



VETERANS
AND
MEDICAL
CANNABIS



AmericansFor
SafeAccess

Advancing Legal Medical Marijuana Therapeutics and Research

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:

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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.

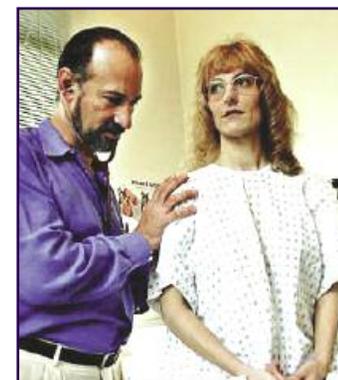
Many of its therapeutic uses are well known and documented, and medical researchers are learning more each day. Cannabis and its constituent components show potential to fight tumors, autoimmune disorders, and serious neurological conditions for which treatment options are limited. As of July 2014, 23 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 brochure 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 qualifying 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 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.^{2,3}



Angel Raich & Dr. Frank Lucido

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 2014, 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 prosecution.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 neurological 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.

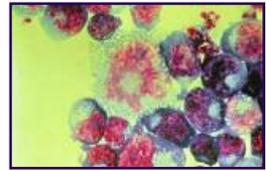
The safety and efficacy of cannabis has been attested to by numerous government studies and reports issued over the past 70 years. These include the 1944 LaGuardia Report, the Schafer Commission Report in 1972, a review commissioned by the British House of Lords in 1997, the Institutes of Medicine report 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.”¹⁹ 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



T4 Immune Cells

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 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 trials 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 fol-

lowing 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 VETERANS CONDITIONS

As of May 2013, there were more than 23 million total living veterans of military service in the US. Of those, almost 17 million served in wars. That includes more than 1.7 million veterans of WWII, 2.2 million veterans of the Korean War, 7.4 million veterans of the Vietnam War, 2.3 million veterans from the Gulf War (1990-1991), and more than 1.3 million who served in Afghanistan or Iraq or both.

Veterans of military service have a disproportionately high rate of certain debilitating medical conditions as compared to the general population. Some of those conditions may result from injury or exposures to toxins, but not all. The correlation between military service and higher rates of the conditions discussed in this booklet are clear and well-documented, but the cause is not known for many.

That has created some barriers to treatment, as the Veterans Health Administration (VHA) has at times resisted classifying conditions affecting veterans as being the result of their military service. Soldiers exposed to radiation during their participation in weapons trials in the 1950's and 1960's, for instance, were sworn to secrecy. Those exposed to Agent Orange in Vietnam had to wait decades for the VHA to acknowledge the cancers and other conditions they suffered were the result of their service. It was more than 20 years before scientists identified the changes in the brains of many of those who returned from the Gulf War with a collection of neurological symptoms.

The VHA has also resisted making all recommended treatments available to veterans. Cannabis has been found to help many patients suffering from conditions that can afflict veterans as a result of their service, including chronic pain, cancer, ALS, traumatic brain injury, post-traumatic stress disorders, and phantom limb pain. State medical cannabis programs making therapeutic use legal with a doctor's recommendation were in place for almost 15 years before the VA changed its policy to allow veterans who use medical cannabis to receive all VA health services. In January, 2011, Robert A. Petzel M.D., the Under Secretary for Health, issued VHA Directive 2011-004, which states that "patients participating in State marijuana programs must not be denied VHA services."

CANNABIS AND CHRONIC PAIN

Veterans can experience persistent and disabling pain as the result of numerous and sometimes multiple causes. Among them are injuries to the back, neck and spinal cord; cancer; arthritis and other rheumatic and degenerative hip, joint and connective tissue disorders; and severe burns.

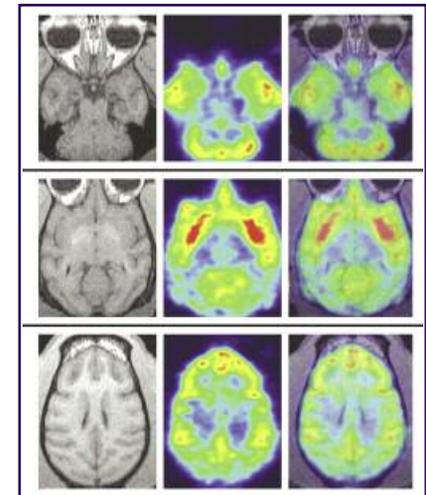
The Congressional Research Service reports that as of February 2013, the number of US military service members wounded in combat in Afghanistan and Iraq totaled 50,450. Combat wounds that can result in chronic pain include spinal and traumatic brain injuries. Between 2000 and 2012, there were more than 48,000 reported cases of moderate to severe brain injuries among active military service members.²⁷

Pain is not a primary condition or injury, but rather a severe, frequently intolerable symptom that varies in frequency, duration, and severity according to the individual. The underlying condition determines the appropriate curative approach, but does not determine the proper symptom management. It is the character, severity, location and duration of the pain that determines the range of appropriate therapies.

Chronic pain is a widespread public health issue. Epidemiological statistics are alarming: In Europe, it is estimated that one in four adults has a chronic pain condition. In the US, it is estimated that at least 38 million adults suffer from chronic pain, and at least 12 million have used cannabis as a treatment.²⁸

For veterans in pain, the goal is to function as fully as possible by reducing their pain as much as possible, while minimizing the often debilitating side effects of the pain therapies. Failure to adequately treat severe and/or chronic pain can have tragic consequences. Not infrequently, people in unrelieved pain want to die. Despair can also cause patients to discontinue potentially life-saving procedures (e.g., chemotherapy or surgery), which themselves cause severe suffering. In such dire cases, anything that helps to alleviate the pain will prolong and improve these veterans' lives.

Cannabis can serve at least two important roles in safe, effective pain management. It can provide relief from the pain itself (either alone or in combination with other analgesics), and it can control the nausea associated with taking opioid drugs, as well as the nausea, vomiting and dizziness that often



Cannabinoid receptors in the brain

accompany severe, prolonged pain. In addition, cannabis significantly enhances the effectiveness of opioid therapies.

Opioid therapy is often an effective treatment for severe pain, but all opiates have the potential to induce nausea. The intensity and duration of this nausea can cause discomfort and additional suffering that can lead to malnourishment, anorexia, wasting, and a severe decline in a patient's health. Some people find the nausea so intolerable that they are inclined to discontinue the primary pain treatment, rather than endure the nausea.

Inhaled cannabis provides almost immediate relief for nausea with significantly fewer adverse side effects than orally ingested Marinol. Inhalation allows the active compounds in cannabis to be absorbed into the blood stream with greater speed and efficiency. It is for this reason that inhalation is an increasingly common, and often preferable, route of administration for many medications. Cannabis may also be more effective than Marinol because it contains many more cannabinoids than just the THC that is Marinol's active ingredient. The additional cannabinoids may well have additional and complementary antiemetic qualities. They have been conclusively shown to have better pain-control properties when taken in combination than THC alone, and mitigate anxiety and other side-effects of THC.

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"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**

Research on cannabis and pain management

Cannabis has been used as an analgesic for at least 5,000 years,²⁹⁻³¹ and patients often report significant pain relief from cannabis, even in cases where conventional pain therapies have failed.³²⁻³⁷ Research has even shown that the natural endocannabinoid system has a role in regulating migraines.³⁸⁻⁴⁰

After reviewing a series of trials in 1997, the U.S. Society for Neuroscience concluded that "substances similar to or derived from marijuana could benefit the more than 97 million Americans who experience some form of pain each year."⁴¹ A 1999 study commissioned by the White House and conducted by the Institute of Medicine also recognized the role that cannabis can play in treating chronic pain: "After nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medicinal use for marijuana."⁴² Between 1975 and 2009, there were more than 300 studies showing that cannabinoids and cannabis can help patients experiencing chronic

pain.⁴³

Orthopedic injuries including loss of limbs can result in chronic pain that is very difficult to treat. Military operations just in Iraq and Afghanistan have resulted in 1,715 amputations as of December 2012.⁴⁴ Amputations commonly result in phantom limb pain, a serious neuropathic pain condition affecting 50-80 percent of amputees, sometimes for many years. Phantom limb pain may occur during the first year after amputation and often remains chronic over months or years, either with no improvement or an increase in pain.⁴⁵⁻⁵⁸

Among U.S. veterans with current significant phantom limb pain, 27 percent had pain for more than 20 days per month, 10 percent for 11 to 20 days, 14 percent for 6 to 10 days, and 49 percent for 5 days or less per month.⁵⁹ Phantom limb pain is often poorly understood and difficult to manage. Current treatments include physical, behavioral, and medical approaches, including opioids and adjunct medications.⁶⁰

A 1984 survey of 5,000 US veterans with amputations related to military service found that 78 percent had current phantom limb pain and only 1 percent had experienced relief from any treatment.⁶¹ A small study of 48 British veterans with phantom limb pain found that 56 percent reported no relief from any pain medications.⁶² That difficulty in relieving pain is common to other types of chronic neuropathic pain, such as may result from cancer, HIV/AIDS, or diabetes.

Cannabinoids may provide relief; some of the most encouraging clinical data on effects of cannabinoids on chronic pain are from studies of neuropathic pain.⁶³⁻⁶⁸ The effectiveness of cannabis and cannabinoids in relieving neuropathic pain has been demonstrated in more than three dozen preclinical and clinical trials.⁶⁹ It is often effective when opioid painkillers have failed to provide relief.⁷⁰ A trial of smoked cannabis to treat HIV-associated daily neuropathic pain in 50 patients showed an average reduction of pain by 30 percent over a treatment course of only five days.⁷¹ Cannabis can be effective for neuropathic pain even at low doses.⁷² Multiple trials indicate that a whole-plant cannabis extract (Sativex®) is effective in reducing pain in patients suffering intractable neuropathic pain.^{72,73} A review of over 20 clinical trials on cannabis and cannabinoids found that whole plant cannabis and extracts are superior to oral THC for the treatment of pain. Health Canada approved Sativex® for prescription in the treatment of HIV-associated neuropathic pain in 2005 and cancer pain in 2007. The mechanism for that analgesic action involves both the body's cannabinoid receptors and direct action on the neurons that transmit pain.⁷⁴⁻⁷⁵

The activity of the more than 100 cannabinoids and other components on the plant may explain its superiority in reducing pain when comparing whole plant cannabis and extracts to THC alone. For instance, the cannabinoids cannabidiol (CBD) and cannabichromene (CBC), the second and third most

common active compounds on the plant, exhibit anti-inflammatory and analgesic actions, although weaker than THC. Similarly, beta-sitosterol, a non-cannabinoid ingredient found in cannabis, was able to decrease inflammation and edema in skin treatment.⁷⁶ And a unique flavanoid found only in cannabis, cannafavin A, inhibits the inflammatory molecule PGE-2, thirty times more potently than aspirin.⁷⁷ Lastly beta-caryophyllene, a cannabinoid found in many plants besides cannabis, has strong anti-inflammatory properties but no noticeable side effects.⁷⁸ Beta-caryophyllen is the most commonly consumed FDA-approved cannabinoid in food.

The IOM report found that “basic biology indicates a role for cannabinoids in pain and control of movement, which is consistent with a possible therapeutic role in these areas. The evidence is relatively strong for the treatment of pain and intriguingly, although less well established, for movement disorder.” According to the IOM Report and numerous independent research articles, a number of areas in the brain that have an established role in sensing and processing pain respond to the analgesic effect of cannabis, adding that cannabinoids have been used successfully to treat cancer pain, which is often resistant to treatment with opiates. The effectiveness of cannabinoids in treating intractable cancer pain has been demonstrated in several subsequent clinical trials of a dosage-controlled sublingual spray.



