ultram, Daypro, Tegretol, Soma, Valium, steroid injections into the trigger point, Dilantin, Duragesic, Zofran and Comapazine for the nausea caused by the opioid pain relievers, and Doloboid and Lodine as nonsteroids. Nothing seemed to work, and the pain persisted. I was growing increasingly depressed by the inability of anything to relieve my pain....

During this period it was clear to me, my caretaker and my physician that nothing was working to combat my pain. My caretaker, Pat, had heard of the success some people experience with the medicinal use of marijuana for pain management. Sometime during the end of 1997, she obtained a sample for me. Although I had never used marijuana in my previous eighty-seven years of life, I was willing to try anything that could alleviate even part of the pain.

The relief I experienced from medical marijuana was almost immediate. I was so pleased with the result that I wrote to Dr. Leff about my use of medical marijuana and we talked about the benefits of the medicine. Dr. Leff examined me and noted that medical marijuana helped me experience less chronic pain and nausea, leading him to recommended medical marijuana as part of my daily pain care regimen....

Ever since trying medical marijuana, my life has drastically improved. Although chronic pain, related to my post-polio syndrome will always be a part of my life, medical marijuana had helped me manage this pain by providing fast and effective relief for my muscle spasms, acute pains, and arthritis

Since I began using medical marijuana, my pain is no longer persistent or debilitating. When I do suffer from pain, I am usually able to "get ahead of it" by using medical marijuana and make it manageable....

Margaret

I am a 45-year-old granny, and I smoke marijuana for medicinal reasons. I was 25 when I was diagnosed with rheumatoid arthritis. The doctor told me it was a painful, crippling disease and I would end up in a wheel chair. He gave me prescriptions for the arthritis and pain and sleeping pills.

Some of the pills had side effects and I would have to change to different

ones. My arthritis was getting worse and I was depressed all the time. I started taking anti-depressants. For years I abused codeine, anti-depressants and sleeping pills. I don't smoke tobacco or drink alcohol. My friends smoked marijuana but it didn't interest me to try it.

I smoked my first joint when I was 30. One night I was in a lot of pain and feeling terribly uncomfort-

AMERICAN NURSES ASSOCIATION

In 2003 the American Nurses Association passed a resolution that supports those health care providers who recommend medicinal use, recognizes "the right of patients to have safe access to therapeutic marijuana/cannabis," and calls for more research and education, as well as a rescheduling of marijuana for medical use.

able. My friend Ed was with me and said he had heard marijuana helps relieve pain. I was willing to try anything and had a few tokes. After a few minutes I was relaxed and the pain seemed to have dulled. I was also more limber with my joints. I had a very restful sleep that night. I have been smoking marijuana every day since then. I have also been happier and no longer need anti-depressants. I now control my pain with marijuana.

Alfred

I'm a 23-year-old male currently employed as an accounting assistant. This fall I began work on my Master's Degree. I am inflicted with Gout, a hereditary form of arthritis, which I have had for 6 years. When an attack arises the pain is in the main joint of my left foot and on the side of my big toe. When these attacks happen it is virtually impossible for me to walk.

I take Vicodin for the pain. I'm also given steroid shots for the pain in the doctor's office. In addition, I take Allopurinol, this helps my body to get rid of the uric acid build up which leads to the pain of Gout. The reason that I have uric acid build up is because my kidneys do not function properly and rid my body of the uric acid.

The main side effects of Vicodin and Allopurinol are drowsiness, which are very bad if you are a full time college student and also employed. But, I have to have some kind of pain medicine to be able to walk, I have learned that marijuana helps a great deal with the pain, and I have found that I am able to walk and also function much better on marijuana than Vicodin. Allopurinol

takes a terrible toll on my stomach. I would say 73% of the time I puke the medication up. I tried using marijuana in combination with the Allopurinol and I've found that this has helped drop the number of times that I throw the medication up. Now, I puke it up around 18% of the time, which is a big deal to me.

