

# Professional Perspectives On Addiction Medicine

Volume 2

*Beyond Medical Marijuana:  
Toward Cannabinoid-Based Medicines*



Edited By

Mark Stanford, Ph.D.  
Donald Avoy, M.D.

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Santa Clara Valley Health & Hospital System  
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Beyond Medical Marijuana: Toward Cannabinoid-Based Medicines

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Santa Clara Valley Health & Hospital System  
Department of Alcohol & Drug Services  
Addiction Medicine and Therapy Program  
2425 Enborg Lane  
San Jose, CA 95128

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To Professor Raphael Mechoulam

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## PREFACE

Robert Garner

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The controversy over the issue of “medical marijuana” may essentially be over since medical research has made significant advances about the science of cannabinoid-based medicines. Synthetic analogs and other drugs acting on the human body’s own internal cannabinoid system are beginning to provide a myriad of potential therapeutic benefits attributed to marijuana, without the smoke, the contaminants, and the variable potency.

In a seminal 1999 report, the Institute of Medicine (IOM), recognized the medical value of cannabinoids, the active compounds in the marijuana or cannabis plant, for several important indications. The IOM report only cautiously endorsed short-term interim studies of smoked marijuana for a few limited indications, stating instead that, “the future of medical marijuana lies in classical pharmacological drug development”.

The Santa Clara County Department of Alcohol & Drug Services looked to the IOM for guidance and direction for the use of medical marijuana under certain circumstances for patients who are also in treatment for drug addiction. From a policy perspective, the challenge was to provide effective treatment and at the same time consider a known addictive substance as an ancillary treatment for certain medical conditions in patients recovering from drug addiction.

According to the IOM, because of the health risks associated with smoking in general, smoked marijuana should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern. Until a non-smoked rapid-onset cannabinoid drug delivery system becomes available, the IOM acknowledges that there is no clear alternative for some people suffering from chronic and debilitating conditions that might be relieved by smoking marijuana. In the meantime there are patients

with debilitating symptoms for whom smoked marijuana might provide relief. The use of smoked marijuana for those patients should weigh both the expected efficacy of marijuana and ethical issues in-patient care, including providing information about the known and suspected risks of smoked marijuana use.

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

1. failure of all approved medications to provide relief has been documented.
2. the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs.
3. such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness.
4. client is willing to sign a consent for the release of information for counselor and/or program physician to communicate with the physician who has authorized medical marijuana use.
5. used for illness identified by the IOM and CMA to be appropriate for this treatment protocol, such as terminal illness, intractable pain, chemotherapy induced nausea and vomiting, and AIDS wasting syndrome. Illnesses such as anxiety disorders and mood disorders would not be acceptable as appropriate for this type of treatment.
6. if approved by a physician, medical marijuana authorization should only be provided after a good faith medical exam and an exploration of all other alternatives has been exhausted.

Because THC and other cannabinoids do have medical value when isolated in a pharmaceutically pure form, formal clinical studies are being conducted to discover effects, side effects, drug interactions and importantly, contraindications for use.

The collection of essays that comprise this book offer the reader a comprehensive review of how neuroscience research has cast new light on the function of the human endogenous cannabinoid (EC)

system and how cannabinoid-based medicines will be of significant therapeutic value in the not-so-distant future.

Just as nicotine is not tobacco, or taxol is not yew tree bark, and digoxin is not foxglove, cannabinoids are not marijuana. By using powerful new research tools, the varied functions of the EC system are being elucidated and the potential for the development of novel new medications is now being described. And, as the reader will discover in the chapters ahead, we are clearly moving beyond the limitations and problems associated with medical marijuana and moving more toward cannabinoid-based medicines.



# INTRODUCTION

## Cannabis: An Historical Perspective

Donald Avoy, M.D.

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It can truly be said of our planet that the only constant is change. Species come and go. Some are obliterated by predators, others by changing conditions that diminish or remove sources of nourishment, or habitat. New species appear, better suited, at least temporarily, to the current environment. And so it proceeds.

In selecting cannabis as a project, we are peering into a history that goes back as least as far as the end of the second Ice Age. As Jared Diamond, the celebrated author and archeologist puts it, “At that point everyone (and every species) began at the same starting line. We can follow that history up to the present. We don’t know how many species that survived the Ice Age were subsequently erased by the forces of competition. But we do know, from artifacts, that the plant we call *Cannabis sativa* was present 12 thousand years ago, at the end of the ice age.

The issue to be explored here is the relationship of this plant with our species i.e. how it has been assimilated into different, disparate cultures. That we are still using, and discussing it, strongly implies a complex, varied and powerful relationship. This survey will review the ways in which various cultures and societies have incorporated the hemp plant.

Obviously, the more uses a plant has in any culture, the more likely it is to be sustained, protected and shared with other societies. One important aspect in determining the size of its footprint on the planet is how well it survives in various climates and soils. Some species survive well although they have restrictive requirements for temperature, rainfall, and growing season, such as those plants that survive only in the tropics or in surroundings, which mimic the tropics. Not so the hemp.

In the early history of our species, an important transition was gradually accomplished as tribes learned to domesticate plants and animals, which permitted them to establish fixed habitats rather than following the herds and the seasons. By first observing which plants the herds relied on, and then experimenting with other available species, they were able to gradually accumulate a tribal wisdom about which plants were safe and which were not. They then learned how to separate and cultivate the seeds and to use the fibers of certain plants by twisting them into strands that could be woven into nets, or cloth. And that, presumably, was the way it all started.

### Botany

*Cannabis* is one of the plants in the family Cannabaceae, which also includes hops. It is an annual and is considered to be an herb. The genus *Cannabis* is made of a single species, *Cannabis sativa* with two subspecies, *indica* and *sativa*. It is a very hardy plant, and under favorable conditions of sunlight and irrigation can grow to twenty feet tall during a single growing season.

All varieties produce the chemicals known as cannabinoids. There are sixty-six different such compounds which have been identified. The most powerful psychoactive substance is delta-9-tetrahydrocannabinol (THC).

Cultivation strategies are designed to emphasize that portion of the plant that provides the desired substance. For example, growing the plants in a very crowded pattern will induce the production of very fine fibers which can be woven into a fabric resembling silk. To produce high concentrations of THC, plants must be given room to develop the stems that will in turn support the substructures that produce it. Left to its own self-expression, cultivated *Cannabis* will “escape” to a wild form which is more suitable to making hemp, but which is much lower in THC concentration.

*Cannabis* plants are dioecious, having separate male (stamens) and females (pistils) usually on separate plants, but in some cases on the same plant. The long, strong stem contains the valuable fibers that have been used so widely and for so long by many cultures. The

plants that are cultivated for their hemp potential are harvested before flowering takes place. The quality of the fiber is diminished if the plants are allowed to flower. Those strains that are selected for fiber quality produce only very low quantities of THC.

Those strains which are cultivated for their THC production are separated by sex, selecting only the female plants which are then protected from the males to prevent pollination. If fertilization occurs, much of the energy of the plant is diverted into seed production at the expense of THC.

Through the techniques of hybridization and cloning, strains of cannabis can be produced that synthesize high levels of THC. The sites of synthesis are the glands which are present on the leaves, stems and bracts, the small, reduced leaves that are located just below the flower. The flowers themselves do not have glands. Another method of increasing THC secretion is to manipulate the plant's exposure to light. During the first months of the plants growth, long days with strong sunlight will stimulate the growth. However, continued uninterrupted sunlight will impair flowering. To maximize the production of THC uninterrupted periods of darkness are required.

### Structural uses---Hemp

Hemp fiber is known as *bast*. It forms between the interior bark which lines the central hollow cavity, and the outer woody bark which gives the stalk its strength. A combination of physical, chemical and muscular work is necessary to separate the fiber from the rest of the plant. Historically, it has been worth the effort because the plant is very hardy and grows rapidly. It is virtually impervious to the intrusion of weeds and it produces two and a half times as much fiber as cotton and six times as much as flax per acre.

The fibers grow in the circular ring of vascular cambium, which contains the xylem and phloem, the transport network that directs water and minerals upward to the growing leaves and stems, and the fruits of photosynthesis and metabolism back down to nurture the growth of the plant. After the mature plant is harvested, the bundles are placed in a liquid medium that will permit microorganisms to

reduce the lignins and permit separation of the fibers. This process is known as “retting” (from rotting). This process has been supplanted by steam and mechanical methods that can diminish the cost of labor in those countries, which have made a commitment to large scale production of hemp products.

The final step in separation of the fibers from the woody parts of the stem is called “breaking” and consists of using heavy force to break away the woody residue. One method involved using heavy boards, another using wooden hammers.

### Historical Uses

Archeologists unearthed the remains of an ancient village on the island of Taiwan, off the main coast of China that has been carbon dated as ten thousand years old. Pieces of primitive pottery were found to have remnants of twisted cords of fiber which had been pressed into the clay. Those fibers were hemp, or cannabis. So, also, were the remains of woven garments. This all-giving plant was also used as a food source. Though not as important as mullet or rice, the seed of the plant were a major food source.

There was also a military use for the plant. It was found that bowstrings made from hemp fiber were far superior to those made from bamboo fiber. Realizing this, monarchs set aside fields in which to cultivate the plant.

Much later, in 105 A.D., the Chinese discovered that if hemp fibers were crushed and put in a tank of water with crushed mulberry bark, a crude membrane was formed. When dried, it could be used to write on. Until then, writing had been mostly done on silk, which was very expensive. Centuries later, the Moors learned the secret and began to make paper when they occupied southern Spain.

The Romans used hemp to make the stout ropes for hauling heavy materials along the roads that connected their far-flung empire. They also used it to make sails for their sturdy ships. When they invaded England in the second century A.D., they decided not just to import the finished products, but began to cultivate the cannabis in England

Remnants of hemp ropes have been found in Iceland, carried there by the Vikings who were seeking other places to locate their homes. Cannabis seeds and cloth made of hemp have been found on Viking ships that have been dated to the 9<sup>th</sup> Century.

The Italians were also a formidable sea power during the medieval period which made hemp a very valuable commodity. They were unwilling to rely on foreign supply and so they developed a vigorous agricultural support close to the important seaports such as Venice. In fact, competition developed between different seaports such as Venice and Bologna for which area could be made to cultivate and spin the finest hemp products. By this time, the more skilled weavers had refined their craft to produce fine fabrics for high fashion.

Throughout medieval times, small villages had their fields to grow hemp, again for making not only clothes, but also sheeting and blankets. In the larger towns, silks and satins were available to the wealthy but not to the common folks.

In the 15<sup>th</sup> and 16<sup>th</sup> Centuries, when the European exploration of other lands was in full flower, hemp rode the waves on the ships of discovery from Spain and Portugal to the New World. When England became a major naval power after the defeat of the Spanish Armada in 1588, hemp became extremely important to its success. The English were having to pay high prices for hemp being grown in Eastern Europe and Russia.

In the 17<sup>th</sup> Century, England decided she wanted to partake of the riches of the New World. Watching Spain and Portugal shipping back their gold and silver from South and Central America whetted their appetite. The new Stuart dynasty was convinced that the way to accomplish this was to license companies to establish colonies franchised to share their profits with the crown.