Several studies have found that cannabinoids have analgesic effects in animal models, sometimes equivalent to codeine.⁷⁹⁻⁸³ Cannabinoids also seem to synergize with opioids, which often lose their effectiveness as patients build up tolerance. One study found morphine was 15 times more active in rats with the addition of a small dose of THC. Codeine was enhanced on the order of 900 fold.⁸⁴ In 1990, researchers conducted a double-blind study comparing the antispasmodic and analgesic effects of THC, oral Codeine, and a placebo on a single patient suffering from a spinal cord injury.⁸⁵ Their findings confirmed the analgesic effects of THC being “equivalent to codeine.” A 1997 study made similar findings related to morphine.⁸⁶

A 1999 article reviewing the body of scientific animal research concerning the analgesic effects of marijuana concludes that “[t]here is now unequivocal evidence that cannabinoids are antinociceptive [capable of blocking the appreciation or transmission of pain] in animal models of acute pain.”⁸⁷

The report further notes that multiple cannabinoids and noncannabinoid components can serve as anti-inflammatory agents, and so have potential in preventing and reducing pain caused by swelling (such as arthritis).

In short, the research community recognizes the potential benefits of

cannabis for certain patients, including:

- Chemotherapy patients, especially those being treated for mucositis, nausea, and anorexia.
- Postoperative pain patients (using cannabinoids as an opioid adjunct to reduce the nausea and vomiting).
- Patients with spinal cord injury, peripheral neuropathic pain, or central post-stroke pain.
- Patients with chronic pain and insomnia.
- AIDS patients with cachexia, AIDS neuropathy, or any significant pain.

Britain's House of Lords reached similar conclusions and called for making cannabis available by prescription.⁸⁸

VETERANS AND CANCER

Veterans have higher rates of some cancers than the general population. The Armed Forces Health Surveillance Center reported in 2010 that, in the previous ten years, service members had higher rates of melanoma, brain, non-Hodgkin lymphoma, breast, prostate and testicular cancers than civilians. The Medical Surveillance Monthly Report in 2008 also found service members have higher rates of prostate and breast cancers. In some cases, those higher cancer rates are linked to exposures to chemicals, toxins, or radiation, in other cases the reasons have not yet been identified.⁸⁹

Cancer rates vary by branch of service, gender and race, as well as dates and location of active duty. A 2009 study at Walter Reed Army Medical Center comparing reported cancer cases between 1990 and 2004 in the military and general population found higher incidence rates of prostate and breast cancers in the active duty military. Female soldiers have breast cancer rates 20-40 percent higher than other women.⁹⁰

Researchers speculate chemical exposures may be a contributing factor in these breast cancer cases. Though the disease is extremely rare in men, dozens of male soldiers at Camp Lejeune have also developed breast cancers, possibly linked to a water supply that was contaminated with industrial solvents, benzene, and other chemicals from 1957 to at least 1987. Service members and their families stationed at Camp Lejeune in that time period also have unusually high rates of several other cancers, including esophageal, lung, bladder, multiple myeloma, scleroderma, non-Hodgkin's lymphoma, leukemia, and other serious medical conditions.⁹¹

Exposures to chemicals or other toxins may also explain why thyroid cancer rates are significantly higher in the military than in the general population among white women, black women, and black men, according to a 2011 study of reported cases from 1990-2004 in individuals 20 to 49 years of age. As with other cancers, the study found the higher incidence rate of thyroid cancer varied by branch of service.⁹²

Nuclear radiation has been a cancer factor for hundreds of thousands of vet-

erans. Approximately 200,000 in Japan during the occupation in WWII were exposed to residual radiation from the use of atomic bombs at Hiroshima and Nagasaki. Another 200,000 were exposed during nuclear weapons testing between 1945 and 1962. Those who served the Gulf War and Operation Iraqi Freedom may have been exposed to depleted uranium. Among the types of cancer radiation can cause are thyroid, bone, breast, brain, colon, esophagus, lung, stomach, and pancreas as well as many others.⁹³

Many veterans who served in Vietnam were also exposed to chemicals linked to cancer, in particular Agent Orange, an herbicide used extensively to destroy jungle foliage, that was frequently contaminated with dioxin, a dangerous toxin linked to increased risk of cancers, Type 2 diabetes, and Parkinson's disease. The cancers linked to Agent Orange exposure include soft-tissue sarcoma, Hodgkin's disease, Non-Hodgkin's lymphoma, multiple myeloma, chronic lymphocytic leukemia, and cancers of the prostate, lung, larynx, trachea and bronchus. For some cancers, the rates are dramatically higher for veterans exposed to Agent Orange. A 2008 study found they are more than twice as likely to have prostate cancer as the general population.⁹⁴

A 2013 study of more than 2,700 veterans similarly found significantly higher rates of the deadliest, most-aggressive forms of prostate cancer. Researchers reported the overall risk of high-grade prostate cancer detection by biopsy is 52 percent higher in veterans exposed to Agent Orange, and the likelihood of finding the most aggressive form is 75 percent higher.⁹⁵

CANNABIS AND CANCER

Cannabis has been found to help cancer patients with the symptoms that usually accompany cancer such as pain, nausea, wasting, and loss of appetite.⁹⁶ Notably, in a meta-analysis of 30 clinical studies on the therapeutic use of cannabis for chemotherapy-induced nausea and vomiting, Delta9-THC (dronabinol, AKA marinol) proved superior to modern anti-emetics.⁹⁷ Additionally, patients showed a clear preference for cannabinoids as anti-emetic medication over conventional drugs, when receiving chemotherapy.

Only one clinical trial has ever been published on the effects of Delta9-THC on cancer growth in humans.⁹⁸ Doctors administered oral Delta 9-THC to nine patients who experienced tumor progression despite surgical therapy and radiation treatments. The major finding of the study was that Delta 9-THC was safe and did not cause any obvious psychoactive effects in a clinical setting. Furthermore, extensive pre-clinical research clearly indicates that cannabinoids can have tumor-reducing and anti-cancer properties.⁹⁹

Research on cannabis and chemotherapy

One of the most widely studied therapeutic applications for cannabis and the pharmaceutical drugs derived from cannabinoids is in the treatment of nausea and vomiting associated with cancer chemotherapy. Numerous clinical and preclinical studies conducted over nearly three decades have consistently reported that the use of cannabis reduces pain, nausea, vomiting, and stimu-

lates appetite, thereby reducing the severity of cachexia, or wasting syndrome, in patients receiving chemotherapy treatment.¹⁰⁰⁻¹⁰⁸

The 1999 Institutes of Medicine report noted that for "patients already experiencing severe nausea or vomiting, pills are generally ineffective, because of the difficulty in swallowing or keeping a pill down, and slow onset of the drug effect. Thus an inhalation (but, preferably not smoking) cannabinoid drug delivery system would be advantageous for treating chemotherapy-induced nausea." For certain individuals unresponsive to conventional anti-emetic drugs, the use of smoked or vaporized cannabis can provide relief more effectively than oral THC (Marinol) which may be difficult to swallow or be vomited before taking effect. The IOM report concluded, "nausea, appetite loss, pain and anxiety ... all can be mitigated by marijuana."¹⁰⁹

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**Marijuana and Medicine:
Assessing the Science Base, 1999**

A 1997 inquiry by the British Medical Association found cannabis more effective than Marinol, and a 1998 review by the House of Lords Science & Technology Select Committee concluded that "Cannabinoids are undoubtedly effective as anti-emetic agents in vomiting induced by anti-cancer drugs. Some users of both find cannabis itself more effective."^{110, 111}

In 2009, a clinical trial involving 177 patients, with intractable cancer pain and experienced inadequate relief from opiates, showed remarkable reductions in pain scores from using a cannabis extract which contained THC and CBD. This THC:CBD extract was more effective than an extract containing only THC.¹¹²

The effects of cannabis may also provide an improvement in mood. In addition to THC, other cannabinoids on the plant such as CBD, can inhibit the side effects of THC, as well provide relief from anxiety and depression. By contrast, several conventional medications commonly prescribed for cancer patients, e.g. phenothiazines such as haloperidol (known as "major tranquilizers") may produce unwanted side effects such as excessive sedation, flattening of mood, and/or distressing physical "extrapyramidal" symptoms such as uncontrolled or compulsive movements.

Anti-cancer potential of cannabis and cannabinoids

Recent scientific advances in the study of cannabinoid receptors and endocannabinoids have produced exciting new leads in the search for anti-cancer treatments. Several hundred research articles have been published on the effects of cannabinoids on cancer cells.¹¹³⁻¹³⁸ We now know cannabinoids stop

many kinds of cancers from growing and spreading, including brain, breast, leukemic, melanoma, pheochromocytoma, liver, and other kinds of cancer. Cannabinoids have been repeatedly shown in animal and other studies to promote apoptosis (programmed cell death of the tumor cells) and halt angiogenesis (blood vessel production to the tumor) in many types of human cancers.¹³⁹⁻¹⁴³ In one study, injections of synthetic THC eradicated malignant brain tumors in one-third of treated rats, and prolonged life in another third by as much as six weeks.¹⁴⁴

Scientists have established that the anti-cancer properties of cannabinoids are mediated through cannabinoid receptors. CB1 and CB2 cannabinoid receptors are abundantly expressed throughout the human body, making them an excellent target for disease treatment. Research on the complex interactions of endogenous cannabinoids and receptors is leading to greater scientific understanding of the basic mechanisms by which cancers develop. Research studies on pituitary cancers suggest that cannabinoids may be the key to regulating human pituitary hormone secretion that affects tumor development.¹⁴⁵⁻¹⁴⁸

The mechanism of the anti-cancer activity of cannabinoids has been repeatedly demonstrated with breast cancers, with numerous studies showing that cannabinoids are effective in fighting breast cancer tumors and metastization.¹⁴⁹⁻¹⁵³

Recent research has found that the non-psychoactive cannabinoid cannabidiol (CBD) inhibits the invasion of both human cervical cancer and human lung cancer cells. By manipulating cannabidiol's up-regulation of a tissue inhibitor, researchers may have revealed the mechanism of CBD's tumor-fighting effect. A further in vivo study demonstrated "a significant inhibition" of lung cancer metastasis in mice treated with CBD.¹⁵⁴⁻¹⁵⁶

In 2009, scientists reported on the anti-tumor effects of the cannabinoid THC on cholangiocarcinoma cells, an often-fatal type of cancer that attacks the liver's bile ducts. They found that "THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis." At low levels, THC reduced the migration and invasion of cancer cells, while at high concentrations, THC triggered cell-death in tumors. In short, THC reduced the activity and number of cancer cells.¹⁵⁷

Laboratory research on the effects on cancer tumors of the non-psychoactive cannabinoid cannabidiol (CBD) has found that it inhibits human glioma and glioblastoma multiforme cells, the most common and aggressive forms of brain cancer, in part by cutting off blood supply to tumors. Research on cannabinoids and gliomas, a type of aggressive brain cancer for which there is no cure, holds promise for future treatments. A study that examined both animal and human glioblastoma multiforme (GBM) tumors, the most common and aggressive form of brain cancer, describes how cannabinoids controlled glioma growth by regulating the blood vessels that supply the tumors.¹⁵⁸ In another study, researchers demonstrated that the administra-

tion of the non-psychoactive cannabinoid cannabidiol (CBD) significantly inhibited the growth of subcutaneously implanted U87 human glioma cells in mice. The authors of the study noted that "... CBD was able to produce a significant antitumor activity both in vitro and in vivo, thus suggesting a possible application of CBD as an antineoplastic agent.¹⁵⁹ The targeted effects of cannabinoids on GBM were further demonstrated in 2005 by researchers who showed that the cannabinoid THC both selectively inhibited the proliferation of malignant cells and induced them to die off, while leaving healthy cells unaffected.¹⁶⁰ While CBD and THC have each been demonstrated to have tumor-fighting properties, research published in 2010 shows that CBD enhances the inhibitory effects of THC on GBM cell proliferation and survival.¹⁶¹



Similarly, researchers reported in 2010 that the way cannabinoid and cannabinoid-like receptors in brain cells "regulate these cells' differentiation, functions and viability" suggests cannabinoids and other drugs that target cannabinoid receptors can "manage neuroinflammation and eradicate malignant astrocytomas," a type of glial cancer.¹⁶² This research confirms the findings of multiple studies which have indicated the effectiveness of cannabinoids in fighting gliomas.¹⁶³⁻¹⁷⁰

Indications of the remarkable potential of cannabinoids to fight cancer in humans have also been seen in three large-scale population studies done recently. The studies were designed to find correlations between smoking cannabis and cancers of the lung, throat, head and neck. Instead, the researchers discovered that the cancer rates of cannabis smokers were at worst no greater than those who smoked nothing at all or even better.¹⁷¹ One study found that 10-20 years of cannabis use significantly reduced the incidence of head, neck and throat cancers.¹⁷² Researchers suggest that cannabinoids may produce a prophylactic effect against cancer development, as seen in the anti-proliferation effect that has been demonstrated in vitro and in vivo.