NEW ENGLAND JOURNAL OF MEDICINE

"A federal policy that prohibits physicians from alleviating suffering by prescribing marijuana to seriously ill patients is misguided, heavy-handed, and inhumane.... It is also hypocritical to forbid physicians to prescribe marijuana while permitting them to prescribe morphine and meperidine to relieve extreme dyspnea and pain...there is no risk of death from smoking marijuana.... To demand evidence of therapeutic efficacy is equally hypocritical"

Jerome P. Kassirer, MD, editor N Engl J Med 336:366-367, 1997

Matt Glandorf

I have arthritis in both hands and my chest, but here is the real kicker-- I am severely allergic to aspirin. I can't even take a Motrin without breaking out into a rash. I was born with a chest deformity called pectus excavatum (funnel chest and encaved chest are a couple other names for it.) I had corrective surgery in 1976 to try to make my rib cage bigger. In that surgery they break all the ribs and actually break the sternum in half, remove it, flip

it over, and put it back together after removing most of the cartilage and muscle. Now I have arthritis along with lung problems and asthma. I usually spend two to three weeks a year in the hospital with lung infections and make numerous visits to the doctor for chest pain.

Needless to say, I have eaten a lot of pain killers and tried nerve blocks and so on. All have had little success and make me so stoned that I can't even drive a car. So I started using pot and went from four Vicodin a day to one, and with watching my activities and a healthy diet I can go with no doctor's meds for weeks on end.

Bob Burrill

I am a Canadian medical marijuana advocate. Osteoarthritis of the cervical spine is my problem. I have constant severe pain from many large bone spurs, compressed discs, and so on. Many narcotic and other types of pain reduction prescriptions have been tried with limited success. I have self-medicated with marihuana for the past 7 or 8 months, under my doctor's care, with great success. My doctor and I have applied to the Canadian government to obtain a written ministerial exemption from prosecution so that I can cultivate and consume marijuana for a medical purpose.

Without medical marihuana, I have no life. I am restricted to bed or the

couch and stuck inside the house. It's about time governments and the public alike awakened to the fact that this is not "Cheech and Chong medicine" but one of the safest and user-friendly herbs on the planet. I only wish I had tried it a lot sooner. I can't say enough about the merits and benefits of medical marijuana

THE EXPERIENCE OF DOCTORS

Ethan Russo, M.D.

Patients have long told us that cannabis has been helpful to them in the treatment of their arthritic conditions. Science has now demonstrated that the THC component of cannabis is a very effective analgesic (pain killer), and that the CBD (cannabidiol) component has unique immunomodulatory benefits as an antagonist of tumor necrosis factor-alpha, supporting benefits in treatment of rheumatoid arthritis, as well as Crohn's disease and psoriasis. It appears that cannabis-based medicines will likely be an important component of arthritis treatment in the 21st century.

Ethan Russo, MD, is a board-certified child and adult neurologist in Missoula, MT, and researcher in migraine, ethnobotany, medicinal plants, cannabis and cannabinoids in pain management. Dr. Russo currently serves in a consultancy position as Senior Medical Advisor to the Cannabinoid Research Institute, the division of GW Pharmaceuticals established to promote exploratory research. He holds faculty positions as adjunct associate professor in the Department of Pharmaceutical Sciences of the University of Montana, and clinical associate professor in the Department of Medicine of the University of Washington. He has published numerous articles in scientific journals and is co-editor of Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. Dr. Russo is the founding editor of Journal of Cannabis Therapeutics.

Arnold S. Leff, M.D.

I currently treat at least 20 patients for whom I believe marijuana is medically appropriate in responding to treatment-induced nausea or for appetite stimulation. In my medical judgment, in some cases medical marijuana may be the only effective medicine.

Two of my patients, Hal Margolin and Dorothy Gibbs, have benefited tremendously from [medical cannabis]. Both suffer from chronic pain. Ms. Gibbs, who is 93 years old and who had not previously tried marijuana until joining WAMM, has found marijuana to be a highly effective analgesic for treating acute and chronic pain associated with post-polio syndrome and complications arising there from [including arthritis].

Ms. Gibbs turned to marijuana only after trying a wide range of conventional prescription pharmaceuticals and therapies prescribed by me, but to little or no avail. These treatments, including powerful and highly addictive opioid analgesics, either did not work, gradually lost their efficacy, or caused such debilitating side effects (particularly nausea and dizziness) that Ms. Gibbs found intolerable.

Ms. Gibbs is a good example of a patient who experiences episodic acute pain for which Marinol is too slow-acting and who, when stricken with acute pain, often requires the faster analgesic and antiemetic effects produced by smoked marijuana. I have been pleasantly surprised at the degree to which marijuana has afforded Ms. Gibbs relief from the agony that she suffered.