The colonists quickly realized that there were no easy mineral riches to be had. In 1611, the Jamestown colonists received royal word that they were to begin cultivating hemp that was needed in the mother country. By 1616 the crops were beginning to look promising, but the

colonists had also begun to plant tobacco, which was spectacularly profitable. Ignoring the crown, they chose to grow tobacco.

Hemp was successfully grown in the Maryland and Virginia colonies, but little of it ever reached the British Isles. There was a burgeoning trade business in New England and the merchants wanted, and were willing to pay a good price for the hemp.

Massachusetts and Connecticut colonies also mandated the cultivation of hemp, and because of the growth of the shipping and fishing industries they were able to develop robust local markets. Ropewalks began to appear. By the time of the revolution, Boston had fourteen.

There was another problem. The tenets of mercantilism held that the colonies were supposed to supply raw materials to the mother country that would, in turn, supply finished products that would be sold to the colonists. The problem was that the colonists had no money to buy the finished products, so they began spinning and weaving the hemp and flax fibers into the clothing they so desperately needed. As the prospect of the revolution became a certainty, the need for local production of tents, cordage, uniforms, knapsacks and other necessary soldierly equipment, plus the ropes and sails need by the navy became essential, as did planting and cultivating hemp.

George Washington and Thomas Jefferson both planted hemp and urged their fellow farmers to do the same. The first draft of Jefferson's Declaration of Independence was done on hemp paper.

In the 19<sup>th</sup> Century, cotton became the principal crop in the south and hemp was used to bale the cotton. The Civil War interrupted the cotton success and the hemp cultivation suffered a blow from which it never recovered, although it continued to have some success in the states of Kentucky, Missouri and Mississippi.

World War I stimulated a brief period of hemp prosperity, but it was brief and concerns about marijuana use proved to be its final death knell in the United States.

## The Current Worldwide Situation

Textiles. Only a small portion of the world's textile production is currently derived from hemp. Flax is the only plant fiber that is currently widely used and it only contributes about 3% of the world market - three times as much as hemp. Because of its ability to keep labor costs low, China currently maintains the dominant position.

Paper Products. With current concerns about the long-term effects on forests throughout the world, and the secondary effects on erosion, there has been interest in considering hemp as a more ecologically satisfactory alternative. In addition, the chlorine bleach that is used to process wood pulp is not environmentally friendly. However, some studies have shown that it would be far more expensive than wood pulp, which has limited its use for some products. On the other hand, some technical filters, art paper, teabags and bank notes are being produced from hemp in Europe.

Construction products. Europe is also incorporating hemp fiber into insulation materials and into concrete to increase its tensile strength. Automobile manufacturers in Europe are blending hemp with plastics which are used to mold certain panels for their cars. The fiber makes the plastic more flexible and impact-resistant, qualities that are desired in door panels and dashboards.

Miscellaneous. The oil extracted from hemp seeds has been used in cosmetics. When the oil has been extracted, the remaining oil-poor seed cake has been used as feed for livestock. Those countries that allow this do so only after inspections verify the lack of THC in the feed.

Overall, there is enough commercial interest in many countries, including Australia, Canada and Japan, to justify the expense of studies that are designed find a way to produce a gland-free variety that would eliminate the THC concerns.

## Medical and Other Uses

In preparing an outline for this presentation, the author considered different sections for a historical survey of medical uses and a separate

one for the psychiatric/recreational uses. However, the reality does not support such a separation.

In dealing with ancient societies and cultures, it quickly becomes apparent that divisions that are relevant to our current society do not apply. Distinctions that would be appropriate for current use would have absolutely no meaning. What was real were the processions of the sun and moon, the seasons and the need to provide food and shelter.

In the selection of plants to be used as food, the safest method was to follow the experience of the herds. The animals were the most reliable “tasters”. If they did not get ill, chances were the plant was safe. Adventures in such selections could be rewarded with wonderful results. They could also result in death, which would be ascribed to the unfortunate reality that the selected plant was proscribed by the gods, and insulting or defying the deities was obviously being punished by illness and/or death. And so the experiences of the individuals became the wisdom of the tribe, passed on from generation to generation.

Which introduces the conceptual framework for “illness” in general. While the healthy state of being was presumed to be a reward for a correctly lived life, illness was believed, generally, to be either the result of the displeasure of the gods, or the invasion of evil spirits. In either case, to terminate the suffering required the intervention of a special person, one who could communicate with, and perhaps command, the spirits that were involved. Such persons were extremely powerful. In fact, they were often on a par with the Chief of the tribe, who relied on the imprimatur of the priest, or shaman to maintain his power. The people had to believe that the chief had the assent of the gods to maintain power, and the one person who could vouch for that assent was the shaman.

Medications and potions were not just prescribed and handed over to the afflicted. They were presented in a somber ritual which enhanced the spiritual dimension of the illness and its treatment.

In the following sections, examples of the history in several different regions will be discussed. These examples are not intended to be exhaustive, but rather illustrative.

## China

Chinese medicine illustrates the manifold utility of the hemp plant. The woody stem could be carved and used as magical wand during medicinal ceremonies.

The father of Chinese herbal medicine was Shen-Nung, who compiled a pharmacopeia in 2737 B.C. He advocated the use of hemp in a variety of illnesses including gout, malaria, rheumatism, constipation, absent-mindedness and female disorders. Hemp was often used with a variety of other substances that were usually blended into a beverage that often contained wine.

In more recent times, Chinese herbalists, included hemp as an important compound in the therapeutic approach to such diverse afflictions as poisoning, complications in labor, hemorrhoids, and scorpion bites.

But as in all aspects of life, the maintenance or achievement of celestial harmony was the fulcrum of Chinese philosophy. This often called for acupuncture or massage in addition to the herbal potion. The harmonious state sometimes included attention to alleviating constipation, and improving sexual function. The herbalists were aware that excess amounts of the resin from the plant could cause hallucinations and gait disturbances. When used solely for pleasure it was often combined with opium.

## Greece and Rome

In the *Odyssey*, Homer provides a description of the effects of Nepenthe, and elixir introduced by the Egyptians to banish unhappiness. Helen, the wife of Menalaus, is the hostess at a dinner at which one of the guests is Telemachus, the son of Odysseus. Missing his father, and beset by the insistence of numerous suitors for his mother's hand, Telemachus is in a sour mood, which spreads to the rest of the guests. Concerned, and determined to repair the mood of

her guests, she adds some ingredients to the wine. After ingesting the potion, a cloud of happiness descends on the guests, whose sorrow is forgotten, at least for the time being.

The precise formulation of Nepenthe has never been discovered, but it has been variously attributed to the effects of opium, henbane, belladonna and cannabis.

Democritus (c.470 B.C.) described a substance that caused excessive laughter and hallucinations, which followed smoking of an unknown substance.

Seers and oracles would use trances to put themselves in communication with the gods. Cannabis may have been among the ingredients, which made these important communications possible.

In Rome, Pliny the Elder in the first century A.D. described some of the virtues of the hemp plant, including its utility in making rope. He also described its use in extracting worms from the ear canal, and its value in arthritis, gout and diarrhea.

### The Middle East

As mentioned above, the Egyptians employed the use of substances to achieve cures for certain ailments. They had a hieroglyph for the hemp plant. Remnants of the plant have been found in ancient crypts and tombs suggesting a role in Egyptian burial rites. There is also evidence that it was used topically for certain ocular diseases and vaginal infections.

The Sumerians also used potions in their exorcisms of the evil spirits presumed to be responsible for certain illnesses. Similar to the Egyptians, they employed potions containing vegetable and fruit juices combined with opium, hemp, mandrake and henbane. Hemp was also used in incense as an inhalant.

### India

For the Hindus, the legends of one of their most important gods, Shiva, includes his discovery of the hemp plant, which resulted in his being known as “The Lord of Bhang”. Bhang is a liquid refreshment

containing some fourteen ingredients including cinnamon, cloves and cannabis. But there is more.

Another beverage contains shredded flowers and upper leaves from the hemp plant. It is more potent than bhang and is called ganja. Most potent is Charas, which contains the resin well known as hashish.

Arabic medicine by the middle ages was well grounded in the ancient writings of Hypocrates, Dioscorides, Pliny and Galen. One of the mainstays of the Arabic pharmacopeia was “theriac”. It contains multiple components including hemp, snake meat, opium, herbs and spices. It was considered to be a universal antidote and panacea.

In contrast with the Hindu religion, the Islamic religion forbade the use of cannabis. However, a secret order, the Sufis, involved its members in experimentation with psychoactive substances including mushrooms and hemp. Islamic physicians did use non-inebriating hemp for earaches, as a diuretic, and an appetite stimulant.

### Germany

Hemp seeds were found in Thuringia and dated to the Stone Age. There is some evidence that cannabis may have been included in burial ceremonies as early as the 5<sup>th</sup> century B.C.. Known as “hanef” (also a common male name), it was grown with other common crops. The fiber was incorporated into household use and the plant was used in annual ceremonies welcoming the return of spring that had strong erotic content.

In medieval times, Hildegard von Bingen, was a Catholic mystic who became famous as a seer, visionary, physician, and, to some, a saint. In her writings she described her use of hanef. She encouraged its use by healthy people to promote “remaining wholesome”, and making the good humours strong while diminishing bad humours. However, she cautioned that its use might cause headache.

However, the widespread use of the substance by midwives led to suspicions and allegations of witchcraft. In 1484, Pope Innocent VIII issued his “Witches Bull” which forbade the use of cannabis, perhaps the first anti-cannabis legislation.

Homeopathy is an alternative medicine founded by Samuel Hahomen in the 18<sup>th</sup> Century in Germany. Its practitioners believe that if they administer a diluted mixture containing a substance that produces the same symptoms as the illness, they can achieve a cure. The homeopath introduces serial ten-fold dilutions sequentially to the patient.

It should be remembered that this concept was introduced at a time when blood-letting, enemas and purging were the cornerstones of “conventional” medicine. Hahneman published his book of *Materia Medica Pura* in 1840 including treatment for sixty-five conditions. He and his colleagues found over forty pages of symptoms for which cannabis was useful, including asthma, nightmares, sexual exhaustion and nervous disorders. They found it particularly effective in respiratory and urogenital illness. Hemp was also a contributor to the folk medicine traditions in central and South America as well as in Africa.

In the 19<sup>th</sup> Century, William O’Shaughnessy, an Irish physician working with the British Health service in India, began reporting his successes with cannabis, including a report of its efficacy.

In France, a psychiatrist, Jacques Joseph Moreau, also known as Moreau de Tours, wrote of his experience with cannabis and its effects on the central nervous system, madness and dreams.

### Summary

A companion of our species for many millennia, cannabis has served us well in many ways and still finds a variety of uses in the early 21<sup>st</sup> Century. That it is currently finding its way into the dashboards of automobiles and walls of buildings is a remarkable statement of its eagerness to please.