While clinical research on using cannabis medicinally has been severely limited by federal restrictions, the accumulated data speaks strongly in favour of considering it as an option for most cancer patients, and many oncologists do. A random-sample anonymous survey conducted by researchers at Harvard Medical School in 1990, years before any states had approved medical use, found that 44 percent of oncologists had recommended cannabis to at least some of their patients, and more said they would do so if the laws were changed. Of the oncologists expressing an opinion in 1990, a majority (54 percent) thought cannabis should be available by prescription.¹⁷³

According to the American Cancer Society's data, 1,665,540 Americans will be diagnosed with cancer in 2014.¹⁷⁴ At least 400,000 of them will undergo chemotherapy, meaning as many as 200,000 patients annually may have

cannabis recommended to them to help fight the side effects of conventional treatments.

The authors of the 1999 Institute of Medicine report *Marijuana and Medicine: Assessing the Science Base* acknowledged that there are certain cancer patients for whom cannabis would be a valid medical option. Current research on cannabinoids has shown that activation of both cannabinoid receptors has a well-established anti-proliferative effect on cancer cells and may also have anti-angiogenic, anti-adhesive, anti-invasive, and anti-metastatic properties. Since cannabinoids are generally well tolerated, and patients do not develop the toxic side effects associated with conventional treatments, more studies are warranted to develop a cannabis-based cancer treatment.

VETERANS AND NEUROLOGICAL DISORDERS

Veterans disproportionately develop neurological conditions such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and Parkinsonism for a variety of reasons, ranging from chemical exposures to Traumatic Brain Injury (TBI). From 2000 through the third quarter of 2013, the Department of Defense reports 287,861 diagnosed cases of TBI among active service members. Of those, more than 48,000 are classified as moderate to severe, and more than 10,000 were reported as not classifiable.¹⁷⁵ Even a mild or moderate TBI greatly increases the risk of several neurological disorders, including seizures and neurodegenerative disorders such as Alzheimer's and Parkinsonism.^{176,177}

The risk for Alzheimer's in veterans who suffered a moderate TBI is more than 2.3 times higher, and more than 4.5 times higher for those with a severe TBI. The link between TBI and Parkinsonism has not been studied as extensively but is still well established as a linked condition that may not be seen for between six and 40 years.

Seizures are a common effect of most TBI, regardless of severity, with the risk increasing to as much as 95 times the general population. Post-traumatic epilepsy (PTE), in which seizures recur more than a week after the TBI, is less predictable than the initial seizures, but an increased risk remains for years after the initial injury.¹⁷⁸ PTE is likely to create more serious problems than other forms of epilepsy, with veterans who develop PTE more likely to have shortened lives and cognitive and motor problems.¹⁷⁹ PTE is commonly difficult to treat with conventional drug therapy, with cessation of seizures achieved in only 35 percent of those treated.^{180,181}

Traumatic Brain Injury (TBI) can also result in neurological disorders. A high prevalence of epilepsy and other neurological disorders in US veterans who served in Afghanistan and Iraq were reported at the American Epilepsy Society's 67th Annual Meeting in December, 2013. The researchers found veterans are at a particularly high risk for psychological non-epileptic seizures (PNES) and epileptic seizure. Researchers at Duke found that 87,377 veterans

with seizures diagnoses are currently in the VHA system, with higher incidences among veterans under the age of 46. Researchers at Baylor College of Medicine found a correlation between psychogenic non-epileptic seizures (PNES) among Afghanistan and Iraq veterans who had PTSD or TBI diagnoses or both. Researchers who reviewed records for veterans diagnosed with PNES treated at the Portland, Oregon VAMC EMU from 2000-2011 found the majority continued to report seizures, even after three years of follow up, and only 21 percent were seizure free.

Cannabis may provide a superior alternative to other seizure medications, as clinical experience and more than 30 years of scientific research on how cannabinoids such as CBD and THC can reduce seizure activity have shown that it may work when other alternatives have failed. In addition to reports from patients and their families, the most recent studies in animal models found that CBD significantly reduced the percentage of those experiencing severe seizures and significantly reduced the mortality rate.¹⁸²⁻¹⁸⁵

Many people with seizure disorders treat their conditions with cannabis, and in late 2012 GW Pharmaceuticals received FDA approval to test a highly purified CBD extract named Epidiolex® on a limited number of US children with seizure disorders. So far, seven US pediatric epilepsy specialists have been approved to treat 125 children with Dravet syndrome, Lennox-Gastaut syndrome, and other pediatric epilepsy syndromes.¹⁸⁶

Many veterans develop neurological disorders related to chemical exposures. Veterans who served in Vietnam may have been exposed to Agent Orange or other herbicides that can produce neurological disorders. Those who served in the Gulf War may have been exposed to nerve agents or other neurotoxic chemicals. A federal review in 1994 of research studies on the possible link between parkinsonism and chemicals used as herbicides and pesticides in Vietnam concluded that parkinsonian syndromes have been associated with both chronic and acute exposures to herbicides and pesticides.¹⁸⁷ Veterans with Parkinson's disease who were exposed to Agent Orange or other herbicides during military service may be eligible for disability compensation and health care.

More than 200,000 veterans who served in the Persian Gulf during Operations Desert Shield and Desert Storm in 1990-1991 developed health problems that eventually became known as Gulf War illness. Research indicates that damage

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 the central nervous system is related to chronic symptoms of Gulf War Illness. While many symptoms of possible neurological disorders have been reported—including cognitive impairment, autonomic dysfunction, debilitating fatigue, and chronic widespread pain—no consensus on the diagnosis of the illness or its cause has been reached, though research published in 2013 describes changes to brain structure that explain many symptoms.

Brain imaging of Gulf War veterans found evidence that two types of changes in their brain structure correlate to a heightened sensitivity to pain, increased feelings of fatigue, and difficulties regulating heart rate and blood pressure, as well as memory problems – all symptoms of Gulf War Illness. Two other studies out of Georgetown also found evidence of neurological damage in Gulf War veterans, including abnormalities in the nerve cells in the brain that register fatigue and pain.^{188,189}

A 2006 review of 22 studies of neurological function in Gulf War veterans also found that their incidence of amyotrophic lateral sclerosis (ALS) is significantly higher than among those who did not serve in that theater.¹⁹⁰

CANNABIS AND NEUROLOGICAL DISORDERS

Neurodegenerative diseases and movement disorders, which are sometimes interlinked, are among the many conditions that cannabis and cannabinoids may be particularly well suited to treat. Cannabinoids can protect the brain and central nervous system from the damage that leads to various neurological disorders. More than 100 research articles have been published on how cannabinoids act as neuroprotective agents to slow the progression of neurodegenerative diseases that disproportionately affect veterans. Researchers have also established that cannabinoids can alleviate the damage caused by strokes, as well as traumatic brain injury, spinal cord injury, and multiple sclerosis. No other medication offers the combination of anti-oxidative, anti-inflammatory and neuroprotective qualities of cannabis and cannabinoids.¹⁹¹⁻¹⁹³

The therapeutic use of cannabis for treating neurological disorders has been known to western medicine for nearly two centuries. In 1839, Dr. William B. O'Shaughnessy wrote about cannabis that doctors had "gained an anti-convulsive remedy of the greatest value."¹⁹⁴ In 1890 Dr. J. Russell Reynolds, physician to Queen Victoria, noted in an article in *The Lancet* that for "organic disease of a gross character in the nervous centers . . . India hemp (cannabis) is the most useful agent with which I am acquainted."¹⁹⁵

Extensive modern studies in both animals and humans have shown that cannabis can treat many movement disorders affecting people with neurological disorders because cannabinoids inhibit neurodegeneration and have antispasticity, analgesic, antitremor, and antiataxia properties.¹⁹⁶⁻²¹⁴

Research published in 2013 shows the active chemicals in cannabis are uniquely suited to fighting neurodegenerative diseases that can result from trauma, such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS).²¹⁵⁻²¹⁷

The neuroprotective effects of cannabis, based on the combination of anti-inflammatory and anti-oxidant properties of the primary cannabinoids THC and CBD, is undergoing intense preclinical research for treating numerous neurodegenerative disorders.²¹⁸ Recent research has revealed that chemicals similar to those in cannabis can also reduce the effects of serious brain injury and keep badly head-injured people alive.²¹⁹

Neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases all share a number of common mechanisms: inflammation and over-stimulation of neurons and problems with supplying energy and oxygen to them. A 2012 review of experimental studies on the body's cannabinoid system concluded that it operates on both cellular and molecular levels to protect neurons. Cannabinoids have antioxidant and anti-inflammatory effects that suppress the neuroinflammatory processes that contribute to neurodegenerative diseases as well as the progression of brain aging. Cannabinoids play a protective role in regulating the mitochondrial activity that maintains the supply of energy and oxygen to brain cells, modulating molecular clearance processes to protect neurons, and regulating the production of new brain cells.²²⁰

In many neurodegenerative disorders, the body's natural cannabinoid system has recently been found to be altered. That's why much new research is devoted to determining how to manipulate the endogenous cannabinoid system with plant or synthetic cannabinoids to neurodegenerative disorders.^{221,222}

Research has repeatedly demonstrated that plant cannabinoids exert the same neuroprotective effects as the body's natural endocannabinoids. Recent studies of both animal models and human cell cultures of Parkinson's disease have shown that the plant cannabinoids THC and CBD directly fight the disease and, in the case of the animal model, relieves its symptoms.²²³⁻²²⁵

Huntington's disease is another neurodegenerative disorder for which there are currently limited treatment options but strong evidence for the benefits of cannabis-based medicine. Experimental studies of an animal model of Huntington's disease found the progression of the disease was slowed by treatment with the plant cannabinoids THC and CBD. Both CB1 and CB2 receptors were shown to be involved in the protective, disease-fighting effects, something also indicated by a separate study that showed blocking the CB1 receptor in mice worsened the disease.²²⁶⁻²²⁸ Researchers concluded that "cannabis-based medicine" is "capable of delaying disease progression."