Dr. Leff has been an advisor on national drug control policy and public health to the administrations of Presidents Nixon, Ford and Carter. He has worked with the Department of Defense and State Department developing drug abuse programs in foreign countries and for U.S. military troops, and has consulted with local law enforcement officials on drug treatment. He served as Director of Health Services for Contra Costa County, California and has held teaching positions on the medical school faculties of the University of Cincinnati and the University of California.

Harvey L. Rose, M.D.

Both my research and my many years as a clinician have convinced me that marijuana can serve at least two important roles in safe and effective pain management. Ample anecdotal evidence and clinical observations, as well as significant research findings, strongly indicate that marijuana, for whatever reason, is often effective in relieving pain. This is true across a range of patient populations, including the elderly, the terminally ill seeking comfort in their final days, young adults stricken with life-threatening conditions, and cancer patients unable to tolerate the devastating effects of potentially life-saving therapies. Marijuana is also widely recognized as an antiemetic that reduces the nausea and vomiting often induced by powerful opioid analgesics prescribed for chronic, severe pain, as well as the nausea, vomiting and dizziness which often accompany severe and/or prolonged pain. I have had the benefit of consultations on this subject over many years with a range of treatment providers, including physicians, oncologists, pharmacologists, family practitioners, hospice workers, and pain specialists....

Specifically, I have found that cannabis can have an important opioid-sparing effect for pain patients. That is to say, that patients who are prescribed high doses of opioid analgesics can significantly reduce their reliance on these medications and improve their daily functioning by incorporating cannabis into their pain care regimen.

Marijuana not only has important analgesic properties but it also is an effec-

tive and important adjuvant therapy for patients suffering acute and/or chronic pain. No experienced and respected physician will deny that for such patients opioid therapy is central to palliative care. By the same token, the same experienced physicians will readily acknowledge that opioids often induce nausea and vomiting. For a number of pain patients, standard prescription antiemetics (e.g., Compazine, Zofran and Reglan) simply do not substantially reduce their nausea. For many, those medications are substantially less effective, or produce more debilitating side effects, than marijuana....

Quite simply, marijuana can serve much the same function for pain patients undergoing opiate therapy that it does for cancer patients undergoing chemotherapy: it suppresses the nausea and vomiting associated with treatment, and reduces the pain associated with prolonged nausea and retching, thereby increasing the chances that the patient will remain compliant with the primary treatment. With both chemotherapy and long-term pain management, failure to obtain and continue proper palliative and adjutant care can have dire, even fatal, consequences....

Finally, it is important to note that in my clinical experience observing patients who ingest cannabis for relief from pain and nausea and/or to stimulate appetite, I have witnessed no adverse complications. By contrast, many of the first-line pharmaceuticals used to combat cancer, HIV/AIDS, and pain associated with these and other illnesses can induce a variety of iatrogenic effects, including, in some instances, death. While patients may face serious legal implications related to their use of medical marijuana, as a physician I have yet to encounter a medical downside to their cannabinoid therapy....

[A]gainst the backdrop of a growing body of scientific research, the reports of myriad pain patients, and the burgeoning clinical experience of physicians like myself, it is my considered opinion that cannabis can constitute an acceptable and sometimes necessary medicine to alleviate the immediate suffering of certain patients.

Dr. Rose served as a medical officer in the Air Force before entering private practice. During his 40-year career, he has taught at UC Davis School of Medicine and consulted with state legislative bodies.

THE HISTORY OF CANNABIS AS MEDICINE

While the federal government has resisted restoring cannabis to its place in the US Pharmacopeia, its own research studies acknowledge that the "use of cannabis for purposes of healing predates recorded history" and that it was included in "the 15th century BC Chinese Pharmacopeia, the Rh-Ya." Ancient Egypt, India and Persia all made medical use of it more than 2,000 years ago. British herbalists in the 17th century noted its medicinal properties, but it did not become widely

used in British medicine until the mid-nineteenth century. In 1890, Queen Victoria's personal physician, Sir Russell Reynolds, wrote in the first issue of *The Lancet*, "When pure and administered carefully, [it is] one of the most valuable medicines we possess." ⁶³

William O'Shaughnessy, a British East Indian Company surgeon who studied its use while posted in India, expanded western understanding of its range of applications and championed its use upon his return to Britain in 1841 and election to the Royal Society, the scientific advisory body to the British government. Between 1840 and 1900, European and American medical journals published more than 100 articles on the therapeutic applications of cannabis, known then as Cannabis Indica or Indian hemp. Common indications for its use in the nineteenth century included "muscle spasms, menstrual cramps, rheumatism, and the convulsions of tetanus, rabies and epilepsy; it was also used to promote uterine contractions in childbirth, and as a sedative to induce sleep."