Its role in medicine is more troubled. Currently outlawed in many countries, it has not been established as a safe, effective contributor to our armamentarium despite the many pages of testimonials that have followed it through the ages (many perhaps written on hemp). While in this country there are many advocates of the use of the plant for

some specified conditions, the only approval by the FDA has been for the synthetic cannabinoid Marinol (dronabinol) for cancer patients and subsequently for the wasting syndrome associated with HIV infection. The plant and its extracts are still listed in Schedule I indicating a high liability for abuse, and no clear medical utility. Whether or not different formulations such as inhalants will make it acceptable to the DEA remains to be seen.

All this should be viewed as “prelude”. As will be presented by the authors following, we have entered a new and exciting era ushered in by the discovery of cannabinoid receptors. Molecular scientists both in botany and in neurophysiology and neuropharmacology have begun an exciting new discourse about the role of this plant and the molecules it produces.



## Marijuana and Medicine: The Need for a Science-Based Approach

Nora D. Volkow, M.D.

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Marijuana is not just a single drug—it is a mixture of dried flowering leaves from the hemp plant *cannabis sativa*. It contains more than 400 chemicals. Over 60 of these chemicals are referred to as *cannabinoids*. Delta-9-tetrahydrocannabinol or (THC) is the main psychoactive cannabinoid or ingredient in marijuana and the one that causes intoxication.

Scientists have learned a great deal about how THC acts in the brain to produce its many effects. When someone smokes marijuana, THC rapidly passes from the lungs into the bloodstream, which carries the chemical to organs throughout the body, including the brain. In the brain, THC connects to specific sites called cannabinoid receptors on nerve cells and thereby influences the activity of those cells. Some brain areas have many *cannabinoid receptors*; others have few or none. Most cannabinoid receptors are found in the parts of the brain that influence pleasure, memory, thought, concentration, sensory and time perception, and coordinated movement. Recently researchers have also found that cannabinoid receptors are found outside the brain. The newly discovered cannabinoid 2 receptors, for example, are found mostly in areas associated with immune function.

### Health Effects of Marijuana

There are numerous deleterious health consequences associated with short and long-term marijuana use, including the possibility of becoming addicted. During the period of intoxication, marijuana disrupts short-term memory, attention, judgment, as well as other cognitive functions. In addition, marijuana has also been shown to impair coordination and balance, and can increase an individual's heart rate. Longer lasting cognitive deficits have been reported in heavy marijuana users, although these have been shown to be reversible following a period of sustained abstinence. New research published last year shows that those who engage in a lifetime of heavy marijuana

use reported an overall dissatisfaction with their mental and physical health as well as their life achievement.

Recently we have learned that there is in fact a marijuana withdrawal syndrome that can last several days to a week following abstinence. This syndrome is characterized by increased anxiety, increased drug craving, sleep difficulties, and decreased appetite. It is very similar to the withdrawal that many users report after abstaining from nicotine and may explain why quitting marijuana can be difficult for some.

New research is also showing us that marijuana can affect almost every organ in the body, from the central nervous system to the cardiovascular, endocrine, respiratory/pulmonary, and immune systems. Because marijuana is typically rolled into a cigarette or "joint" and smoked, it has been shown to greatly impact the respiratory system and increases the likelihood of some cancers. Marijuana users typically inhale more deeply and hold their breath longer than tobacco smokers do, exposing them to the 50 percent to 70 percent more carcinogenic hydrocarbons than tobacco smoke has. Also, animal studies show us that THC can impair the immune system's ability to fight off infectious diseases thus increasing the likelihood of adverse health consequences. In humans however, the overall effect on the immune system is not clear. One clinical study on short-term exposure (21 day) to marijuana cigarettes in HIV-infected adults who were on a stable antiretroviral regimen did not find an effect of marijuana on the immune system in this population. Whether marijuana exerts significant immune effects when administered over long periods of time has not been studied.

Also, we are finding that early exposure to marijuana is associated with an increased likelihood of a lifetime of subsequent drug problems. A study, published in 2007 in the Journal of the American Medical Association of over 300 fraternal and identical twin pairs, who differed on whether or not they used marijuana before the age of 17, found that those who had used marijuana early had elevated rates of other drug use and drug problems later on, compared to their twin who did not use marijuana before age 17.

Finally, there are also some known subtle effects associated with children born to mothers who used marijuana frequently while pregnant. An ongoing longitudinal study that has been investigating the consequences of prenatal exposure to marijuana, for example, recently published results in this now adolescent aged population and found that prenatal exposure was associated with worse performance on tasks that required visual memory, analysis, and integration.

#### Research on Medical Uses of Marijuana: Two Significant Reports by the NIH and IOM

Marijuana is currently listed as a Schedule I drug. Schedule I under the Controlled Substances Act means that the drug has a high potential for abuse and that there is no current accepted medical use in the United States. However, there continue to be claims about the potential medical uses of marijuana, particularly smoked marijuana. THC, the main active ingredient in marijuana, produces effects that can be useful for treating several medical conditions. Several early studies supported by NIH to examine claims, for example, that marijuana relieved the nausea and vomiting accompanying cancer chemotherapy, have in fact led to the FDA approval of a synthetic form of oral THC for nausea associated with cancer chemotherapy.

More recently, the FDA has approved oral THC for treatment of AIDS wasting. There have been at least two exhaustive and comprehensive reports written in the past decade regarding the medical potential of marijuana by the National Institutes of Health (NIH) and the Institute of Medicine (IOM). In February 1997, the NIH convened a panel of eight non-federal experts in fields such as cancer treatment, infectious diseases, neurology, and ophthalmology for a two-day meeting to examine the extant research on the medical uses of marijuana and its active constituents, primarily THC. In 1999, the Office of National Drug Control Policy commissioned the IOM to do an exhaustive study as well. "Marijuana and Medicine: Assessing the Science Base" was published in 1999. Both reports found that there are too few scientific studies to determine marijuana's therapeutic utility, but that research is justified into marijuana's use for certain conditions or diseases including pain, neurological and movement disorders, nausea in

patients who are undergoing chemotherapy for cancer, and loss of appetite and weight (cachexia) related to AIDS.

The reports noted that there is greater promise in purifying the active constituents of marijuana and developing alternate delivery systems, such as inhalers, rather than studying smoked marijuana. The reports also noted that alternative FDA-approved medications already exist for treatment of the majority of proposed uses of smoked marijuana. For example, synthetic oral forms of THC, the major active ingredient in marijuana, have been approved by the FDA for use by patients undergoing chemotherapy and by patients with AIDS.

#### Facilitating Research on the Medical Uses of Marijuana

Additional research on the possible medical uses of marijuana and its constituents has continued since these reports were issued. The NIH has continued to accept proposals to investigate potential therapeutic uses of marijuana through its peer review process, and those that are scientifically meritorious have been considered for funding. Since the Reports by the IOM and NIH have been written, there have been two studies that have been supported by the NIH. One study looked at the effects of smoked marijuana on HIV levels and appetite and reducing weight loss associated with HIV-related wasting syndrome. Another ongoing study is looking at the effects of THC (smoked marijuana and oral) in individuals who have the human immunodeficiency virus infection (HIV+) with unintended weight loss (<90 percent body cell mass/height). In addition to studying food intake and body composition, they are also studying mood and physical symptoms (e.g. nausea stomach pain), psychomotor task performance and sleep to determine the specificity of the drug effects on food intake in relation to other behaviors.

In May 1999, the Department announced it would create a new mechanism to provide research-grade marijuana not only for NIH-funded research but also for scientifically valid research that is funded by other sources. A multi-agency Public Health Service (PHS) committee now reviews non-NIH funded studies and assesses them both for scientific quality and the likelihood that they will yield data on possible benefits.

After the PHS committee approves a study, the researcher applies for an Investigational New Drug Application (IND) from the FDA and must also obtain a DEA registration number for Schedule I substances. When these are obtained, NIH provides research-grade marijuana for the project on a reimbursable basis (researchers reimburse NIDA's contractor for the costs of growing and producing the research-grade marijuana). Since NIDA's inception in 1974, it has been the administrator of a contract to grow marijuana for research purposes on behalf of the US government. In this way, NIH is able to produce and supply research-grade marijuana for a variety of clinical studies that would not otherwise be possible. Most of the research approved by the PHS committee so far is sponsored by the Center for Medicinal Cannabis Research at the University of California in San Diego, a state funded research center. Currently there are 17 pre-clinical or clinical studies that have been approved by HHS for this Center. Topics to be covered include cannabis for spasticity/tremors in multiple sclerosis patients, sleep disorders, CD4 immunity in AIDS, and for neuropathic pain. This represents a substantial increase in scientifically valid research studies involving marijuana.

### The Promise of Research

Researchers have made much progress in the past 15 years in understanding how marijuana exerts its effects. In fact, the support of basic research on marijuana led to the discovery of the endogenous cannabinoid system. Since 1988, scientists have discovered two major classes of cannabinoid receptors, one that is mostly found in the brain, "CB1," and "CB2," which is not in the central nervous system and is predominantly found on immune system cells. This cannabinoid system is involved in a number of physiological functions, including pain regulation, appetite, movement and motor function, memory, as well as its role in marijuana's abuse liability and addiction.

These breakthroughs have led to research advances and medicinal developments at a rapid pace. The presence of this newly discovered receptor system in the brain circuitry controlling learning and memory is yielding new insights into how marijuana disrupts memory traces. Additionally, recent research shows that there are connections between the cannabinoid system and the neuronal processes connected with

relapse to cocaine abuse, lending further support to the commonality in the brain processes mediating addiction.

The discovery and characterization of the cannabinoid receptors has allowed scientists to begin to develop potential medications to treat a variety of ailments, including obesity, pain, and addictive disorders. In 1994, researchers produced the first CB1-specific cannabinoid receptor antagonist, SR141716, (now called Rimonabant) which is able to block THC's ability to activate the CB1 receptor. Preclinical and clinical research suggests that Rimonabant blocks the subjective high elicited by marijuana and may also be useful in preventing relapse to other drug use. Two large clinical trials supported by the pharmaceutical industry also have found that Rimonabant may help people lose weight and stop smoking.

Today marijuana-related research continues to yield valuable insights into the effects of THC on critical brain functions, such as cognition and memory, the role of the drug's receptor system in addiction and relapse, as well as insights into the treatment of marijuana addiction and the potential role of cannabinoid-based medications in treating a variety of medical conditions. Finally, these insights are leading us to an overall greater understanding of neurobiology, memory, and immunity. They also provide us with proven strategies that can be employed to help us elucidate other systems.

## Conclusion

Marijuana is not a benign drug. It is illegal and has significant adverse health and social consequences associated with its use. Given the fairly recent discovery of the endogenous cannabinoid system and the tremendous science advances that followed, the development of useful cannabinoid-based medicines is an important area of investigation that should prove fruitful for a variety of health conditions. However, the use of smoked marijuana as a medicine is problematic due to its adverse health consequences and the inherent difficulties with respect to accurate dosing and the purity of the formulation. Approval for the use of marijuana, or perhaps more importantly purified compounds based upon the chemicals found in marijuana, as therapeutic agents must show substantial evidence of effectiveness and show the product

is safe under the conditions of use in the proposed labeling. Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

*From Dr Volkow's presentation before the House Committee on Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources United States House of Representatives. April 1, 2004*



## The Endocannabinoid System

Maximillian Peters, B. Pharm Msc.