Brain injuries can also be mitigated by cannabinoids. The neuroprotective effects of cannabinoids such as CBD have also been shown in four separate studies published in 2013 to help fight the effects of several types of brain injury.²²⁹⁻²³² In one recent animal study of several types of brain injury, even a single very low dose of THC—three to four times less than create a noticeable behavioral effect—created a significant protective effect that lasted at least seven weeks.²³³

Multiple sclerosis, once thought to be primarily an autoimmune disorder, is now understood to be neurodegenerative.^{234, 235} In a federal court brief filed in support of physicians' right to recommend cannabis, the American Public Health Association notes that "a survey of British and American MS patients reports that after ingesting marijuana a significant majority experienced substantial improvements in controlling muscle spasticity and pain. An extensive neurological study found that herbal cannabis provided relief from both muscle spasms and ataxia (loss of coordination), a multiple benefit not achieved by any currently available medications."²³⁶ Cannabinoids have also been shown to have powerful neuroprotective effects.^{237, 238}

The endogenous cannabinoid system in the human body appears to be intricately involved in regulating normal physiology, including the control of movement. Central cannabinoid receptors are densely located in the basal ganglia, the area of the brain that regulates body movement, and appear to play a role in the manipulation of transmitter systems—increasing transmission of certain chemicals, inhibiting the release of others, and affecting how they are absorbed.²³⁹⁻²⁴⁴

Because they operate as modulators, endocannabinoids have paradoxical effects on the nervous system: sometimes they block neuronal excitability and other times they augment it. As scientists are developing a better understanding of the physiological role of the endocannabinoids, it is becoming clear that problems with the production or processing of these chemicals may be involved in the pathology of several neurological diseases.

Parkinson's disease has been linked to dysfunction in the body's dopamine system, specifically the production of too much of the neurotransmitter glutamate and oxidative damage to dopaminergic neurons. Studies have found a tight association between cannabinoids and dopamine, and recent research has produced anatomical, biochemical, and pharmacological evidence supporting a role for the endogenous cannabinoid system in the modulation of dopaminergic transmission.²⁴⁵

Oxidative stress in the brain is a major hallmark of motor and neurological diseases such as Parkinson's and Alzheimer's disease. Cannabinoids are able to protect neurons from oxidative damage.²⁴⁶ The neuroprotective action of cannabinoids appears to result from their ability to inhibit reactive oxygen species, glutamate, and tumour necrosis factor. THC, CBD, and synthetic AM404 all contain phenolic groups in their chemical structure and are thus able to reduce radical oxygen species. Notably CBD has extraordinary antioxidant properties and can effect calcium homeostasis, both of which lead to positive effects against a wide range of neurodegenerative diseases.²⁴⁷

Few clinical trials have looked at cannabinoids and Parkinson's disease. However, research has shown that 25 percent of Parkinson's patients smoke cannabis, and 46 percent of these patients report improvement of side effects from long-term levodopa treatment.²⁴⁸ A randomized placebo controlled study using extracts of cannabis produced significant improvements in

patients' cognition. The authors note that they did not see improvements in pain or sleep disorders. They speculate that the oral route (versus inhaled) of cannabis ingestion leads to too much variability of cannabinoids in blood.²⁴⁹

Many diseases of the brain involve changes in inflammatory responses that lead to disease progression. Inflammation in the brain is mediated by microglial cells and treatments which target these cells can protect neurons from damage that leads to degeneration. Multiple Sclerosis, Parkinson's and Alzheimer's disease are neuro-degenerative conditions for which cannabis and cannabinoid therapies show promise, both for treating the symptoms and the underlying disease by targeting microglial cells through cannabinoid receptors.²⁵⁰

Oxidative stress in the brain is a major hallmark of neurological disorders such as Parkinson's and Alzheimer's disease. Cannabinoids have well-established antioxidant properties that protect neurons from oxidative damage. Alzheimer's disease, characterized in part by a decrease in the production of new neurons, is associated with oxidative stress due to the membrane action of beta-amyloid peptide aggregates. A laboratory study published in 2004 indicates that one of the cannabis plant's primary components, cannabidiol (CBD), exerts a combination of neuroprotective, anti-oxidative and anti-apoptotic effects by inhibiting the release of the toxic beta-amyloid peptide.²⁵¹

Recent studies suggest that endocannabinoids may control the growth and maturation of new neurons through the CB1 receptor.²⁵² Therefore, cannabinoids could reduce inflammation and protect brains in neurodegenerative conditions. The neuroprotective action of cannabinoids appears to result from their ability to inhibit reactive oxygen species, glutamate, and tumour necrosis factor. THC, CBD, and synthetic AM404 all contain phenolic groups in their chemical structure that can reduce oxidative stress on brain cells. Notably, CBD has extraordinary antioxidant properties and can affect calcium homeostasis, both of which lead to positive effects against a wide range of neurodegenerative diseases.

Cannabinoids represent an emerging therapeutic option for neurological disorders and neurodegenerative diseases. Targeted cannabinoid therapies are still in an early phase of development, but research suggests that they can be useful drugs for the treatment of many diseases.

This new research on cannabinoids and neurodegenerative diseases, coupled with the extensive work done on other neuroprotective and neurogenic qualities of cannabis and its components, indicates that cannabis may become the source of the most effective treatments for battling the neurological disorders that afflict millions of veterans.

CANNABIS AND MULTIPLE SCLEROSIS

An estimated 350,000 people in the United States are living with multiple sclerosis (MS), a debilitating and sometimes fatal disorder of the central nervous

system. Because physicians are not required to report new cases, and because symptoms can go undetected for some time, the prevalence and incidence rate of MS can only be estimated. Nonetheless, MS is the most common debilitating neurological disease of young people, typically appearing between the ages of 20 and 40, affecting approximately twice as many women as men. Veterans appear to be significantly more likely to develop MS than the general population.

Members of the US military who served in the Gulf War era have one of the highest incidence rates of MS ever found (between 9.6 per 100,000 per year), according to a 2012 study of all military medical records from the time period. Researchers discovered that those who served in the Air Force and Army have double the rate of those who served in the Marines, and women in all services have more than triple the rate of their male counterparts.²⁵³

Another 2012 study of US military medical records from 2000-2009 found an even higher incidence rate of MS among service members of 12.9 per 100,000 person-years, the highest disease rate ever reported for MS. Researchers note that the increase incidence of MS among military personnel have manifested over the past two to three generations, speculating that "there may be unique environmental exposures within the military that increase ones risk for multiple sclerosis above that of the general population."²⁵⁴

MS is a disease of the central nervous system (CNS) that manifests due to the immune system attacking the myelin of neurons and dendrites. As the disease progresses, normal neurotransmission is inhibited and such additional symptoms develop as: pain, spasms, spasticity, limb tremor, fatigue, and incontinence. All of the disease symptoms have a large negative impact on the quality of life of MS patients. MS most frequently presents at onset as a relapsing and remitting disorder, where symptoms come and go.

MS exacerbations appear to be caused by abnormal immune activity that causes inflammation and the destruction of myelin (the protective covering of nerve fibers) in the brain or spinal cord. After repeated attack from the immune system, nerves lose plasticity, which creates stress in nerve tissue. This stress leaves nerve tissue vulnerable to progressive damage and death.

Current treatment of MS is primarily symptomatic, focusing on such problems as spasticity, pain, fatigue, bladder problems and depression. Although symptom-specific treatments exist, these are often associated with adverse side effects. This has prompted many people who suffer from MS to seek alternative therapies. Cannabinoids, the active ingredients in cannabis, have demonstrated the ability to control aspects of MS disease progression.

Anecdotal reports on the self medication of cannabis to treat the symptoms of MS are supported by recent advances in the understanding of the biology of cannabis and the cannabinoid receptors.²⁵⁵⁻²⁵⁷ Controlled studies have

found that cannabis and cannabinoids can help manage such symptoms as pain, spasms, spasticity, and incontinence.

The leading effects of prolonged neurodegeneration in MS cause permanent disabilities. This neurodegeneration has yet to be effectively treated. Initial neurodegeneration occurs with inflammation, cannabis and cannabinoids have been shown to have neuroprotective effects during immune attacks on the CNS.²⁵⁸⁻²⁶²

Surveys and Clinical Research on Cannabis Use for MS

Numerous case studies, surveys and double-blind studies have reported improvement in patients treated with cannabinoids for symptoms including spasticity, chronic pain, tremor, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance (ataxia), and memory loss.²⁶³⁻²⁷⁵

A 1998 House of Lords report concludes, "We have seen enough evidence to convince us that a doctor might legitimately want to prescribe cannabis to relieve ... the symptoms of multiple sclerosis and that the criminal law ought not to stand in the way." Many of those who testified for that report shared the British Medical Association's view that "[a] high priority should be given to carefully controlled trials of cannabinoids in patients with chronic spastic disorders." The British Medical Association has requested that the synthetic cannabinoids Nabilone and Dronabinol be officially licensed for use in MS and other spastic disorders.

A survey of MS patients in the UK found that 43 percent of respondents used cannabis therapeutically. Among them, nearly three quarters said that cannabis mitigated their spasms, and more than half said it alleviated their pain. A survey published in August 2003 in the *Canadian Journal of Neurological Sciences* reported that 96 percent of Canadian MS patients believe that cannabis is therapeutically useful for treating the disease. Of those who admitted using cannabis medicinally, the majority found it to be beneficial, particularly in the treatment of chronic pain, spasticity, and depression.²⁷⁶ The accompanying editorial states, "This is an exciting time for cannabinoid research. There is a growing amount of data to suggest that cannabis (marijuana) can alleviate symptoms like muscle spasticity and pain in patients with MS."²⁷⁷

The published results of a number of GW Pharmaceuticals Phase III studies show that pain relief was significantly superior to placebo and there were subjective improvements in spasm frequency, bladder control, spasticity and sleep. The authors of one such trial concluded that "the results of this study suggest that Sativex® is an effective treatment for spasticity associated with MS." In April 2005, GW announced that it had received approval to distribute

Sativex in Canada for the symptomatic relief of neuropathic pain in adults with Multiple Sclerosis.²⁷⁸

A U.K. study published in the journal *Lancet* looked at 630 multiple sclerosis patients after 15 weeks of orally delivered treatment. Fifty-seven percent of the patients taking a whole cannabis extract said their pain had eased, compared with 50 percent who took capsules containing THC and 37 percent who were given placebo capsules. Patients also reported improved sleep and fewer or less intense muscle spasms and stiffness. Those who could walk were significantly more mobile as measured by a walking test. The investigators also noted there were fewer relapses in the treatment groups; however, the study was not designed to investigate impact on relapses.²⁷⁹ An accompanying editorial suggests that current data supporting the benefit of cannabinoid treatment of spasticity in MS is now as strong as for any available pharmaceutical agent.²⁸⁰

Pain is a common problem in MS, and many patients who report using cannabis say it helps.^{281,282} In clinical trials, an oral cannabis extract was not initially shown not to be effective; however, pain relief became evident after long-term treatment. This may be due to the neuroprotective effects of plant cannabinoids that promote the repair of damaged pathways.

Studies have described the role of CB1 and CB2 cannabinoid receptors in regulating CNS automimmune inflammation and other factors that contribute to MS symptoms.^{283,284} Researchers have an animal model for MS, called experimental allergic encephalomyelitis (EAE), that allows testing for symptom suppression and disease progression. Animal studies in transgenic mice without cannabinoid receptors has shown that the cannabinoid system play an important role in MS. Mice lacking the CB1 receptor, experience rapid neurodegeneration in a model of MS. Pre-clinical reports have found that cannabinoids lessened both tremor and spasticity in mice with EAE. The CB2 receptor also influences inflammatory events in animal models. Mice lacking the CB2 receptor exhibit increased severity of MS compared to normal mice.²⁸⁵ It is thought the CB2 receptor may control the production of inflammatory signals and immune cell migration into tissue that are part of MS.