The American Medical Association in an article on the first federal law restricting legal access to cannabis noted that "No evidence has been produced to show the existence of addiction to cannabis arising out of the medicinal use of the drug." The AMA's lobbyist, Dr. William C. Woodward, testified to Congress that "The American Medical Association knows of no evidence that marihuana is a dangerous drug," and that any prohibition "loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis."

The first state medical cannabis law was passed in 1996 by California voter initiative. Since then, 23 states, the District of Columbia, and the US Territory of Guam have removed criminal penalties for their citizens who use cannabis on the advice of a physician and established legal means of obtaining it. Ten of those states plus the District of Columbia established their medical cannabis laws through voter ballot initiative, while the legislatures in 13 others have enacted similar bills. Limited bills that allow only the use of specific cannabis extracts for highly restricted conditions have been passed by the legislatures in 15 other states. Currently, nearly 50 percent of the U.S. population resides in a state with a medical cannabis program, and legislation is introduced in more states each year.

Federal Policy is Contradictory

Federal policy on medical cannabis is filled with contradictions. Cannabis was widely prescribed until the turn of the century, and an estimated one million Americans currently use it under medical supervision. Congress in 1970 classified cannabis is a Schedule I drug, defined as having no medic-

inal value and a high potential for abuse, yet its most psychoactive component, THC, is legally available as Marinol and is classified as Schedule III. The U.S. federal government also grows and provides free cannabis for a small number of patients today as part of an Investigational New Drug (IND) compassionate access research program created by court order in 1976. Though the program provided up to nine pounds of cannabis a year

to these patients, and all reported being substantially helped by it, the application process was extremely complicated, and few physicians became involved. In the first twelve years, the government accepted only a handful of patients. But in 1989 the FDA was deluged

AMERICAN ACADEMY OF FAMILY PHYSICIANS

"The American Academy of Family Physicians [supports] the use of marijuana ... under medical supervision and control for specific medical indications."

1996-1997 AAFP Reference Manual

with new applications from people living with AIDS, and 34 patients were approved within a year. In June 1991, the Public Health Service announced that the program would be suspended because it undercut the administration's opposition to the use of illegal drugs. The program was discontinued in March 1992 and the remaining patients had to sue the federal government on the basis of medical necessity to retain access to their medicine. Today, four surviving patients still receive medical cannabis from the federal government.

Despite this successful federal program, thousands of scientific articles, and dozens of successful clinical trials, as well as an unparalleled safety record, cannabis remains classified as a Schedule I substance. Healthcare advocates have tried to resolve this contradiction through legal and administrative channels. In 1972, a petition was submitted to reschedule cannabis in order to remove barriers to medical research and patient access. The DEA stalled hearings for 16 years, but after exhaustive hearings in 1988 their chief administrative law judge, Francis L. Young, ruled that "marijuana, in its natural form, is one of the safest therapeutically active substances known... It would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance." The DEA refused to implement this ruling based on a procedural technicality and continues to insist cannabis is a substance with no medical use. In 2009 the American Medical Association, the nation's largest organization for physicians with a guarter million members, joined the chorus of professional medical groups calling on the federal government to reconsider the classification of cannabis and urging comprehensive clinical trials.

Widespread support, state laws passed, new policy issued

Public opinion is strongly in favor of ending the prohibition of medical cannabis and has been for some time, with every national poll conducted over the past two decades showing a substantial majority in support. A CBS News national poll in January 2014 found that 86 percent of Americans think doctors should be allowed to prescribe cannabis for patients suffering from serious illnesses. In 2004, the 35 million-member American Association of Retired Persons (AARP) released a national poll of older Americans showing 72 percent of seniors agreed that "adults should be allowed to legally use marijuana for medical purposes if a physician recommends it." Every national poll for more than a decade has found similar super-majorities of support.

The refusal of the federal government to act on this widespread public support has meant that advocates have had to turn to the states for action. Currently, laws that effectively remove state-level criminal penalties for growing and/or possessing medical cannabis are in place in: Alaska, Arizona, California, Colorado, Connecticut, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Vermont, Washington, the District of Columbia, and Guam. Another 15 states have established limited laws that allow the legal medical use of a cannabis plant extract. Thirty-six states have symbolic medical cannabis laws (laws that support access to medical cannabis but do not provide patients with legal protection under state law).