Raphael Mechoulam, Ph.D.

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Although Cannabis preparations had been – and still are - the most widely used illicit drugs in many parts of the world for centuries, their chemistry, was not well known until the mid 1960s. The psychoactive Cannabis constituent had not been isolated in a pure form, its structure (or structures, as it was generally assumed that there are numerous psychoactive constituents) had not been elucidated. This was in sharp contrast with the knowledge on morphine and cocaine, the two other major illicit drugs, which already had been isolated during the 19<sup>th</sup> century, and whose chemistry, biology and therapeutic effects had been investigated for many decades. The reason for this disparity was presumably technical. Morphine and cocaine are alkaloids, which can easily be converted into crystalline salts, derivatives which are easy to separate and purify. By contrast, 19<sup>th</sup> century research showed that extraction of hashish or marijuana with various solvents led to a mixture of compounds, which together showed 'Cannabis' activity in animals, but could not be separated. Pharmacologists do not like to work on mixtures as the results obtained are qualitative only and seldom fully reproducible.

Roger Adams in the US and Lord Alexander Todd in the UK did important chemical work in the 1930s and early 1940s, but the separation methods available at that time were not suitable for identification of the constituents, including the active ones. Over the next 20 years very little work was reported on Cannabis, as laws, particularly in the US, made research on Cannabis difficult to undertake in academic laboratories. In the early 1960s we initiated a Cannabis research project, which led to the isolation in pure form and the elucidation of the structure of the active constituent,  $\Delta^9$ -tetrahydrocannabinol (THC). Numerous additional plant cannabinoids were isolated and identified by our group and later by groups in Japan and Germany.<sup>1</sup>

The natural cannabinoids were assayed for psychotropic activity on rhesus monkeys: only THC showed potent activity. The rhesus monkeys became sedated and sleepy after an intravenous dose of 0.5 mg THC per kilogram bodyweight. None of the other constituents showed any activity except cannabiol, which was much less potent. When a mixture of the major constituents was administered to monkeys, all the activity could be attributed to THC alone.<sup>2</sup> This picture has not changed much over the last four decades.

In the body THC undergoes a rapid oxidation to produce initially hydroxylated products, one of which is as active as THC itself. Hence Cannabis activity is apparently due both to THC and to some of its metabolites. A further metabolite, an acid that has no THC-like activity, is formed and remains (attached to a sugar) in the body for many weeks. It is slowly excreted in the urine and can be detected by sensitive immunoassays available today up to 45 days after smoking marihuana.<sup>3</sup>

The first synthesis of THC was reported over 40 years ago by our group. Since then other synthetic approaches have been taken and for many years synthetic THC has been available and has been the object of thousands of pharmacological, biochemical and clinical trials.

THC is an approved, orally administered drug against nausea and vomiting caused by cancer chemotherapy. Unfortunately, at the doses required to suppress these effects some of the patients report side effects, mostly mood changes. Therefore use has remained limited. A much larger number of patients seem to smoke Cannabis, which acts rapidly and which is claimed to cause fewer side effects than oral administration.<sup>4</sup>

The reason why the plant *Cannabis sativa* spends energy for the production of its unique cannabinoids is still a scientific mystery, but we can surely assume that it is not for the sake of human therapy or mood. Most probably the plant cannabinoids disrupt some (yet unidentified) biochemical system in plant enemies, thus serving as a protective agent.

Although the chemistry of Cannabis was mainly elucidated in the 1960s and 1970s and over the next two decades we learned much about its neurochemistry, neurophysiology and overt behavioral effects, the molecular basis of THC action remained an enigma. It was mostly believed that cannabinoids alter the membrane of cells and exert their effects in this way. But the possibility remained that THC actually acts through an unknown receptor system, or by interfering with an enzyme. The first evidence that cannabinoids act through receptors was brought forward by Allyn Howlett's group in Saint Louis. Shortly thereafter a group at NIH cloned this cannabinoid receptor, which is now designated CB<sub>1</sub>.<sup>5</sup> A second, peripheral receptor (CB<sub>2</sub>) was identified in the spleen by a group at Cambridge, UK.<sup>6</sup>

In the 1970s it was found that morphine, the active principle in opium, which has been in use in medicine for millenia, mimics the action of endogenous mammalian constituents and modulates a specific system in the brain. This assumption led to the identification of the endogenous opioids, the endorphins (endogenous morphines). Following the same line of thought we assumed that the presence of specific cannabinoid receptors indicates the existence of endogenous cannabinoid ligands that activate these receptors. The fact that a plant constituent, namely THC, binds to these receptors could be viewed perhaps as a quirk of nature.

How does one identify an unknown natural substance as a molecule that activates a receptor (a receptor agonist, for short)? The best route is to label a molecule, THC in our case, with a radioactive atom, bind this molecule ("a probe") to the receptor and then try to find out whether brain constituents (or a brain fraction) will displace the probe. The displaced probe can then be quantitatively measured and will give an indication as to the presence of a constituent, which binds to the receptor by itself and has displaced the probe.

For various technical reasons THC itself is not suitable as a probe. However, a much more potent cannabinoid (named HU-243) was found to be suitable and was labeled with tritium. The probe, HU-243, was then bound to the brain receptor forming a HU-243-receptor complex.

To screen for endogenous cannabinoid compounds, we tested the ability of purified fractions from porcine brain extracts to displace HU-243. All plant or synthetic cannabinoids are lipid-soluble compounds. Hence the procedures employed for the isolation of endogenous ligands by our group were based on the assumption that such constituents are lipids, an assumption that ultimately proved to be correct. Porcine brains were extracted with organic solvents, and the constituents present in the extract were separated by chromatography, a method based on differences in the degree of absorption of molecules on certain materials, in our case silica.

A major problem encountered in the isolation of the putative endogenous cannabinoid was its lability: although purity increased on repeated chromatography, the amounts of activity diminished rapidly indicating that the active material was labile. Ultimately, under carefully monitored conditions we isolated a fraction that exhibited all the properties of a single compound on the basis of its behavior in various physical assays (mass spectrometry, for example). We assumed that it was a natural ligand for the cannabinoid receptor. The structure of the brain constituent was shown to be derived from arachidonic acid, a fatty acid used by the mammalian body to prepare numerous active components. We named the active constituent anandamide, based on the Sanskrit word ananda, meaning bliss, and on its chemical nature (an amide).<sup>7</sup>

The identification of a second cannabinoid receptor (CB<sub>2</sub>), some in immune system, led us to look for the presence of additional active endogenous ligands in the gut and later in the spleen, an organ with well established immune functions; again we used fractionation guided by a binding assay. Canine gut or mouse spleen was extracted with methanol, and the extract was chromatographed on a silica gel column (as we had done previously for anandamide) to yield a fraction that was found to bind to CB<sub>1</sub> and to CB<sub>2</sub>. The active fraction consisted of three compounds that, on the basis of physical measurements, were found also to be derived from fatty acids, with the compound based on arachidonic acid (chemical name, 2-arachidonylglycerol, or 2-AG in chemical shorthand) being the only active one. Later 2-AG was found by other groups to be also present in the brain.<sup>8</sup>

2-AG parallels anandamide in its activity, while the other fatty-acid-derived constituents present showed neither binding activity to the cannabinoid receptors nor cannabinoid effects in mice. However, these compounds potentiated the binding of 2-AG to the receptors and its potency in various tests. This effect, which we have named an "entourage" effect, may be of general importance. Biologically active natural products, from either plant or animal origin, are in many instances accompanied by chemically related, though biologically inactive constituents. Very seldom is the biological activity of the active constituent assayed together with the inactive entourage compounds. In view of the results described above, investigations of the effect of the active component in the presence of its entourage compounds may lead to observations of effects closer to those in nature than investigations with the active component only.

In most in vitro tests, as well as in animals, anandamide and 2-AG parallel THC: they inhibit motor activity, reduce body temperature and alleviate pain, affect certain types of memory, cause potent reduction of blood pressure, decrease intraocular pressure and increase appetite. Many of these effects can be blocked by a specific antagonist, named SR-141716A, which binds to one of the cannabinoid receptors but does not activate it.

Despite the cloning of the brain cannabinoid receptor and the identification of its endogenous activators, the biological function of this system was not clear. Based on the observation of human Cannabis users several fields were investigated. The anecdotal reports about impaired short-term memory and lack of motivation in chronic users, as well as an acute increase of appetite provided good starting points for laboratory experiments with animals. A huge part of today's knowledge on the endocannabinoid system is based on the observations of mice lacking the gene for the CB<sub>1</sub> receptor. Comparing these mice with their genetically unmodified relatives can teach us about the functions of the endocannabinoid system in the human body.

In order to better understand the endocannabinoid system and other neurotransmitter systems, one has to look at the chemical properties of

the neurotransmitters. One of the reasons why the endocannabinoid system was discovered only in the last twenty years, while other neurotransmitters, like acetylcholine, were discovered at the beginning of the last century, is its low water solubility. Other neurotransmitters are present in relatively large quantities in the human body and can easily be extracted and purified in research laboratories.

Endocannabinoids, in contrast, only exist in tiny amounts, have a low water solubility, are sticky and sensitive to a variety of environmental influences. Most of the neurotransmitters are derivatives of amino acids, while the endocannabinoids are derivatives of essential fatty acids like arachidonic acid. Neurotransmitters such as serotonin, histamine, norepinephrine are synthesized and stored in vesicles in the human body and are released when needed. Endocannabinoids on the other hand are either continually synthesized in very small amounts, in order to achieve a constant activity of the endocannabinoid system or synthesized from precursors when and where needed. The lipophilic character allows them to penetrate through lipid barriers in the body. This biochemical background is essential in order to understand the functions of the endocannabinoid system.

The first cannabinoid receptor to be found was the brain cannabinoid receptor (CB1), which is responsible for most, if not all, of the psychoactive effects of THC. It is the most abundant receptor in the human brain. The highest concentrations of cannabinoid receptors are in brain areas involved in memory formation (hippocampus), motor coordination (the cerebellum) and emotionality (prefrontal cortex). This is in good agreement with the effects of THC on human behaviour. But cannabinoids are not only active in the brain, but also exert various actions in the periphery, mainly affecting the immune and the reproductive systems.

A second cannabinoid receptor (CB2), found in 1992, is also activated by plant as well as by endogenous cannabinoids. It is mainly present on cells of the immune system and only under certain pathological conditions in the brain. Again the localization fits the effects caused by Cannabis consumption, namely alleviation of the symptoms of autoimmune diseases and as a potent anti-inflammatory drug.

In pharmacology molecules are classified as agonists and antagonists, i.e. molecules which activate or inhibit a certain receptor. In the case of the endocannabinoid system the issue is further complicated by the fact that the endocannabinoid system is a modulatory, inhibitory system rather than a basic system. Its putative role is to modulate other neurotransmitter systems by inhibiting them. The endocannabinoid system determines the activity of other systems, i.e. a highly active endocannabinoid system reduces the activity of other systems and vice versa. Depending on the nature of the inhibited system the global, observed effects may differ. Therefore depending on the disease and the physiological system involved either inhibition or activation of the endocannabinoid system may give beneficial effects in patients.