These studies of animal models of MS have greatly expanded our understanding of MS and cannabinoid biology. Emerging research suggests that cannabinoids have the potential to measurably lessen MS symptoms and may also slow the progression of the disease.

In addition to studying the potential role of marijuana and its derivatives in the treatment of MS-related symptoms, scientists are exploring the potential of cannabinoids to inhibit neurodegeneration. A study that the American MS Society called "interesting and potentially exciting" demonstrated that cannabinoids were able to slow the disease process in mice by offering neu-

roprotection against EAE. After analyzing the findings, authors at London's Institute of Neurology concluded, "In addition to symptom management, cannabis may also slow down the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis and probably other diseases."²⁸⁶

CANNABIS AND POST-TRAUMATIC STRESS DISORDER

Post-Traumatic Stress Disorder (PTSD) is a severe medical condition resulting from exposure to one or more traumatic events. While most people who are exposed to trauma do not develop PTSD, it is a common condition for combat veterans. For groups such as veterans who may simultaneously experience traumatic events, some will develop symptoms, some will not.²⁸⁷

Traumatic Brain Injury (TBI) is a contributing factor to PTSD symptoms, with veterans who have sustained TBI twice as likely to have them. The Department of Defense reports 287,861 diagnosed cases of TBI among active service members from 2000 through the third quarter of 2013.

PTSD if not treated adequately may lead to a variety of anxiety disorders, including Generalized Anxiety Disorder (six-times more likely), Panic Disorder (four-times more likely), Social Anxiety Disorder (three-times more likely), Obsessive Compulsive disorder, and specific phobias (seven-times more likely).^{288, 289} Veterans with PTSD can exhibit many symptoms and may not be seen for weeks or months after a traumatic event. One study of Iraq war veterans estimated their incidence rate of PTSD at 30 percent.²⁹⁰ That incidence rate may be measured differently now, as diagnostic criteria for PTSD were changed in 2013.²⁹¹

To receive a diagnosis of PTSD, veterans must have been exposed to certain types of traumatic events and exhibit symptoms of four types—intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity. Intrusion or re-experiencing symptoms can be triggered by a variety of events and include nightmares, frightening thoughts, and repeated flashbacks with physical symptoms such as elevated heart rate or sweating. Avoidance symptoms can also be triggered and commonly include actively avoiding things, events or places that remind the person of the trauma, but they can also include emotional numbness or loss of interest in enjoyable activities. Hyperarousal symptoms are generally constant, not triggered, and include difficulty sleeping, being easily startled or angered, or feeling tense or stressed. Hyperarousal may interfere with normal daily activities such as sleeping, eating, or concentrating. Depression, trouble remembering events, or feelings of worry, guilt, or depression are among the negative alterations in thought processes or moods characteristic of PTSD.

Many people will experience one or more of these symptoms following a dangerous or traumatic event, but they are only classified as PTSD when symptoms from each category are present for a month or more, interfere with normal functioning, and cannot be attributed to use of a substance or

another medical condition.

Not everyone exposed to traumatic events will develop PTSD, but recently published research indicates that the endocannabinoid system in individuals with PTSD differs markedly from those without the condition, perhaps connected to the role of endogenous cannabinoids in management of memories and anxiety.^{292, 293}

Those abnormalities in the functioning of the endocannabinoid system were further identified in research published in 2013. Brain scans using MRI (magnet resonance imaging) and PET scans (positron emission tomography) found people experiencing PTSD have substantially different cannabinoid CB1 receptors (17-19 percent more) and endocannabinoid systems than control groups that both had and had not experienced traumas. The receptor distribution abnormality predicted PTSD symptoms in 85 percent of the cases, with the difference most pronounced in female subjects.²⁹⁴

Direct studies of the effects of cannabis on PTSD among veterans have been blocked by the refusal of the federal government to provide research cannabis. However, studies have found many individuals with PTSD use cannabis.²⁹⁵⁻²⁹⁸

For more than 20 years, researchers have known many veterans with PTSD symptoms also use cannabis, either under the direction of a physician or of their own accord.²⁹⁹⁻³⁰²

The correlation between cannabis use and PTSD symptoms may corroborate anecdotal reports that cannabis provides symptomatic relief. Several studies have shown that cannabis and cannabinoids may alleviate some of the symptoms of PTSD.³⁰³⁻³⁰⁵

A 2011 study of veterans who underwent residential treatment for PTSD found that those who had less reduction in the severity of symptoms of hyper-arousal and avoidance or numbing were using more cannabis four months following the treatment than those who had more significant improvement in symptoms. That difference was specific to cannabis and was not found with alcohol or other drugs, indicating that veterans were selecting cannabis specifically for its effects relative to PTSD symptoms.³⁰⁶

In a review article published in August 2013, researchers noted that an "ideal treatment" for PTSD "would be a drug able to block the pathological over-consolidation and continuous retrieval of the traumatic event, while enhancing its extinction and reducing the anxiety symptoms." Cannabinoids fit that description in that they, as the researchers note, "regulate affective states and participate in memory consolidation, retrieval, and extinction."³⁰⁷

Those effects have been both recounted by cannabis users and amply demonstrated in animal models. In cannabis, the psychoactive cannabi-

noid THC has those effects, but multiple animal studies have demonstrated that cannabidiol (CBD), which has no cognitive effects, also produces powerful anti-anxiety actions in an animal model of PTSD.³⁰⁸⁻³¹⁰

Multiple reviews of these and other recent studies of CBD similarly concluded that its anxiolytic action may be useful for treating PTSD, anxiety disorders, and compulsive behaviors.³¹¹⁻³¹⁷

In the past decade, researchers have begun to uncover the mechanism for that effect, with several studies indicating the endocannabinoid system modulates neuronal activity in parts of the brain involved in defensive responses, meaning the endocannabinoid system could be particularly engaged by highly stressful situations such as combat and other traumatic events.³¹⁸⁻³²⁰

The role of endocannabinoids in regulating memory formation mentioned earlier has suggested that targeting the system can be a way of effectively managing recurring traumatic memories that are one of the symptoms of PTSD.³²¹

Israeli researchers have conducted promising studies of treating PTSD patients with cannabis, though methodology problems have prevented publication of the one that showed the best results. One Israeli psychiatrist reports seeing "spectacular results in patients with post-trauma," though the government has only authorized a handful of his PTSD patients to use cannabis.³²² A published case study of a young man with severe PTSD symptoms, including intense flashbacks, panic attacks, and self-mutilation, who was treated with a cannabis extract showed some symptoms were reduced significantly.³²³

One of the few double-blind randomized studies on cannabinoids and PTSD-related symptoms in humans assessed the efficacy of CBD in relieving the symptoms of Generalized Social Anxiety Disorder (SAD), one of the most common anxiety conditions that is sometimes also present in veterans with PTSD. The study with 24 subjects found treatment with CBD significantly reduced anxiety, cognitive impairment, and discomfort as compared to the placebo control group.³²⁴

A similar double-blind study of the effects of CBD treatment on individuals with SAD not only found the subjects reported substantial subjective relief but used functional neuroimaging to identify its effects on activity in limbic and paralimbic brain areas.³²⁵

HOW CANNABIS COMPARES TO OTHER TREATMENTS

Chronic Pain Medications

According to the Institute of Medicine, "All of the currently available analgesic (pain-relieving) drugs have limited efficacy for some types of pain. Some are limited by dose-related side effects and some by the development of tolerance or dependence."

The opioid analgesics commonly used to combat pain include **codeine**

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

In addition, patients in pain are often prescribed muscle relaxants such as Robaxin and Flexeril; anti-anxiety agents such as Valium, Sinequan, Vistaril, Ativan and Xanax; hypnotics such as Halcion, Restoril, Chloralhydrate, Dalmane and Doral and anti-emetics such as Zofran, Compazine, Phenergan, Tigan and Marinol.

Robaxin's side effects include abnormal taste, amnesia, blurred vision, confusion, dizziness, drop in blood pressure and fainting, drowsiness, fever, flushing, headache, hives, indigestion, insomnia, itching, light-headedness, nasal congestion, nausea, pinkeye, poor coordination, rash, seizures, slowed heart-beat, uncontrolled eye movement, vertigo, vomiting and yellow eyes and skin.

Flexeril can cause abnormal heartbeats, aggressive behavior, agitation, anxiety, bloated feeling, blurred vision, confusion, constipation, convulsions, decreased appetite, depressed mood, diarrhea, difficulty falling or staying asleep, difficulty speaking, disorientation, double vision, excitement, fainting, fatigue, fluid retention, gas, hallucinations, headache, heartburn, hepatitis, hives, increased heart rate, indigestion, inflammation of the stomach, itching, lack of coordination, liver diseases, loss of sense of taste, low blood pressure, muscle twitching, nausea, nervousness, palpitations, paranoia, rash, ringing in the ears, severe allergic reaction, stomach and intestinal pain, sweating, swelling of the tongue or face, thirst, tingling in hands or feet, tremors, unpleasant taste in the mouth, urinating more or less than usual, vague feeling of bodily discomfort, vertigo, vomiting, weakness, and yellow eyes and skin.

The newer antiemetics, **Anzamet**, **Kytril** and **Zofran**, are serotonin antagonists, blocking the neurotransmitter that sends a vomiting signal to the brain. Rare side effects of these drugs include fever, fatigue, bone pain, muscle aches, constipation, loss of appetite, inflammation of the pancreas, changes in electrical activity of heart, vivid dreams, sleep problems, confusion, anxiety and facial swelling.

Reglan, a substituted benzamide, increases emptying of the stomach, thus decreasing the chance of developing nausea and vomiting due to food remaining in the stomach. When given at high doses, it blocks the messages to the part of the brain responsible for nausea and vomiting. Side effects include sleepiness, restlessness, diarrhea and dry mouth. Rarer side effects are rash, hives and decreased blood pressure.

Haldol and **Inapsine** are tranquilizers that block messages to the part of the brain responsible for nausea and vomiting. Possible side effects include decreased breathing rate, increased heart rate, decrease in blood pressure when changing position and, rarely, change in electrical activity of the heart.

Compazine and **Torecan** are phenothiazines, the first major anti-nausea drugs. Both have tranquilizing effects. Common side effects include dry mouth and constipation. Less common effects are blurred vision, restlessness, involuntary muscle movements, tremors, increased appetite, weight gain, increased heart rate and changes in electrical activity of heart. Rare side effects include jaundice, rash, hives and increased sensitivity to sunlight.

Benadryl, an antihistamine, is given along with Reglan, Haldol, Inapsine, Compazine and Torecan to counter side effects of restlessness, tongue protrusion and involuntary movements. Its side effects include sedation, drowsiness, dry mouth, dizziness, confusion, excitability and decreased blood pressure.

Benzodiazepine drugs **Ativan** and **Xanax** are prescribed to combat the anxiety associated with chronic pain. Ativan causes amnesia. Abruptly stopping the drug can cause anxiety, dizziness, nausea and vomiting, and tiredness. It can cause drowsiness, confusion, weakness and headache when first starting the drug. Nausea, vomiting, dry mouth, changes in heart rate and blood pressure and palpitations are possible side effects.