On August 29, 2013, the U.S. Department of Justice issued new guidance to federal prosecutors, telling them medical cannabis dispensaries should no longer automatically be considered targets for prosecution. The memo from Deputy Attorney General James M. Cole to all U.S. Attorneys reverses previous federal policy on prosecuting medical cannabis providers and businesses. The new guidance says state and local officials can avoid federal interference in their medical cannabis programs if they "implement strong and effective regulatory and enforcement systems" that reflect eight federal enforcement priorities. The memo does not change federal law, nor does it preclude prosecution of any individual or business, as the U.S. Attorneys' offices are autonomous, and federal prosecutors make independent decisions about which cases to pursue.

22 Americans for Safe Access

PROFESSIONAL ORGANIZATION ENDORSEMENTS

AIDS Action Council

Alaska Nurses Association

American Academy of Family Physicians American Medical Student Association

American Nurses Association

American Preventive Medical Association

American Public Health Association

American Society of Addiction Medicine

Arthritis Research Campaign (UK)

Australian Medical Association

Australian National Task Force on Cannabis

Belgian Ministry of Health

British House of Lords Select Committee

British Medical Association

California Academy of Family Physicians

California Nurses Association

California Pharmacists Association

Colorado Nurses Association

Federation of American Scientists
Florida Governor's Red Ribbon Panel on AIDS

Florida Medical Association

French Ministry of Health Hawaii Nurses Association

Health Canada

Kaiser Permanente

Lymphoma Foundation of America Mississippi Nurses Association

Multiple Sclerosis Society (Canada)

National Acad. of Sciences Inst. of Medicine National Association for Public Health Policy

National Nurses Society on Addictions

Netherlands Ministry of Health

New Jersey State Nurses Association

New Mexico Medical Society

New Mexico Nurses Association

New York State Nurses Association
North Carolina Nurses Association

San Francisco Mayor's Summit on AIDS

San Francisco Medical Society Virginia Nurses Association

Whitman-Walker Clinic

Wisconsin Nurses Association

Legal Citations

- See "The Administration's Response to the Passage of California Proposition 215 and Arizona Proposition 200" (Dec. 30, 1996). https://www.ncjrs.gov/txtfiles/215rel.txt
- 2. See Conant v. McCaffrey, 172 F.R.D. 681 (N.D. Cal. 1997).
- See id.; Conant v. McCaffrey, 2000 WL 1281174 (N.D. Cal. 2000); Conant v. Walters, 309 F.3d 629 (9th Cir. 2002).
- 4. 309 F.3d 629 (9th Cir. 2002).
- 5. Id. at 634-36.
- 6. Criminal liability for aiding and abetting requires proof that the defendant "in some sort associate[d] himself with the venture, that he participate[d] in it as something that he wishe[d] to bring about, that he [sought] by his action to make it succeed. "Conant v. McCaffrey, 172 F.R.D. 681, 700 (N.D. Cal. 1997) (quotation omitted). A conspiracy to obtain cannabis requires an agreement between two or more persons to do this, with both persons knowing this illegal objective and intending to help accomplish it. Id. at 700-01.
- 7. 309 F.3d at 634 & 636.
- 8. Conant v. McCaffrey, 2000 WL 1281174, at *16 (N.D. Cal. 2000).
- 9. 309 F.3d at 634.
- 10. See id.. at 635; Conant v. McCaffrey, 172 F.R.D. 681, 700-01 (N.D. Cal. 1997).
- 11. Gonzales v. Raich, 545 U.S. 1 (2005) 352 F.3d 1222.
- 12. Third Time the Charm? State Laws on Medical Cannabis Distribution and Department of Justice Guidance on Enforcement. Americans for Safe Access. November 25, 2013. http://americansfor-safeacess.org/dojwhitepaper.

Research Citations

- Adler JN, Colbert JA. Medicinal Use of Marijuana Polling Results. N Engl J Med 2013; 368:e30. May 30, 2013. DOI: 10.1056/NEJMcIde1305159
- Hanus LO. Pharmacological and therapeutic secrets of plant and brain (endo)cannabinoids. Med Res Rev. 2009 Mar;29(2):213-71. doi: 10.1002/med.20135.