In the following we want to present some selected fields where the endocannabinoid system plays an important role in human health and disease.

#### Appetite, Food Intake And The 'Munchies'

Cannabis, regardless if it is used as a recreational or a medical drug, stimulates appetite and subsequently food intake. While this is a desirable effect in cancer or HIV patients, obesity is a major health concern in western societies. Giving the observed effects of Cannabis it was hoped that a cannabinoid antagonist, i.e. a compound which prevents the effects of cannabinoids, would prevent excessive food intake. Indeed the first described specific blocker of the brain cannabinoid receptor, SR141716A, developed by Sanofi is now marketed in Europe for the treatment of obesity under the trade name of Acomplia. Although the endocannabinoid system is not the only system in the human body responsible for appetite and food intake, blocking its activity in mice pups leads to their death by starvation.

Although perfectly healthy they refuse to suck milk from their mothers. In adult humans, endocannabinoids modulate food intake, but not as the sole player. Despite considerable weight reduction of obese patients in clinical trials and a substantial improvement of blood fat levels and abdominal fat, the Food and Drug Administration did not approve this drug because of an increased risk of enhanced anxiety and depression, as the endocannabinoid system is known to positively

affect these conditions. At the beginning it was hoped that this was a specific side effect of Acomplia, but it was later found that a different drug with the same effect on the endocannabinoid system also increased anxiety in human patients. Given the involvement of the endocannabinoid system in emotionality, it is not surprising that its blockade may cause mood instabilities.<sup>9</sup> It should be pointed out however that these side effects apparently appear mostly in patients that are already clinically anxious or depressed.

### Endocannabinoids And Drug Addiction

In 1991 it was observed that cannabinoids enhance the analgesic properties of opioids in laboratory animals. But is it possible that not only the beneficial analgesic properties, but also the addictive properties of morphine are enhanced by cannabinoids? The possible interaction between cannabinoids and opioids was scientifically backed, when in 1997 it was found that mutations in the gene encoding the cannabinoid receptor are associated with drug addiction in humans. Furthermore, when factors influencing the severity of heroin addiction were investigated it was found that simultaneous consumption of heroin and marijuana enhanced the chances of relapse.

Although there were several indications that the endocannabinoid system may be involved in drug addiction, a significant proof was still needed. This was achieved in 1999 when mice lacking the brain cannabinoid receptor were created for the first time and this phenomenon was investigated in greater detail. Mice without cannabinoid receptors were totally unresponsive to THC, while morphine showed normal acute effects. The short term effects like analgesia were thus identical to those in normal mice, but the long term effects were different. The lack of cannabinoid receptors lead to a decrease in the severity of the morphine withdrawal as measured by several behavioural parameters.<sup>10</sup>

Based on the research of numerous groups worldwide one has now a better picture how the endocannabinoid system works in the brain of addicted humans. One of these neurotransmitter systems, the dopaminergic system, is one of the major players in the neurobiology of addiction. All substances (e.g. food, sweets, drugs of abuse) or

activities (marathon running, sexual activity) inducing a feeling of pleasure in humans and animals result in an increase of dopamine in certain areas of the brain, i.e. they are activating the reward system in the brain. This system is modulated by an inhibitory system, both for fine tuning of the resulting signal and to prevent excessive signals. In this case the endocannabinoid system apparently represents an inhibitory system of the inhibitory system, i.e. activation of the endocannabinoid system inhibits the inhibitory system and therefore increases the dopaminergic stimulus.

### Endocannabinoids As Stout Guards Of The Brain

The human body has developed numerous ways to counteract or ameliorate the effects of many (possibly most) diseases. The endocannabinoid system seems to be one of its protective tools. A good example is the production (on-demand) of endocannabinoids in closed head injury. In an animal model, after this kind of injury, the levels of the major endocannabinoid, 2-AG, in the brain are strongly enhanced. Further enhancement of the endocannabinoid system, either by administration of endocannabinoids or inhibition of their breakdown improves the outcome after such an injury<sup>11</sup>. The endocannabinoids thus play a protective role.

A related observation has been made in brain inflammation. While there are only small amounts of cannabinoid type 2 receptors in a healthy brain, the concentration of these receptors is strongly enhanced in certain neurological diseases, such as multiple sclerosis or Alzheimer's disease. Also the number of these receptors is dramatically increased in autoimmune diseases, such as inflammatory bowel disease. It is well established that in certain diseases the immune system causes inflammation, which is initially beneficial. However if the inflammation is prolonged or too powerful it may be deleterious. In such cases an increase of the tone of the endocannabinoid system can modulate the inflammation by action on the immune system and thus prevent excessive damage.

### Endocannabinoids and Memory Extinction

One of the most common effects of chronic Cannabis abuse is an impaired short-term memory. At first this sounds like an unwanted

effect, but on the other hand it is desirable in human life to forget negative, traumatic events. In animal experiments it was clearly shown that mice without cannabinoid receptors needed more time to forget the association of a painful foot shock with a ringing sound than regular mice. But both mice strains were able to associate a pleasing reward with a specific place. THC apparently facilitates the extinction of negative memory, without taking away positive memories. When the breakdown of endocannabinoids is slowed down and therefore the endocannabinoid system is more active, animals tend to “forget” negative association much faster than under normal conditions. It is not a classic example of impaired memory but rather a relearning of associative behavior. Thus, the endocannabinoid system is involved in the extinction of aversive memory. This Cannabis trait may perhaps explain the desire of humans to abuse Cannabis in cases of post traumatic stress disease (PTSD). Unfortunately this effect has not yet been investigated in a well structured clinical setting<sup>12</sup>.

### Stone Bones and Stoned Heads

Cannabinoids and the skeleton are two things which are not generally associated with each other. But there is mounting evidence that the brain regulates bone growth and density. The association between depression and osteoporosis (a disease with increased risk of bone fractures and decreased bone density, commonly found in elderly people) is known since the early 1980s. Depression is a disease which causes chronic stress to the human body. Cells which are responsible for the formation of bones are inhibited by this kind of stress. On the other hand the endocannabinoid system inhibits stress. The process occurs in the brain as well as in the periphery. In this case the endocannabinoid system has a dual role, on the one hand brain cannabinoid receptor 1 modulates stress and on the other hand the peripheral cannabinoid receptor 2, present in bones, directly promotes bone growth. Mice without brain cannabinoid receptors have normal bone growth, but their bones react worse to stress. The lack of the peripheral endocannabinoid receptor causes impaired bone growth and density. Osteoporosis could be successfully prevented either by increasing the tone of the endocannabinoid system or by stimulation of the peripheral cannabinoid receptor (CB<sub>2</sub>). It is certainly of interest that although the endocannabinoid system was investigated and

discovered because of the psychoactivity of Cannabis, it is now found to be involved in such fundamental processes like bone formation.<sup>13</sup>

### Summary

Although initially, the presence of the endocannabinoid system in the brain was considered quite odd, in view of its association with the psychoactive effects of Cannabis, over the last few years it has become a major research field due to the plethora of effects caused by it. It is an essential modulatory and protective system, which allows the human body to adapt to various external and internal stimuli. The interest in this system is shared by physiologists, who want to understand the human body and brain, pharmacologists and medical researchers who want to treat diseases, as well as pharmaceutical companies that hope to successfully market drugs modulating this very system. While the immune systems protects us against bacteria, viruses and parasites it seems to be very unlikely that there is no such system to protect us against other kind of threats, such as head injury, osteoporosis or depression. The endocannabinoid system is certainly one such system.

The above analogy is true for some negative physiological effects. We desire a strong immune system in order to stay free of infections, but for some people the immune system becomes a threat, when the human body attacks itself or a minor injury causes a chronic inflammation. The endocannabinoid system prevents excessive reactions by other systems in the human body, but under certain conditions it may become a health threat. An immune system, which has gone wrong, may cause autoimmune diseases; likewise an overactive endocannabinoid system may cause obesity and negatively affect drug addiction. However both systems are generally protective ones and cause relief in a wide variety of diseases.

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## Toward Cannabinoid-Based Medicines

Mark Stanford, Ph.D.

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### Prologue

The therapeutic value of the cannabis plant has been referenced for approximately four millennia by a variety of sources and throughout different countries. While cannabis has been used medicinally for quite some time, it wasn't until rather recently that neuroscience research has discovered safer and more effective treatment possibilities. In the 1990s, scientists found and were able to replicate receptor-proteins located on the surface of cells that are responsible for many of the actions of  $\Delta^9$ -tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis (Devane, 1994, Mechoulam, 1995, Bayewitch, 1996.). This new understanding has allowed scientists to develop a foundation for a cannabinoid pharmacology that can provide the way for a more efficient therapeutic direction way beyond medical marijuana and toward cannabinoid-based medicines.

### Cannabis Naturally In the Human Body?

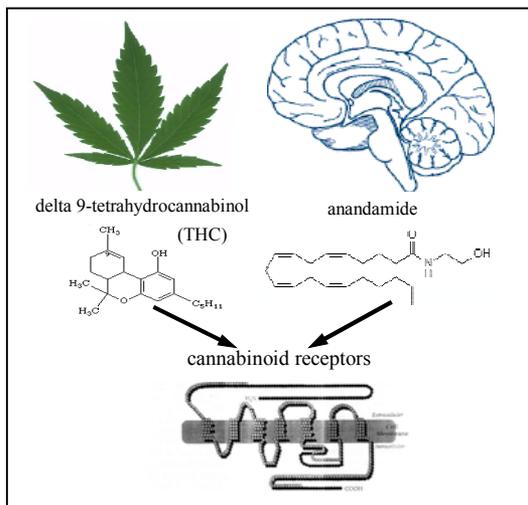
Well, sort of. In the way the body has its own natural morphine (endorphins), chemically similar to morphine from the opium plant, the body also has its own versions of chemical agents of the cannabis plant, called *endocannabinoids*. These chemical messengers help regulate processes of brain and body functions. Since science has now developed a more sophisticated understanding of the endocannabinoids, new medicines can be developed to treat a variety of health conditions including obesity, Type 2 diabetes, non-morphine analgesics, and addiction medicines, to name a few.

In the not so distant future, it is plausible to expect that neuroscience research will discover novel medicinal ways to facilitate changes within the endocannabinoid system that can further help treat other conditions, from addiction and alcoholism, to epilepsy, pain, anxiety, and depression.

## About the Cannabis Plant

The marijuana plant, *Cannabis sativa* (*C. sativa*), is both a widespread illegal drug of abuse and a recognized medicinal plant. One of the challenges for neuroscience was to isolate the active components of the plant associated with potential therapeutic uses and at the same time try to develop cannabinoid-based medicines without any adverse effects. After four decades of research, there is a much greater understanding about the pharmacology of plant-derived cannabinoid compounds (called *phytocannabinoids*) and how they relate to the endogenous cannabinoids within the human body (Mechoulam, 1995.).