Cancer Medications

The American Cancer Society lists 269 medicines currently prescribed to treat cancer and its symptoms, and to treat the side effects of other cancer drugs. Some drugs are prescribed for pain caused by cancer, and cancer patients report pain relief with cannabis therapy. Many chemotherapy agents cause severe nausea and 13 drugs are currently prescribed to treat nausea, including Marinol, a synthetic form of delta-9-THC, the primary psychoactive component in cannabis.

Antiemetic medications used for treating nausea, and medications such as antihistamines that are sometimes prescribed in combination with antiemetics, are all discussed above, under pain medications.

Decadron (dexamethasone), a corticosteroid, is given with other chemotherapy drugs as an adjunct medication. Common side effects include increased appetite, irritation of stomach, euphoria, difficulty sleeping, mood changes, flushing, increased blood sugar, decreased blood potassium level. Possible



Angel Raich using a vaporizer in the hospital

side effects upon discontinuing the drug include adrenal insufficiency, weakness, aches, fever, dizziness, lowering of blood pressure when changing position, difficulty breathing, and low blood sugar.

Benzodiazepine drugs **Ativan** and **Xanax** are also prescribed to combat the effects of chemotherapy. Ativan causes amnesia. Abruptly stopping the drug can cause anxiety, dizziness, nausea and vomiting, and tiredness. It can cause drowsiness, confusion, weakness, and headache when first starting the drug. Nausea, vomiting, dry mouth, changes in heart rate and blood pressure, and palpitations are possible side effects.

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.

In addition, in April 2003 the FDA approved the drug **Emend** (aprepitant) to help control delayed-onset nausea. It is given along with two other anti-nausea drugs. A regimen of three pills costs \$250. The most common side effects with Emend are fatigue, nausea, loss of appetite, constipation and diarrhea.

Neurologic Medications

Benzodiazepines, levedopa, baclofen, dantrolene sodium, and tizanidine are the most widely used agents for reduction of spasticity. At high dosages, oral medications can cause unwanted side effects that include sedation, as well as changes in mood and cognition.

Benzodiazepines, which include Diazepam (Valium) and Clonazepam (Klonopin, Rivotril) are centrally acting agents that increase the affinity of GABA to its receptor. Diazepam is the oldest and most frequently used oral agent for managing spasticity. Benzodiazepine side effects include sedation, weakness, hypotension, GI symptoms, memory impairment, incoordination, confusion, depression and ataxia. Tolerance and dependency may occur and withdrawal on cessation. Tolerance may also lead to unacceptable dosage escalation.

Levedopa is common long-term treatment option for Parkinson's disease. Long-term use can result in dyskinesia and is often a reason for not taking the drug. Dyskinesia can lead to less control of voluntary movements and can result in tics or chorea. Dikynesia can result in excessive tongue rolling and after years of use it can manifest as "jerky" movements of the head and arms.

Baclofen (Lioresal) has been widely used for spasticity since 1967. It is a GABA agonist. Tolerance to the medication may develop. Baclofen must be slowly weaned to prevent withdrawal effects such as seizures, hallucinations and increased spasticity. It must be used with care in patients with renal insufficiency as its clearance is primarily renal. Side effects are predominantly from

central depressant properties including sedation, ataxia, weakness and fatigue. May cause depression when combined with tizanidine or benzodiazepines.

Dantrolene Sodium (Dantrium) acts peripherally at the level of the muscle fiber and works best for cerebral palsy and traumatic brain injury. Because the action of dantrolene sodium is not selective for spastic muscles, it may cause generalized weakness, including weakness of the respiratory muscles. The side effects include drowsiness, dizziness, weakness, fatigue and diarrhea. In addition, hepatotoxicity (liver damage) occurs in < 1 percent of patients who take dantrolene sodium.

Tizanidine (Zanaflex) facilitates short-term vibratory inhibition of the H-reflex. Tizanidine in conjunction with baclofen or benzodiazepines has potential additive effects, including sedation and the possibility of liver toxicity. Dry mouth, somnolence, asthenia and dizziness are the most common side effects. Liver function problems and hallucinations may also occur.

Multiple Sclerosis Medications

A recent review of all available medications for MS concluded that "forthcoming information relating to the use of cannabinoids in MS may result in there being better evidence of the effectiveness of new treatments than of any of the currently used drugs."³²⁶

Over 40 medicines are listed by the Multiple Sclerosis Society as commonly used by MS patients. Symptoms and medications prescribed include "acute exacerbations" (Decadron, Solu-Medrol); depression (Effexor, Paxil, Prozac, Wellbutrin, Zoloft); erectile dysfunction (Papaverine, Levitra, MUSE, Prostin VR, Viagra); fatigue (Amantadine, Cylert, Provigil, Prozac); itching (Atarax); nausea (Antivert); pain (Aventyl, Dilantin, Elavil, Neurontin, Gabapentin, Pamelor, Tegretol); urinary tract infections (Bactrim, Cipro, Hiprex, Macrochantin, Nitrofurantoin, Pyridium); and urinary frequency or bladder dysfunction (DDAVP, Ditropan, Oxytrol, Pro-Banthine, Tofranil). Interferon-based medicines are also prescribed as "disease-modifying agents."

Drugs commonly prescribed for muscle spasticity and tremor include Klonopin, Dantrium, Baclofen, Zanaflex and Valium. Klonopin (clonazepam) and Valium (diazepam) are both **benzodiazepines**, central nervous system (CNS) depressants manufactured by Roche. Overdoses of these medications, especially when taken with alcohol, may lead to unconsciousness and death. They frequently cause people to become drowsy, dizzy, lightheaded, clumsy, or unsteady. Other common side effects include slurred speech; abdominal cramps or pain; blurred vision or other changes in vision; changes in sexual drive or performance; gastrointestinal changes, including constipation or diarrhea; dryness of mouth; fast or pounding heartbeat; muscle spasm; trouble with urination; trembling. Studies in animals have shown that clonazepam and diazepam can cause birth defects or other problems, including death of the animal fetus. Overuse of clonazepam during pregnancy may cause the baby to become dependent on it and it may pass into breast milk

and cause drowsiness, slow heartbeat, shortness of breath, or troubled breathing in nursing babies.

Dantrium is a muscle relaxant manufactured by Proctor & Gamble. It has been shown to cause cancer and non-cancerous tumors in animals, can cause liver damage, and should not be taken with alcohol. Common side effects include diarrhea, dizziness, drowsiness, weakness, nausea, unusual tiredness, abdominal cramps, blurred or double vision, chills and fever; constipation, frequent urination, headache, loss of appetite, speech difficulties, sleep difficulties and nervousness.

Baclofen (Medtronic) may be administered orally or with a surgically implanted pump in the spine. Its side effects include high fever, altered mental status, spasticity that is worse than was experienced prior to starting ITB Therapy, and muscle rigidity. Symptoms of overdose include shortness of breath or troubled breathing, vomiting, seizures, loss of consciousness and coma. Abruptly stopping implanted baclofen has been fatal.

PTSD Medications

Two antidepressant medications are the only FDA-approved for treating PTSD symptoms: **sertraline** (Zoloft) and **paroxetine** (Paxil). In some individuals, these medicines may help control some PTSD symptoms, such as sadness, worry, anger, and feeling numb. Both drugs have common side effects, including headache, nausea, drowsiness, agitation, and sexual dysfunction including reduced sex drive, difficulty having or enjoying sex, or difficulty climaxing. More serious side effects include increased risk of suicide or thinking about suicide.

Though other medications are not approved for treating PTSD, doctors may treat PTSD symptoms with other types of medications, such as benzodiazepines, antipsychotics, and other antidepressants such as tricyclic or atypical antidepressants and monoamine oxidase inhibitors (MAOIs) and mood stabilizers such as carbamazepine (Tegretol) and lithium (Lithobid or Eskalith), though there is little information about how well they work for people with PTSD and each can produce significant side effects.

Side effects of **benzodiazepines** include memory problems and dependency. **Antipsychotics** are usually given to people with schizophrenia and other serious mental disorders; side effects include weight gain and increased chance of heart disease and diabetes. **Prazosin** (Minipress) may be prescribed to reduce recurrent nightmares; side effects may include hypotension (low blood pressure), fainting, and hallucinations. Side effects of **carbamazepine** include possibly fatal skin reactions and very serious blood disorders (aplastic anemia, agranulocytosis).

Cannabis vs. Other Medications

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, though it can also provide symptomatic relief in refractory schizophrenia. 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 potentially 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 ischemias. In summary, a low risk profile is evident from the literature available. Serious complications are extremely rare and are not usually reported during the use of cannabinoids for medical indications.

Why cannabis is 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*:

One of marijuana'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. Marijuana 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 marijuana is an openly recognized medicine, solutions may be found; ultimately a technology for the inhalation of cannabinoid vapors could be developed.³²⁷

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.³²⁸ Additionally, pharmaceutical companies have developed sublingual sprays and capsule 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

non-smokers.³²⁹ 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.³³⁰

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**

Dr. Grinspoon notes, "the greatest danger in medical use of marijuana is its illegality, which imposes much anxiety and expense on suffering people, forces them to bargain with illicit drug dealers, and exposes them to the threat of criminal prosecution." This was also the conclusion reached by the House of Lords, which recommended rescheduling and decriminalization.

In January 2013, the American Herbal Products Association (AHPA), which has a 30-year

history of developing standards for the herbal products industry, issued recommendations for effectively regulating all aspects of cannabis distribution for patients. The regulatory recommendations, developed over two years by the AHPA Cannabis Committee address guidelines for cultivation, quality-assurance, analytics, cannabis product manufacture and labeling, storefront and delivery services, and personnel training.

In December 2013, the American Herbal Pharmacopoeia (AHP) released a monograph identifying cannabis as a botanical medicine. Written and reviewed by the world's leading experts on cannabis, the monograph provides a full scientific understanding of the plant, its constituent components, and its biologic effects. It also establishes comprehensive standards for the plant's identity, purity, quality, and botanical properties.

Following the release of the monograph, ASA launched Patient Focused Certification, the first non-profit, third-party certification program based on the AHPA regulatory recommendations and the AHP standards. Patient Focused Certification (PFC) audits cultivators, distributors, manufacturers and laboratories to verify compliance with best-practice standards. PFC includes employee training, compliance inspections, ongoing monitoring, and an independent complaint process for customers, as well as comprehensive reviews of formulations and materials, independent testing, and facility inspections.

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 more than 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. THC and other cannabinoids have been shown to be effective in controlling nausea,³³¹⁻³³⁵ but many severely nauseated patients experience difficulty in swallowing and keeping a pill down, a problem avoided by use of inhaled cannabis, which decades of studies have shown to be highly effective for treating nausea.^{336, 337}

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 percent relief from nausea and vomiting, while those who used THC capsules experienced 76-88 percent relief."³³⁸ 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.^{339, 340} As the House of Lords states, "Some users of both find cannabis itself more effective."³⁴¹ That is at least in part because the various cannabinoids and terpenes found in cannabis work in concert with one another to create an "entourage effect" that provides enhanced therapeutic efficacy.³⁴²

THE EXPERIENCE OF PATIENTS

Jim Champion — Multiple Sclerosis

As a member of the 502nd infantry, 101st airborne, my unit was deployed to the kingdom of Jordan in the late 1980's. Soon after, I found myself diagnosed with MS awaiting a medical discharge instead of starting my second enlistment.

I've presently had MS for over 25 years, but I first tried cannabis for my condition about 11 years ago. Each time I went to the doctor with spasms or atrophy that was bending my body into painful and unnatural positions, I'd walk out with a new muscle relaxer or pain pill. By 2003 I found myself taking a cocktail of approximately 59 pills a day, which did little for the pain and spasms and instead turned me into what felt like a sleeping zombie. I'd literally fall asleep in the middle of a conversation! I was a prisoner in my own body.