- Grant I, Rael Cahn B. Cannabis and endocannabinoid modulators: Therapeutic promises and challenges, Clinical Neuroscience Research, Volume 5, Issues 2-4, November 2005, Pages 185-199.
- Alexandros Makriyannis, Raphael Mechoulam and Daniele Piomelli, Therapeutic opportunities through modulation of the endocannabinoid system, Neuropharmacology, Volume 48, Issue 8, June 2005, Pages 1068-1071.
- Cecilia J. Hillard and Abbas Jarrahian, Accumulation of anandamide: Evidence for cellular diversity, Neuropharmacology, Volume 48, Issue 8, June 2005, Pages 1072-1078.
- Pacher, P., & Kunos, G. (2013). Modulating the endocannabinoid system in human health and disease–successes and failures. FEBS Journal.
- Aggrawal S et al. 2009. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. J Opioid Manag. May-Jun;5(3):153-68.
- Grant I, Atkinson JH, Gouaux B, Wilsey B. (2012). Medical Marijuana: Clearing Away the Smoke. The Open Neurology Journal. 2012 May 4, 6:18-25. DOI: 10.2174/1874205X01206010018.
- Abrams DI et al (2003). Short-Term Effects of Cannabinoids in Patients with HIV-1 Infection: A Randomized, Placebo-Controlled Clinical Trial. Ann Intern Med. Aug 19;139(4):258-66.5.
- 22 Russo EB, Mathre ML, et al. (2002). 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(1).
- 23. Russo EB. (2008) Cannabinoids in the management of difficult to treat pain. Therap and Clincial Risk Manag 4(1) 245-259.
- 24. Barnes MP (2006). Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother, 7:607-15.
- Perez J (2006) Combined cannabinoid therapy via an oral mucosal spray. Drugs Today (Barc.), 42:495-501.
- Selvarajah D et al (2010). Randomized placebo-controlled double-blind clinical trial of cannabisbased medicinal product (Sativex) in painful diabetic neuropathy. Diabetes Care. 33(1):128-30.
- 27. Bab I and Zimmer A (2008). Cannabinoid receptors and the regulation of bone mass. Br J Pharmacol 153(2):182-188.
- 28. Buckley NE, et al (2000) .Immunomodulation by cannabinoids is absent in mice deficient for the cannabinoid CB(2) receptor. Eur J Pharmacol 396(2-3):141-149.
- Idris AI, et al (2009). Cannabinoid receptor type 1 protects against age-related osteoporosis by regulating osteoblast and adipocyte differentiation in marrow stromal cells. Cell Metab 10(2):139-147.
- 30. Ofek O, et al (2006). Peripheral cannabinoid receptor, CB2, regulates bone mass. Proc Natl Acad Sci U S A 103(3):696-701.
- Tam J, et al (2006). Involvement of neuronal cannabinoid receptor CB1 in regulation of bone mass and bone remodeling. Mol Pharmacol 70(3):786-792.
- 32. Tam J, et al (2008). The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. Faseb J 22(1):285-294.
- 33. Huang QY, et al (2009). Multiple osteoporosis susceptibility genes on chromosome 1p36 in Chinese. Bone 44(5):984-988.
- 34. Karsak M, et al (2005). Cannabinoid receptor type 2 gene is associated with human osteoporosis. Hum Mol Genet 14(22):3389-3396.
- 35. Karsak M, et al (2009). The cannabinoid receptor type 2 (CNR2) gene is associated with hand bone strength phenotypes in an ethnically homogeneous family sample. Hum Genet.
- Russo EB (2002). Role of cannabis and cannabinoids in pain management. In: Weiner RS, editor. Pain management: A practical guide for clinicians. 6th ed. Boca Raton, FL: CRC Press. p. 357-375.
- 37. Marcandier M (1764). Treatise on hemp. London: T. Becket and P.A. de Hondt.
- 38. Formukong E et al (1988). Analgesic and Antiinflammatory Activity of Constituents of Cannabis Sativa L. Inflammation 12: 361.
- 39. Barret ML et al (1985). Isolation from Cannabis sativa L. of Cannflavon a novel inhibitor of prostaglandin production. Biochem. Pharmacol. 34: 2019
- 40. Burstein SH et al (1989). Antagonism to the actions of platelet activating factor by a nonpsychoactive cannabinoid. J Pharmacol. Exp. Therap. 251: 531-5
- 41. Sofia RD (1989). Antiedemic and analgesic properties of delta-9-THC compared with three other drugs. Eur. J. Pharamacol. 41: 705-9
- 42. Zurier RB et al (1998). Dimethylheptyl-THC-11 Oic Acid: A Nonpsychoactive Antiinflammatory Agent with a Cannabinoid Template Structure. ARTHRITIS AND RHEUMATISM January; volume 41, number 1, pages 163-170.
- 43. Costa B et al (2004). Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. Naunyn Schmiedebergs Arch Pharmacol. Mar;369(3):294-9. Epub 2004 Feb 12.