*C. sativa* contains over 60 phytocannabinoids, some of which are bioactive - defined by their ability to target and activate specific receptors in the brain, the *cannabinoid receptors*. The best-known phytocannabinoid is  $\Delta^9$ -tetrahydrocannabinol (THC), the most psychoactive phytocannabinoid and the one that probably mediates the addictive properties of *C. sativa*. In the 1990s, the discovery of specific cellular receptors of THC revealed a whole endogenous signaling system now referred to as the *endocannabinoid system* (see figure below).



## Endocannabinoids

The Endocannabinoid System (ES) is a physiological system consisting of cannabinoid receptors and corresponding chemical messengers that is believed to play an important role in regulating body weight, glucose and lipid metabolism, pain, movement, cognitive functioning and even addiction.

The word, *endocannabinoid*, is a word condensed from two other words; *endogenous*: from within, and *cannabinoid*: substances resembling the components within the *C. sativa* plant. The two major endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). As their chemical names suggest, both are derived from arachidonic acid, which is also the precursor for the prostaglandins, which allows one to see the potential role of the ES in pain and inflammation treatments.

## Cannabinoid Receptors

Basically, the scheme of the ES begins with the endocannabinoids where they are released into synapse and bind to and activate distinct cannabinoid receptor. To date, 2 types of cannabinoid receptors have been identified; CB<sub>1</sub> and CB<sub>2</sub>. CB<sub>1</sub> receptors are found primarily in the brain and the CB<sub>2</sub> receptors are located mainly in immune cells and in peripheral tissues of the body in adipocytes (or “fat cells”) that are associated with lipid and glucose metabolism.

It is the CB<sub>1</sub> receptor that is presumed to mediate all the CNS effects of the cannabinoids. The number of CB<sub>1</sub> receptors in the brain is large, comparable to the numbers of receptors for the monoamines, serotonin and dopamine. The large number of CB<sub>1</sub> receptors, called *receptor reserve*, tells us how a partial agonist like THC is able to produce a response. Namely, the more receptors in the system, the greater the likelihood of an activator-inhibitor interaction. Signal transduction studies have revealed that THC is not a very strong partial activator.

The distribution of CB<sub>1</sub> receptors within the brain is rather heterogeneous, with the largest concentrations found in basal ganglia,

cerebellum, hippocampus, and the cerebral cortex. CB<sub>1</sub> receptor activation is particularly expressed in an area of the brain called the nucleus accumbens, a small subcortical area believed to be important in motivational processes that mediate the incentive value of food, and which may also play an important part in the establishment and maintenance of drug addiction.

CB<sub>1</sub> receptors are also integral in initiating food intake and, when activated, will stimulate the ingestion of food. Research indicates that endocannabinoids may play a role in appetite control. This is achieved by modulating the expression and release of appetite suppressing and appetite stimulating neurotransmitters in the hypothalamus region of the brain.

The CB<sub>2</sub> receptor is not expressed in the brain. It was originally detected in macrophages and is particularly abundant in immune tissues, where the largest concentrations have been detected in B-cells and natural killer cells. The functions of the CB<sub>2</sub> receptor in the immune system are less clear. Most of the research studies seemed to suggest that the cannabinoids are primarily immunomodulatory in nature. That is, depending on dosage, some immune cells are suppressed while others are stimulated.

### Cannabinoid-based Medicines

Significant advances came when scientists discovered ways to more efficiently modify endocannabinoid activity indirectly, thereby avoiding abuse potential and unwanted side effects associated with THC (Piomello, 2000. Pacher, 2003, Fowler, 2006). The most current pharmacological methods either decrease endocannabinoid activity by blocking the receptors where they exert their effect, or increase the action of endocannabinoids by inhibiting their breakdown, usually by blocking the enzymes that deactivate them.

As research progresses, scientists will be able to develop better approaches that will use the potential of the endocannabinoid system to treat more diseases and conditions. Cannabinoid-based medicines will more than likely act through the activity-inhibition mechanisms at selective cannabinoid receptor sites, through reuptake inhibition,

and/or by targeting the degrading enzymes responsible for endocannabinoids.

In addition to appetite stimulation and suppression of nausea and vomiting, possible therapeutic uses of cannabinoid receptor agonists would include treatment of:

- postoperative pain, cancer pain, and neuropathic pain;
- inflammatory disorders.
- metabolic syndrome (obesity, high blood pressure, increased triglycerides, Type 2 diabetes)

Of all these potential indications, analgesia has probably received the most research attention. There is an increasing amount of evidence showing that the cannabinoid receptor system is an analgesic system. Research into pain medicines is allowing scientists to measure the specific effects of cannabinoids on various pain pathways. This system appears quite distinct from the endogenous opioid system, which indicates there are different types of pain and that certain pain types not responsive to opioid drugs might be better treated with cannabinoid-based medicines. While there is no drug as of yet with a selective pharmacologic profile, there are several distinct chemical classes of compounds known to interact with the CB<sub>1</sub> receptor.

#### A Growing Formulary of Cannabinoid-Based Medicines

In the 1970s, Pfizer pharmaceutical company launched a cannabinoid research program that resulted in the development of a cannabinoid analog, *levonantradol*, which was 1,000 times more potent than THC. Clinical trials showed efficacy for postoperative pain and chemotherapy-associated nausea and vomiting; however, side effects (sleepiness, dysphoria, dizziness, thought disturbance, and hypotension) were judged to be excessive, and the project was discontinued.

Approved in 1985 by the Food and Drug Administration, Marinol (dronabinol), a synthetic oral preparation of THC encapsulated with sesame oil, was introduced for the treatment of chemotherapy-associated nausea and vomiting. Marinol was later approved for

management of AIDS-associated wasting and anorexia. It is also being studied for possible benefit in alleviating mood and behavioral changes associated with Alzheimer's disease. Marinol's usefulness is limited by the fact that it is poorly absorbed by the human body and its delayed onset of action.

Peak blood levels are not reached until 2–4 hours after dosing. In cases of intractable vomiting, the idea of swallowing anything, let alone a medicine pill, is not very realistic. Unimed Pharmaceuticals, which manufactures Marinol, and Roxane Laboratories, which jointly markets Marinol, are currently studying new aerosol, nasal spray, and sublingual formulations that may achieve a more rapid onset of action.

Developed by GW Pharmaceuticals, **Sativex** is a cannabis plant extract indicated for relief of symptoms of multiple sclerosis (MS) and for treatment of severe neuropathic pain. Sativex is administered by means of a spray into the mouth rather than smoked. The spray is composed primarily of  $\Delta^9$ -tetrahydrocannabinol (*Tetranabinex*) and cannabidiol (*Nabidiolex*), a nonpsychoactive cannabinoid with additional beneficial effects.

Both are extracts of chemically and genetically characterized *Cannabis sativa L.* plants and are delivered in a 2.7-mg/25-mg ratio, with each application being under the tongue or on the inside of the cheek. Although the mechanism of action is unclear, the product is thought to exert its action by acting on cannabinoid receptors distributed throughout the central nervous system and in immune cells.

In 2005, Health Canada began using Sativex as a buccal spray for adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

Clinical trials data from a double-blind parallel group study showed that the addition of cannabinoid-based treatment to existing opioid and other analgesic medication significantly improved pain relief relative to placebo in patients with cancer pain not responding adequately to

strong opioids. Furthermore, more than 40% of patients were able to achieve a clinically important reduction in pain.

In 2006 in the United Kingdom, **rimonabant** (Acomplia) was approved for use and is the first drug to target the endocannabinoid pathway by inhibiting the actions of anandamide and 2-archidonyl-glycerol on CB<sub>1</sub> receptors. Rimonabant blocks the central effects of the endocannabinoid pathway involved in obesity and weight control.

Blockade of CB<sub>1</sub> receptors leads to a decrease in appetite and also has direct actions in adipose tissue and the liver to improve glucose, fat and cholesterol metabolism so improving insulin resistance, triglycerides and high-density lipoprotein cholesterol (HDL-C) and in some patients, blood pressure.

The Rimonabant in Obesity (RIO) trials have shown that the drug induces weight loss >5% in 30–40% of patients and >10% in 10–20% above both a dietary run-in and long-term hypocaloric management over a 2 year period with a low level of drug-related side effects. Rimonabant therapy is associated with an extra 8–10% increase in HDL-C and a 10–30% reduction in triglycerides and improvements in insulin resistance, glycemic control in patients with diabetes. Therefore, rimonabant has major effects on both the metabolic syndrome and cardiovascular risk factors thus has the potential to reduce the risks of type 2 diabetes and cardiovascular disease.

Approved in 1985 and marketed in 2006, **Nabilone** (Cesamet®) is a synthetic cannabinoid with antiemetic properties which is used for the treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. It is also approved for use in treatment of anorexia and weight loss in patients with AIDS. Unlike Marinol, Nabilone is not derived from the cannabis plant.

**Additional Cannabinoid-Based Medicines: Looking To the Not So-Distant Future**

## Obesity and Metabolic Disorders

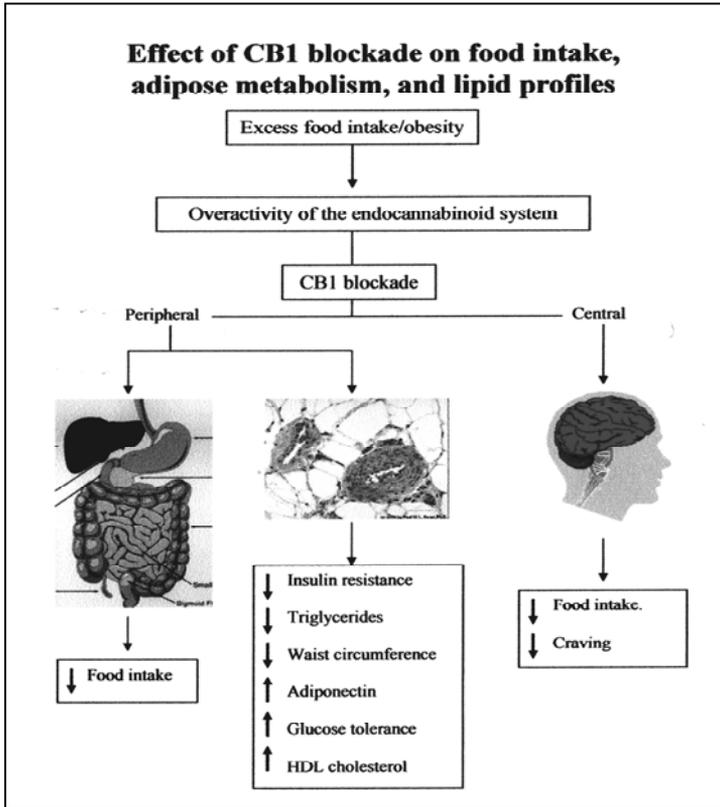
Obesity has reached global epidemic proportions with more than 1 billion adults overweight and at least 300 million of them recognized as clinically obese. Obesity is widely recognized as a major contributor to the global burden of chronic disease and disability and appears on the WHO list of Top 10 global health risks (World Health Organization, 2004.).