Later that year I had a muscle spasm which lasted for days. Nothing I did or took would stop it. My cousin came over and convinced me to try cannabis. By the time we finished my body had stopped twitching, and I felt relaxed for the first time in a long time. I was also experiencing another strange sensation—I was hungry!

At first, my wife didn't like my smoking on top of all the pills I was taking, but cannabis was providing unparalleled relief from the painful spasms and atrophy. No spasms or atrophy, no pain! After discussing it with her, we took inventory of my pills and began tapering down the ones I no longer needed thanks to the relief provided by one cannabis cigarette a day. We not only reduced the overall number of my pills to just 24 per day, we were able to eliminate some intoxicating medicines all together. By the time we were finished I no longer took Valium, Xanax for tremors, Gabapentin, morphine and Vicodin for breakthrough pain, and several others. Also, I reduced the number of methadone I take per day.

Since that time I have literally been a new man. I used to lay in bed for weeks at a time. I neither had the energy nor desire to ever leave my house. The pills were making me sicker and weaker. Now I only stay in bed at night and I go out often (when it's warmer outside) and do the things I love. If I'm not going to a Bears/Blackhawks/Bulls/Cubs game, I'm going to Springfield to help pass our bill. Cannabis has allowed me to enjoy an active life that I thought had long passed me by. Eleven years later, and I still only smoke between one and two cannabis cigarettes per day. If smoking is not for you, they have edibles, vaporizers, tinctures and other ways of dispensing the product.

Michael Krawitz — Chronic Pain

I am a disabled United States Air Force Veteran. I joined through the delayed enlistment program in high school and served from November 1981 thru January 1986 as an avionics [onboard aircraft] Electronic Warfare Systems Technician.

I was serving with the 52nd Avionics Maintenance Squadron in Guam, USA when I was injured in a motorcycle accident on my way home from dinner. My last Friday night on Guam, I talked my buddy into letting me ride his shiny new motorcycle home from our celebratory dinner and in my zeal to be careful on his new bike I was traveling in the far right lane which, much to my surprise, became a turning lane with no sign for warning. The right lane of the road I was on suddenly ended in a curb and I hit it, launching me over the bars into a stop sign pole that was intended for the entering traffic and to which I was only able to see in profile. That injured my spleen, nicked my pancreas, and broke my leg badly enough that I needed an artificial hip. A secondary infection meant they had to leave my abdomen open for a month and a half after they removed part of my intestine and performed an end to end bowel resection. I was in the hospital in Hawaii that I was medi-evaced to for 85 days recovering and battling pain.

My first medical marijuana: I wasn't in very good condition even after I was finally released from the general surgery ward into a private room in the orthopedics ward. I was still segregated because of my infection. The nurse wheeled me into a common bay so I could be near other troops and see the TV, I guess to cheer me up a bit. While watching TV one of the other injured

soldiers in the ward with me offered me a butt end of a joint. I figured I wasn't going back to my unit, and I could see no reason why not to indulge. I really didn't see this as a medicine but recreation sounded pretty darn good at that moment. I wheeled into my bathroom in my wheelchair to smoke it and what I found from the cannabis was not a giddy feeling of getting high that I would have expected but more of a release from the tension and pain that had gripped my body as my stomach slowly healed. Over the coming days I would smoke the cannabis whenever I could, and in just a few days I was able to lower my bed flat enough that all at once every bone in my back seemed to pop back into its rightful place. My mother and father had visited me just weeks before and they hoped to hear progress but were shocked when the nurse told them I had ambulated off the ward on my own. At first a Ranger in a walking cast would push me out to the parking lot to smoke a joint and later I had fashioned a cane to my long arm cast on the left and with my cast covering my whole right leg I had crutch walked out of the hospital on my own so that I could smoke freely. Cannabis definitely helped me get me out of the hospital faster than they expected. Those trips to the parking lot were my work-outs. It took me a long time to put together that I was getting therapeutic benefit from it though. Back in my duty station I was relegated to a desk job while they figured out what to do with me and they kept me comfortable with pain pills. It wasn't until after that duty station at Offutt AFB in Omaha, after my service ended, that I actually started seeing myself as a medical cannabis user.

By then I was dealing with long-term chronic pain issues. My treatment at the VA was trial and error. They had all this treatment, all these options, and they put me through them all: kinesio therapy, hydro therapy, heat, steroids etc. Some of it was pretty cruel stuff with little potential gain but lots of down side. Until the mid 1990's, I never even asked twice. I tried everything, all with the same effect – very little. I was given significant amounts of Tylenol with everything, 300mg times 2 in my pain meds plus, 1,500-2,000mg separately per day. When the Internet became available Tylenol's bad history of kidney damage in chronic users was one of my first discoveries. I requested and received from that point on only Tylenol free pain treatment. If I have the need I now take Tylenol very rarely.

Ultram was the very last drug I took on faith. It really messed me up. I couldn't pee, couldn't walk, and had vicious headaches. Suddenly, I now empathized with someone beating his head on the floor because it hurt so much that I had seen previously on a TV Migraine documentary.

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

After that, I decided I'm not going to take anything without checking. A VA doctor tried to prescribe me Amitriptyline, Next one tried Nortriptyline. Gabapentin was the third I turned down.

Around that time is when I discovered the history of cannabis. I grew up in the antiques business, so I knew antiques but had never run into a cannabis antique and if you looked up information before the Internet you were caught up in propaganda under the word marijuana.. I quickly found that the pharmaceutical companies Parke Davis and Eli Lilly in the 1920's had cannabis text book references in all the key doctors' teaching manual's expressly mentioning it as key therapy for patients who have stomach issues and pain. They presented cannabis as a first-line medicine if the patient can't tolerate opiates. That really got to me and made me mad. A hundred years ago my doctor would have been trained in this, but today I had to go find it out for myself and then go teach my own doctor.

Because of the bowel resection, I can only take a small amount of opiate painkillers before I have serious GI issues. But a little cannabis, just one to two grams a day, helps the opiates work better. Now I only take the smallest Oxycodone pill, 5mg, twice a day -- a dose so low most doctors don't even know they make it. I've found a regimen that works, and I'm grateful. A couple of times I've had gaps, and that's been tough. With chronic pain, if you take my pain treatment away and force me to suffer, I have a real hard time getting back to stable. The last time I was without cannabis during a very stressful time it had negative consequences I am still working to recover from.

Overall, I receive great care at the VA, particularly for my hip, but the administrative side of the VA has been a big problem. When I was told I must sign a pain contract to continue my care, I said I wanted to take the contract to consult with my lawyer. My lawyer said a contract is only a contract if both sides get something. Since I am a Veteran, the VA is already supposed to provide care, so it didn't seem like I was getting anything in exchange for signing it, so I told them I wouldn't sign it. Because of that, they cut me off from all opiate pain management and tried to switch me to the lesser-controlled gabapentin medicine. They were punishing me by cutting off my previously successfully prescribed medicine. But that's unethical. You can't deny medication as punishment, even with prisoners or drug addicts!. Taking a stand helped get the VHA to create a policy so that now using medical cannabis no longer seems to automatically disqualify you from pain management care. To this day I'm still working with the VHA to get fully back into their system.

What other veterans need to know is that they need to integrate their care. Their VA doctors can't recommend medical cannabis, but if they have an outside doctor who has, they need to tell the VA doctors because you want it to be part of your file. Veterans can't just leave the VA facility or you create a void in your file that the VA may wrongly think means you are no longer disabled.

Perry Parks — Chronic Pain and PTSD

I am a retired Chief Warrant Officer (CW4) with 30 years service in the US Army and National Guard. I am also a disabled veteran. I flew helicopters in Vietnam for 30 months. Then I spent two years in Iran teaching helicopter pilots desert and mountain tactics. When I left active duty, I was recruited by the National Guard because of my experience with Cobra helicopters and spent 18 years with them. I retired in 2003.

I suffer from chronic pain from degenerative disc disease and PTSD that became worse with the beginning of the Iraq war. I was treated at Duke for two years with COX 2 inhibitors, Vioxx, Celebrex, needles in my back to control the pain. As the Iraq war ramped up, I began to experience more PTSD symptoms -- sleeplessness, feeling jumpy or jittery, a lot of different things. The narcotics didn't help me. And oxycodone and other drugs with acetaminophen worried me because of the liver damage they can cause.

I was told cannabis might provide relief, particularly for my chronic pain. I thought it was a joke. I was skeptical. I didn't believe it was real, even though I'd used marijuana when I was younger. I had used cannabis in college and had a 4.0 average, so I knew it didn't kill my motivation.

In Vietnam, I was first offered cannabis by the division flight surgeon. At first I thought it was kind of a joke, but I found that every night when we shared the pipe there was a certain calmness and sense of camaraderie. In a war-zone, there aren't many moments when you have the chance to forget about the war. Looking back, I see it provided tremendous relief. But I never used it during my 18 years in the National Guard.

Now that I was retired, I was no longer being drug tested, so I decided to try it. I was shocked. It worked, not just for my pain but for the PTSD, too. I sleep more peacefully and am more at ease. Duke had me down to Level 1 or Level 2 pain, but with cannabis combined with low doses of opiate narcotics I operate pain free. I can do anything I used to do. No pain in my back and I deal far better with the PTSD. I had a large supply of sleeping pills that I no longer use. I had a large supply of narcotics that I no longer take. I had prescriptions for ADHD, which I believe was misdiagnosed because of my PTSD symptoms.

After that, I attended conferences on medical cannabis, and I found out why it works.

I'm a 30-year soldier and disabled veteran, but I'm also a Christian. I was sitting in church one night, and we were reading Acts, and my soul was jarred. To recognize how cannabis worked for me and not tell people is not right. Every church has the goal of seeking the truth. It takes a deep prodding to give up your personal safety, but I have an obligation because this affects people's health. The truth hurts sometimes, but the truth has the greatest need to be told.

More soldiers today die of suicide than combat, and part of that is being

denied medicine that can help. I was one of the five soldiers portrayed in the 2009 documentary *The Good Soldier* that won an Emmy for the shortened television version *Bill Moyers Journal* produced. Three of the soldiers, including me, were subject to arrest because they do not live in states that allow medical cannabis. That's wrong and it needs to stop. The treatment should be decided by a doctor, not by the state you live in. The US Conference of Mayors unanimously passed a resolution urging our government to stop forcing our veterans into the criminal justice system because they choose cannabis instead of narcotics. This issue cannot be dictated from the top down, it has to be demanded from the bottom up.

Jo Daly — Cancer

In 1980, I was appointed by Dianne Feinstein, then Mayor of San Francisco, to serve as police commissioner for the city of San Francisco, an office which I held for six years. On May 24, 1988, I was diagnosed with Phase IV cancer of the colon. By the time it was diagnosed, it had already spread to my ovaries and lymph nodes. My oncologist at the UCSF Hospital prescribed an aggressive regimen of chemotherapy, which lasted six months. I was given large doses of the chemicals, four hours a day, five days a week in the first week of each month.

Each day, when I returned home from the hospital following treatment. . . . I was overcome by a sudden wave of intense nausea, like a nuclear implosion in my solar plexus, and I rushed desperately for the bathroom where I would remain for hours, clutching the toilet and retching my guts out. I had no appetite. I could not hold down what little food that I managed to swallow. And I could not sleep at night.