- 44. Malfait AM et al (2000) .The nonpsychoactive cannabis constituent cannabidiol is an oral antiarthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. Aug 15 97(17):9561-6.
- 45. James JS (1998). Marijuana, inflammation, and CT-3 (DMH-11C): cannabis leads to new class of antiinflammatory drugs. AIDS Treat News. Jan 23;(No 287):1, 5.
- Straus SE (2000). Immunoactive cannabinoids: Therapeutic prospects for marijuana constituents. Proc Natl Acad Sci U S A. Aug 15 97(17):9563.
- 47. Shohami E (2001). Nature. Oct 4;413(6855):527-31.
- 48. Burstein SH (2000). Ajulemic acid (CT3): a potent analog of the acid metabolites of THC. Curr Pharm Des. Sep 6(13):1339-45.
- 49. Burstein SH et al (2004). Ajulemic acid: A novel cannabinoid produces analgesia without a "high". Life Sci. Aug 6;75(12):1513-22.
- 50. Devane WAet al1(1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science.258:1946-1949.
- 51. Barg J et al (1995). Cannabinomimetic behavioral effects of andadenylate cyclase inhibition by two new endogenous anandamides. Eur J Pharmacol.;287:145-152.
- 52. Klein TW et al (1998). Cannabinoid receptors and immunity. Immunol Today. 797:225-233.
- 53. Daaka Y et al (1996). Cannabinoid receptor proteins are increased in jurkat, human T-cell line after mitogen activation. J Pharmacol Exp Ther. 276:776-783.
- Kaminski NE (1996); Immune regulation by cannabinoid compounds through the inhibition of the cyclic AMP signaling cascade and altered gene expression. Biochem Pharmacol; 52(8):1133-40.
- Di Marzo V (1998). 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. Biochimica et Biophysica Acta.1392(2-3):153-75.
- 56. Smith PB et al (1994). The pharmacological activity of anandamide, a putative endogenous cannabinoid in mice. J Pharmacol Exp Ther. 270:219-227.
- 57. Burstein SH (2000). Ajulemic acid (CT3): a potent analog of the acid metabolites of THC. Curr Pharm Des. Sep;6(13):1339-45.
- Zurier RB et al (2003). Suppression of human monocyte interleukin-1beta production by ajulemic acid, a nonpsychoactive cannabinoid. Biochem Pharmacol. Feb 15;65(4):649-55.
- Hazekamp A et al (2006). Evaluation of a vaporizing device (Volcano(R)) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci 95 (6) Apr 24: 1308-1317.
- 60. Sidney S et al (1997). Marijuana Use and Cancer Incidence. Cancer Causes and Control; 8: 722-728.
- Tashkin D (2006). Marijuana Use and Lung Cancer: Results of a Case-Control Study. American Thoracic Society International Conference. May 23, 2006.
- 62. Musty R, Rossi R (2001). Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. Journal of Cannabis Therapeutics. 1: 29-56.
- 63. Lancet 1; 1823.
- United States Assumes Control of Cannabis. JAMA. 1937;109(13):31B-38B. doi:10.1001/jama.1937.02780390177058

DEA CHIEF ADMINISTRATIVE LAW JUDGE

Marijuana, in its natural form, is one of the safest therapeutically active substances known... It would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance.

> The Honorable Francis L. Young, Ruling on DEA rescheduling hearings, 1988

ADDITIONAL RESOURCES

Americans for Safe Access maintains a website with additional resources for doctors and patients. There you will find the latest information on legal and legislative developments, new medical research, and what you can do to help protect the rights of patients and doctors.

With more than 45,000 active members and chapters and affiliates in all 50 states, ASA is the largest national member-based organization of patients, medical professionals, scientists, and concerned citizens promoting safe and legal access to cannabis for therapeutic uses and research.



Advancing Legal Medical Marijuana Therapeutics and Research

888-929-4367 www.AmericansForSafeAccess.org 1806 Vernon Street NW, Washington, D.C. 20009