The combination of a sedentary lifestyle and a calorie-dense diet tends to disrupt the body's energy balance system, leading to obesity and the chronic over activity of the endocannabinoid system (EC). Furthermore, research is showing how some chronic pathologic states, including obesity, lead to on-going over stimulation of the synthesis of endocannabinoids (or under-stimulation of their breakdown), resulting in over activation of the CB<sub>1</sub> receptors, which maintains or exacerbates the symptoms of these disorders (DiMarzo, 2008. Kirkham, 2003. Van Gaal, 2004.).

In these situations of over activity, the EC system is working beyond its normal range and the over stimulation seems to promote fat storage and is associated with insulin resistance, glucose intolerance, elevated triglycerides and low HDL cholesterol levels, all of which are risk factors for cardiovascular disease. CB<sub>1</sub> receptor blockade can modulate this overactive EC system resulting in the restoration of balance.

Blocking the CB<sub>1</sub> receptor eliminates the part of obesity that is controlled by the EC System such as increased appetite, excessive hunger and food intake. It also increases adiponectin levels, which is thought to result in increased fat metabolism and an improvement in glucose metabolism (see figure below).

This may result in reducing cardiovascular risk factors through weight loss and an improvement in metabolic risk factor profile.



### Endocannabinoids and Addiction

As previously discussed, the endocannabinoid (EC) system is a physiological system that assists in the body's overall maintenance of homeostasis and energy balance. The system plays an integral role in regulating body weight, glucose levels, lipid metabolism, pain, movement, and cognitive functioning. Science is also discovering the role of the EC system in drug addiction and how its activation may contribute to the reinforcing and rewarding properties of drugs having abuse potential. More importantly, the implications of this research have a focus on how the EC system can be important in the treatment of drug addiction through anti craving properties and relapse prevention mechanisms.

Although the use of psychoactive drugs begins as a voluntary behavior, in addicted individuals it becomes as uncontrollable as the compulsive, ritualized acts that afflict obsessive-compulsive disorder patients. The overpowering nature of drug addiction and the associated changes in brain structure and function have led to conceptualization of this condition as a chronic disease of the central nervous system. Like other chronic brain diseases, drug addiction goes through recurrent cycles of symptoms remission and relapse, which can be readily triggered when abstinent addicts are confronted with reminders of their drug habit ('conditioned cues') or with emotional distress. The prevention of such relapses is, of course, one of the primary goals of addiction treatment.

### Drug Relapse and the Dopamine–Endocannabinoid Connection

Relapsing behaviors are related to an increased activity of the brain's mesocorticolimbic dopamine system—a neural pathway for reward and reinforcement thought to be activated in behaviors such as eating and mating, and to underlie the rewarding properties of many psychoactive drugs.

Some research studies have shown how elevated dopamine levels produced by cocaine or cocaine-associated cues elicit the release of endocannabinoids, which cause relapse (DeVries, 2001, Shaham, 2000.). It seems that cocaine or cocaine-associated cues elevate endocannabinoid levels, which cause relapse by enhancing dopamine release. These studies have shown that blockade of CB<sub>1</sub> receptors prevents associative-conditioning relapses to cocaine seeking.

Because cannabinoid agonist mechanisms have no effect on cocaine self-administration, these findings suggest that cannabinoid receptors must be selectively involved in triggering cocaine craving during abstinence, rather than in mediating the primary effects of the drug.

These findings are of great therapeutic significance and pave the way for a new direction of addiction medicines by blocking CB<sub>1</sub> receptors.

### Cannabinoid Receptors in Nicotine Addiction

Almost one billion men and 250 million women in the world smoke tobacco. Tobacco use, particularly smoking, remains the leading preventable cause of death in the world.

Nicotine is the chemical within tobacco smoke that causes addiction. In the US, it has been estimated that 70 percent of smokers want to quit, but only 2.5 percent per year succeed in quitting smoking permanently.

It has been demonstrated that chronic nicotine consumption results in persistent over-stimulation of the EC system in animals (Dale, 2004). Dopamine release into the nucleus accumbens is part of the neurochemistry underlying the motivation to consume nicotine. The chronic consumption of nicotine permanently over-stimulates the EC system in the nucleus accumbens, with subsequent reinforcement of dopamine release and continued reinforcement of nicotine abuse. Blockade of CB<sub>1</sub>, and thereby impairing the release of dopamine in the nucleus accumbens, tends to reduce the motivation to use nicotine.

### Cannabinoid Receptors in Cocaine Addiction

Several neurobehavioral studies have demonstrated that the central mechanism involved in cocaine relapse is closely linked to the sites where marijuana has its effect, suggesting that cannabinoid receptor antagonists might be useful as anti-craving agents (DeVries, 2001, Shaham, 2000.).

One large study used the rat reinstatement model to test whether cannabinoid receptors—the target of marijuana’s psychoactive component, THC—have a role in cocaine relapse (DeVries, 2001). They have shown that a cannabinoid agonist can precipitate relapse, whereas a cannabinoid antagonist can prevent relapse-induced by cocaine or cocaine-associated cues, but not relapse induced by stress.

### Cannabinoid Receptors in Heroin Addiction

As with other drugs of abuse, heroin use is characterized by a high incidence of relapse following detoxification that can be triggered by exposure to conditioned stimuli previously associated with drug

availability. Recent findings suggest that cannabinoid CB<sub>1</sub> receptors modulate the motivational properties of heroin-conditioned stimuli that induce relapse behaviors (Ledent, 1999, Alvarez-Jaimes, 2008.). These findings provide new insights into the neural mechanisms through which CB<sub>1</sub> receptors modulate the motivational properties of heroin-associated cues inducing relapse and provide a basis for the development of cannabinoid based as an additional arsenal of medicines for the treatment of opioid addiction.

### Cannabinoid Receptors in Alcohol Addiction

Just over the past several years, some remarkable advances have been made towards understanding the role of the EC system in the development of alcohol tolerance and alcohol-drinking behaviors. These studies have provided strong evidence that CB<sub>1</sub> receptors and the EC system serve as an attractive therapeutic target for the treatment of alcohol tolerance and alcohol-related disorders (Basavarajappa, 1998, Hungdun, 2000.) . The data reviewed here provide convincing evidence that alcohol tolerance involves the down regulation of the CB<sub>1</sub> receptor and its function. The observed neuroadaptation may be due to increased accumulation of the endocannabinoids anandamide and 2-AG. Research has shown that treatment with a CB<sub>1</sub> antagonist led to reduced consumption of alcohol in animal studies. Furthermore, activation of the same endogenous cannabinoid systems by the CB<sub>1</sub> receptor agonist actually promoted alcohol craving, which may be related to the change in the levels of dopamine in the nucleus accumbens.

These observations suggest the involvement of the CB<sub>1</sub> receptors in controlling voluntary alcohol consumption and the involvement of the endocannabinoid system in the development of alcohol tolerance. These studies will lead to the development of endocannabinoid drugs, which will help to reduce both alcohol intake and alcohol craving. Consistent results from a variety of research studies suggest that a cannabinoid antagonist drug is useful as a potential therapeutic agent in alcohol dependence.

## Epilogue

The controversy over the issue of “medical marijuana” may essentially be over since medical research has made important discoveries about the science of cannabinoid-based medicines. Synthetic analogs and other drugs acting on the endogenous cannabinoid receptors will provide a host of therapeutic benefits attributed to marijuana, without the smoke, the contaminants, and the variable potency.

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## Medical Marijuana

Timmen L. Cermak, M.D.

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An anachronism waiting to happen, medical marijuana is a more highly charged issue than medical foxglove (*digitalis*) or medical willow bark (*salicin*, which the body converts to salicylic acid) ever was. The reason is obvious; multitudes enjoy the psychoactive properties of cannabis and multitudes more extol the spiritual value of this plant. Combined with the historical and political forces unique to the current American scene, these forces significantly complicate any discussion of the potential medical usefulness of cannabis.

This chapter approaches a discussion of the medical use of marijuana from the following perspective: Ingestion of cannabis for recreational, ritualistic and traditional medical purposes eventually led to discovery of the brain's endocannabinoid system. As our understanding of the role this neurochemical system plays in a wide-ranging array of physiologic functions expands, multiple possibilities for treating disease conditions by modifying CB1 and/or CB2 endocannabinoid activity become apparent. Before exploring these possibilities, however, it is important to review briefly the core dynamics guiding medicine and the essential parameters within which it operates.

The Scientific Method is medicine's road map, laborious and slow as it may seem at times. By requiring objective measurements, reproduction of results by multiple independent observers and open sharing of findings after being judged for merit by a panel of peers, the scientific method is designed to remove as much prejudice, myth and mere opinion as possible. The scientific method always asks the next question, searching for the simplest, most elegant answer. For example, what aspect of willow bark helps combat fever and inflammation? And so researchers extract the active element, learn to synthesize it, modify it, improve its efficacy and reduce its side effects. Some outside medicine would call this the murder of mystery, while physicians see it as progress.

If all physicians brought to the practice of medicine were science, they would be mere technicians. At its best, the practice of medicine is also a deeply Humanistic endeavor that carries in its heart caring, connection and hope. Even as a physician stares into the mortal abyss with his or her patient and refuses to flinch from the realities that have to be faced, the mystery of human contact needs to be sustained and honored. While science takes knowledge, the challenge of maintaining a human touch and sustaining hope requires wisdom. Medicine calls for living and working in a balance between the hard reality and the human need for compassion.

As our understanding of the endogenous cannabinoid neural system has grown, we have gradually come to understand that this pervasive system is involved in modulating nearly every known physiological function. Perhaps a good perspective on its ubiquitous importance is gained by looking at the fate of what are known as knock-out mice. These are mice in which the genetic code for CB1 receptors has been “knocked out.” As a result, from conception on, these mice have possessed essentially no working cannabinoid system (Zimmer, Zimmer et al. 1999; Kunos and Batkai 2001). They generally appear healthy and fertile, though they exhibit a bit less motility, especially in exploration tasks. They do have better memories, and don’t self-administer morphine (which will be explained later). Most importantly for our purposes here is that CB1 knock-out mice have significantly increased mortality. They die sooner than normal mice. And they die from a broad range of causes. Why is this? My speculation is that the endocannabinoid system is tonically active (always active to some degree), modulating multiple other physiological systems up or down in their activity, and thereby providing an important element of flexibility and resiliency to our physiology. Without an endocannabinoid system, as the knock-out mice are, (or without a well balanced endocannabinoid system) responses to stress become more stereotyped and rigid, less adaptable.

*Marijuana and Medicine: Assessing the Science Base* was published by the Institute of Medicine in 1999. The latest reference cited in their review of the literature was 1998, meaning that the research relied upon was planned and conducted in '96-'97, only 8-9 years after the

CB1 cannabinoid receptor was discovered and 4-5 years after the first endogenous cannabinoid neurotransmitter was isolated. The intervening years have produced such a wealth of research that their conclusions that “Cannabinoids likely have a natural role in pain modulation, control of movement, and memory” and that “The accumulating data indicate a potential therapeutic value for cannabinoid drugs,” appear unnecessarily tentative and obviously true today. The accumulated data have increased exponentially in the past decade. The conclusions about future medications are much more firm. But, the pipeline remains long and products have yet to arrive to alleviate real peoples’ suffering or treat disease, which keeps the question of “medical marijuana” open and vital.