This intense nausea persisted for the two weeks following the treatment. By the third week after treatment, the side effects of the chemicals began to wear off, and I started to feel better. The next week, however, I had to return to the hospital where the chemicals were administered once more, beginning my hell all over again. To combat the nausea, I tried Marinol, a synthetic version of THC, one of the primary chemicals found in marijuana. However, I was often unable to swallow the Marinol capsule because of my severe nausea and retching. A friend then gave me a marijuana cigarette, suggesting that it might help quell my nausea. I took three puffs from the cigarette. One-half hour later, I was calm, my nausea had disappeared, my appetite returned, and I slept that evening.

I told my oncologist about how well marijuana quelled my nausea. My doctor was not surprised. In fact, he told me that many of his patients had made the same discovery. My doctor encouraged me to continue using marijuana if it worked. Although it occasionally produced a slight euphoria, it was not a painful sensation, and I was careful never to leave the house during those rare moments. My use of medical marijuana had a secondary, though by no means minor benefit: I was able to drastically reduce my dependence on more powerful prescription drugs that I was prescribed for pain and nausea.

With the help of medical marijuana, which I ingest only occasionally and in small amounts, I no longer need the Compazine, Lorazepam, Ativan and Halcion.

Vollie Rutledge, Jr. — Neurological Disorder

In July of 1990 I was driving home from work and as I came around a corner doing 55 MPH I came into a herd of deer. I tried to miss them but one of them fell down and my right front tire went up on the deer's hip like a ramp. My car flipped over and went down an embankment. It landed on the roof smashing the driver's compartment down to the level of the top of the seat. I didn't have a seat-belt on so I was able to dive into the passenger's floor-board but even that didn't save me.

I woke up in the hospital a couple of days later with a broken vertebra. Medically it was called "an unstable fracture of the second vertebra" or C-2 fracture. Somehow it didn't kill me, but it did paralyze my left side for a couple of weeks. When the feeling came back all of the nerves reacted spastically. If I reached for something I couldn't control where my hand was going. If I sneezed my hand would fly uncontrollably.

Several times I bloodied my nose with my left hand just sneezing. I finally learned to grab my left arm when I sneezed. I couldn't walk without a cane because I couldn't trust my left leg to go where I wanted it to. It was an extremely difficult time in my life. About two months after the accident my friends had come over to visit and as it happened, I sneezed. My arm came up and hit me in the face and bloodied my nose once again. I was embarrassed to say the least.

One of my friends rolled a joint and something happened... The muscles in my neck relaxed and when I reached for my coffee my arm went where it was supposed to. As long as I moved very slowly, I could move correctly. Within a week I was using my hand to shuffle a deck of cards. I can't explain how dramatic the difference was. I went from not being able to eat with a fork (previously too spastic to grab and hold a fork) to shuffling a deck of cards and dealing them in just one week. Within three weeks I could walk without a cane. Once again I could trust my legs to go where I wanted them. Marijuana is the only drug that any doctor has found, in eight years of trying different drugs, that works.

THE EXPERIENCE OF DOCTORS

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 effective 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 adjuvant 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 has served as a medical officer in the Air Force, taught at UC Davis School of Medicine, and consulted with state legislative bodies.

Howard D. Maccabee, M.D.

In my practice, I commonly use radiation therapy to treat the whole spectrum of solid malignant tumors. Radiation therapy is often used after surgery or chemotherapy, as a second stage in treatment. Sometimes, however, radiation therapy is used concurrently with chemotherapy, or even as the first or only modality of treatment.

Because of the nature of some cancers, I must sometimes irradiate large portions of my patients' abdomens. Such patients often experience nausea, vomiting, and other side effects. Because of the severity of these side effects, some of my patients choose to discontinue treatment altogether, even when they know that ceasing treatment could lead to death.

During the 1980s, I participated in a state-sponsored study of the effects of marijuana and THC (an active ingredient in marijuana) on nausea. It was my observation during this time that some patients smoked marijuana while hospitalized, often with the tacit approval of physicians. I also observed that medical marijuana was clinically effective in treating the nausea of some patients.

During my career as a physician, I have witnessed cases where patients suffered from nausea or vomiting that could not be controlled by prescription anti-emetics. I frequently hear similar reports from colleagues treating cancer and AIDS patients. As a practical matter, some patients are unable to swallow pills because of the side effects of radiation therapy or chemotherapy, or because of the nature of the cancer (for instance, throat cancer). For these patients, medical marijuana can be an effective form of treatment.

Kate Scannell, M.D.

Because I was a cancer patient receiving chemotherapy at the same hospital where I worked, the elderly women with whom I shared the suite quickly surmised that I was also a doctor. The clues were obvious: the colleagues dropping by, the "doctor" salutations from co-workers and the odd coincidence that one of my suitemates was also one of my patients.

I braced myself for this woman's question, both wanting to make my-self available to her but also wishing that the world could forget that I was a doctor for the moment. After receiving my cancer diagnosis, dealing with surgery and chemo-therapy and grappling with insistent reminders of my mortality, I had no desire to think about medicine or to experience myself as a physician in that oncology suite. And besides, the chemotherapy, anti-nauseants, sleep medications and prednisone were hampering my ability to think clearly.

So, after a gentle disclaimer about my clinical capabilities, I said I'd do my best to answer her question. She shoved her IV line out of the way and, with great effort and discomfort, rolled on her side to face me. Her belly was a pendulous sack bloated with ovarian cancer cells, and her eyes were vacant of any light. She became short of breath from the task of turning toward me.

"Tell me," she managed, "Do you think marijuana could help me? I feel so sick."

I winced. I knew about her wretched pain, her constant nausea and all the prescription drugs that had failed her—some of which also made her more constipated, less alert and even more nauseous. I knew about the internal derangements of chemotherapy, the terrible feeling that a toxic swill is invading your bones, destroying your gut and softening your brain. I knew this woman was dying a prolonged and miserable death. And, from years of clinical experience, I, like many other doctors, also knew that marijuana could actually help her. From working with AIDS and cancer patients, I repeatedly saw how marijuana could ameliorate a patient's debilitating fatigue, restore appetite, diminish pain, remedy nausea, cure vomiting and curtail down-to-the-bone weight loss. I could firmly attest to its benefits and wager the likelihood that it would decrease her suffering.

Still, federal law has forbidden doctors to ... prescribe marijuana to patients [though doctors may legally recommend it.] In fact, in 1988 the Drug Enforcement Agency even rejected one of its own administrative law judge's conclusions supporting medicinal marijuana, after two full years of hearings on the issue. Judge Francis Young recommended the change on grounds that "marijuana, in its natural form, is one of the safest therapeutically active substances known to man," and that it offered a "currently accepted medical use in treatment."

Doctors see all sorts of social injustices that are written on the human body, one person at a time. But this one—the rote denial of a palliative care drug like marijuana to people with serious illness—smacks of pure cruelty precisely because it is so easily remediable, precisely because it prioritizes service to a cold political agenda over the distressed lives and deaths of real human beings.

Denis Petro, M.D.

As a practicing neurologist, I saw many patients for whom uncontrollable spasticity was a major problem. Unfortunately, there are very few drugs specifically designed to treat spasticity. Moreover, these drugs often cause very serious side effects. Dantrium or dantrolene sodium carries a boxed warning in the *Physician's Desk Reference* because of its very high toxicity...The adverse effects associated with Lioresal Baclofen are somewhat less severe, but include possibly lethal consequences, even when the drug is properly prescribed and taken as directed. Unfortunately, neither Dantrium or Lioresal are very effective spasm control drugs. Their marginal medical utility, high toxicity, and potential for serious adverse effects, make these drugs dif-

icult to use in spasticity therapy.

[Dr. Petro then related his experience with a patient who was smoking cannabis for his symptoms. Dr. Petro and colleagues examined the patient and then asked him to refrain from smoking for six weeks. He continues:]

After six weeks he returned for another examination. At this time, he reported an increase in his symptoms to the point where he had leg pains, increased clonic activity, and uncontrolled leg spasms every night. More disturbing to him was urinary incontinence, which occurred on two occasions during leg spasms. On objective examination, in layman's terms, this patient's spasticity had increased dramatically in six weeks. This spasticity made his legs extremely rigid, he was finding it increasingly difficult to walk or sleep, and he was losing bladder control.

Following our examination, and at the patient's request, he left the clinic then returned one hour later to be examined for a second time. This second examination was remarkable. The earlier findings of moderate to severe spasticity could not be elicited. Deep tendon reflexes were brisk, but without spread, ankle clonus was absent, and the plantar response was flexor on the left and equivocal on the right.

In short, this patient had undergone a stunning transformation. Moreover, this unmistakable improvement had occurred in an incredibly brief period of time. Less than an hour separated the two examinations. On questioning, the patient informed us he had smoked part of one marijuana cigarette in the interval between examinations.

Denis Petro, M.D is a former FDA Review Officer and principal investigator on spasticity and cannabis.

Leo E. Hollister, M.D.

Patients with spinal cord injuries often self-treat their muscle spasticity by smoking cannabis. Cannabis seems to help relieve the involuntary muscle spasms that can be so painful and disabling in this condition. A muscle relaxant or antispastic action of THC was confirmed by an experiment in which p.o. doses of 5 or 10 of THC were compared with placebo in patients with multiple sclerosis. The 10 mg of THC reduced spasticity by clinical measurement. Such single small studies can only point to the need for more study of the potential use of THC or possibly some of its homologs. Diazepam, cyclobenzaprine, baclofen, and dantrolene, which are used as muscle relaxants, all have major limitations. A new skeletal muscle relaxant would be most welcome.

Leo E. Hollister, Veterans Administration Medical Center and Stanford University School of Medicine, Palo Alto, California

Lester Grinspoon, M.D.

There are many case reports of marijuana smokers using the drug to reduce pain: post-surgery pain, headache, migraine, menstrual cramps, and so on.

Ironically, the best alternative analgesics are the potentially addictive and lethal opioids. In particular, marijuana is becoming increasingly recognized as a drug of choice for the pain that accompanies muscle spasm, which is often chronic and debilitating, especially in paraplegics, quadriplegics, other victims of traumatic nerve injury, and people suffering from multiple sclerosis or cerebral palsy. Many of them have discovered that cannabis not only allows them to avoid the risks of other drugs, but also reduces muscle spasms and tremors; sometimes they can even leave their wheelchairs.

The years of effort devoted to showing that marijuana is exceedingly dangerous have proved the opposite. It is safer, with fewer serious side effects, than most prescription medicines, and far less addictive or subject to abuse than many drugs now used as muscle relaxants, hypnotics, and analgesics.

Thus cannabis should be made available even if only a few patients could get relief from it, because the risks would be so small. For example, as I mentioned, many patients with multiple sclerosis find that cannabis reduces their muscle spasms and pain. A physician may not be sure that such a patient will get more relief from marijuana than from the standard drugs baclofen, dantrolene, and diazepam—all of which are potentially dangerous or addictive—but it is almost certain that a serious toxic reaction to marijuana will not occur. Therefore the potential benefit is much greater than any potential risk.

Dr. Grinspoon is professor emeritus at Harvard University School of Medicine, and the author of numerous publications.

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.”³⁴³

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.”³⁴⁴

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.”³⁴⁵ The AMA's lobbyist, Dr. William C. Woodward, testified to Congress that “The American Medical Association knows of no evidence that marijuana 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 and the District of Columbia 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. Currently, nearly 50 percent of the U.S. population resides in a state that permits medical use, and medical cannabis legislation is introduced in more states every 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 as a Schedule I drug, defined as having no medicinal 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 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 quarter 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 fifteen 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.

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3. 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).
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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

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