Our scientific understanding of the human endocannabinoid neural system suggests multiple legitimate possibilities for intervening on disease processes. For example, CB1 receptor sites and endocannabinoids are heavily concentrated in the hippocampus, the site where scratch pad memory is formed and boosted into longer-term storage (Tsou, Brown et al. 1998) (Mackie 2005). Everyone who has smoked pot has experienced the impact on short-term memory of stimulating the hippocampal cannabinoid system – it is (often hilariously) disrupted. An individual may forget the topic of a sentence before getting to the end of what he was intending to say. Nearly every study of marijuana verifies impairment of short-term memory (Sullivan 2000).

When rats are introduced to each other they undertake an initial snout sniffing familiarization procedure. If separated for more than 2 hours, they will repeat the snout sniffing to refamiliarize themselves; if less than 2 hours, the routine will be unnecessary. When treated with THC, however, the olfactory memory is not maintained as well and snout sniffing is required after shorter periods of separation (Terranova, Storme et al. 1996).

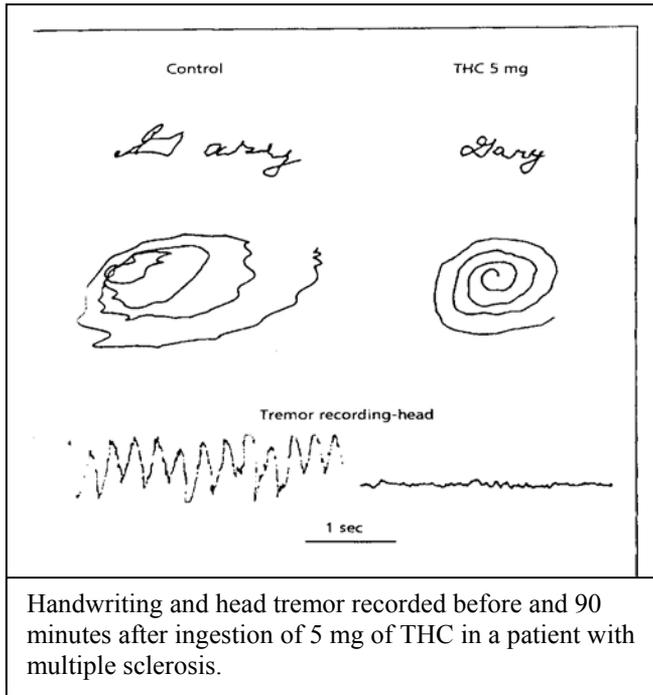
Since the endocannabinoid system is tonically active, it can also be diminished by introducing a blocking agent (SR141617A). When senile rats (2 years old) that have begun to lose their ability to maintain their snout sniffing olfactory memories for the full 2 hours

are administered a cannabinoid blocker, their memory is improved (Terranova, Storme et al. 1996). This introduces the idea that diminishing cannabinoid activity in the hippocampus may provide some benefit in early dementias and diseases affecting memory.

I introduce the idea of a cannabinoid blocker first to destroy the box created in people's thinking by the concept of "medical marijuana." The proper framework to consider is "cannabinoid chemistry," which includes the full range of agonists (endocannabinoid receptor stimulators), partial agonists, antagonists (blockers), reuptake inhibitors, and enzymatic blockers. Medicine is developing a wide array of mechanisms to modify cannabinoid activity in an effort to ameliorate suffering.

CB1 receptors and their endocannabinoid ligands (the natural endocannabinoid neurotransmitters) are highly concentrated in two areas that are central to our motor control – the basal ganglia and the cerebellum. Descriptions of being high often include both a physical relaxation and an enjoyable sense of "motor flow," whether dancing, running, or playing music, for examples. Researchers have repeatedly described that THC reduces spontaneous motor behavior until an animal becomes nearly cataleptic, though not paralyzed (Shi, Luo et al. 2005). If aroused by sufficient stimulation, the animal is fully capable of well coordinated movement (although fine motor control is slightly impaired). It should come as no surprise that many teenagers suffering from ADHD find their way to smoking marijuana, claiming that it is the natural antidote for their condition. While it undoubtedly quells their hyperactivity, performance on the Connor's CPT shows no improvement in attentional mechanisms (author's unpublished data).

The underlying physiology of the endocannabinoid neural system does make sense of observations by patients with multiple sclerosis that muscle spasms are reduced (Baker, Pryce et al. 2001). The tremor of multiple sclerosis is dramatically reduced by 5 mg of THC in the tracings [Figure 1] published in *Therapeutic Uses of Cannabis* (1997) (Iverson 2000).



[Figure 1]

High concentrations of endocannabinoids and CB1 receptors can also be found in areas of the hypothalamus and amygdala that modulate appetite (Wenger and Moldrich 2002) (Kirkham, Williams et al. 2002). Again, anyone who has experienced the “munchies” understands the strong desirability that comfort food can have when stoned on marijuana (Williams and Kirkham 2002). Orally ingested THC is capable of having a beneficial effect for those suffering the wasting syndrome secondary to HIV/AIDS (DeJesus, 2007). Efforts to use orally ingested THC (Marinol) are less efficacious due to greater difficulty titrating the dose and slower onset. Several related phenomena bear on Abrams’ work. To begin, the period in extrauterine life when endocannabinoids are naturally at their highest concentration is at the time of birth. Rat pups given a cannabinoid blocker (SR141617A) during the first 24 hours of life fail to suckle and soon die (Fride, Ginzburg et al. 2001). Clearly, a well functioning cannabinoid system is of critical importance to all mammalian life,

and is perhaps even a part of the mechanism of bonding. Stimulating CB1 receptors with exogenous chemistry leads not only to increased appetite, but often to feelings described as “connectedness,” and even “warmth” and “love.”

Could there be help here for the obese? The cannabinoid blocker SR141617A is currently being marketed in Europe as Rimonabant / Acomplia. By reducing the level of cannabinoid activity, appetite is suppressed – the “antimunchies.” (McLaughlin, Winston et al. 2003) On average, a twenty pound weight loss is maintained over 2 years by morbidly obese patients (Pi-Sunyer, Aronne et al. 2006). Intriguingly, Rimonabant is also being found to decrease the desire for smoking tobacco. It would be an extraordinary medication that could help with smoking cessation and control weight at the same time. Unfortunately, one out of every eight people can not tolerate having their endocannabinoid system turned way down. Anxiety and depression develop, sometimes with suicidal ideation.

Why would diminishing cannabinoid activity lead to anxiety, depression and anhedonia? The heavy concentration of endocannabinoids and CB1 receptors in the amygdala provide a portion of the answer. Much of the modulation of our fight and flight responses lies within the amygdala. Electrical stimulation within different portions of this nucleus in the anterior temporal lobe sends an animal into states of terror or surreal calm. Our endocannabinoid chemistry contributes to the substrate for modulating this fight-or-flight mechanism. Low dose cannabinoid stimulation is generally calming in naïve smokers, while higher dose tends to be agitating. Knocking out the system altogether results in a loss of resilience and a loss of the ability to achieve maximal performance. In addition, the sense of novelty, which is added to incoming sensory stimuli by the amygdala’s ongoing comparative function, is under exquisite endocannabinoid control (Schwartz, Wright et al. 2003). Increasing cannabinoid activity dishabituates an animal to stimuli, thereby diminishing the threshold for perceiving a stimulus as novel. Boredom is reduced. Marijuana makes the mundane fascinating again. But a cannabinoid blocker has the capacity to empty the world of novelty, or even of interest, thereby creating anhedonia and depression. This

raises the possibility that cannabinoid agonists could be developed that contribute to the treatment of anhedonic depression. I have observed low dose Marinol provide substantial relief to a small number of patients when used to augment traditional antidepressants that had produced only partial relief.

A second clue to why diminishing cannabinoid activity with a blocker like SR141617A (Rimonabant) can cause serious depression and anhedonia lies in the interactions between our endocannabinoid and endorphin neural systems. Brain researchers now see the endogenous opioid and cannabinoid systems in the central nervous system as two independent but parallel and overlapping physiological regulatory systems. Both are involved in controlling our sensitivity to pain, and both may be involved in some way in the reward mechanisms of the brain. The parallels between these two systems are so great that pretreatment with naloxone blocks the release of dopamine in the nucleus accumbens (the reward center) by administering either an opiate or THC, but not by any other drug of addiction (Tanda, Pontieri et al. 1997). Cannabinoids and endorphins provide two varieties of pleasure and relief of pain, complementing each other in a harmonious duet. And herein lies one of the most promising medical uses for using cannabinoid medications to alleviate disease and suffering.

Chronic pain can be a debilitating condition, whether from end of life disseminated cancer or from musculoskeletal conditions that degrade the quality of life for an otherwise healthy individual. Two problems are gradually becoming recognized with over-reliance on opiates for analgesia: the production of hyperalgesia and eventual ineffectiveness. When opiate analgesia is used over extended periods of time, mu-opiate receptor sites become significantly downregulated. This results in increased sensitivity to pain unless the exogenous opiate being administered is maintained at high levels, which unfortunately also results in considerable sedation and eventually obtundation. By activating the parallel endocannabinoid system, however, similar levels of analgesia can be maintained with lower levels of morphine (Smith, Cichewicz et al. 1998; Cichewicz, Martin et al. 1999) (Cichewicz 2004). Combination therapy (opiate and cannabinoid) will ultimately enable clinicians to minimize the issue of opiate induced

hyperalgesia. In a similar way, combining the analgesic properties of both the endorphin and the endocannabinoid neural systems may provide an effective response to recent findings that opiate treatment for lower back pain is ineffective after 6 months (Martell, O'Connor et al. 2007).

Not all pain is the same, which may account for why our body contains two independent, parallel neural systems for regulating pain. The endorphin system most effectively provides analgesic relief for tissue injury pain. A novel cannabinoid, AM1241, is being developed to act on CB2 receptors only (Ibrahim, Deng et al. 2003). Located primarily outside the central nervous system, CB2 receptor stimulation provides relief of neuropathic and inflammatory pain without any sedating side effects. The benefit of having a medication that reduces pain without central effects is inestimable, since sedation and addiction have long limited the usefulness of many of our stronger analgesics.

Cannabinoid receptors and endocannabinoids are found throughout the gut (Pertwee 2001) (Massa, Storr et al. 2005). One unfortunate patient came to me after being seen by a doctor for many years who was well known for advocating the use of marijuana for a wide variety of illnesses and conditions. He was treating this patient primarily for depression and hysterical outbursts. As her depression and emotional volatility worsened, he advised her to increase the dose. At the time I met her she weighed 90 pounds, was bed ridden, suicidal, anorexic and only able to move her bowels by giving herself an enema each morning. After entering a drug treatment program, it took her bowels three months to regain function. Her colon had become completely atonic. Stimulation of the intestinal cannabinoid receptors reduces peristalsis. In the fight against diarrhea, a killer of infants world-wide, cannabinoid medications could eventually bolster our pharmacopeia.

If cannabinoid based antidiarrheal medications could be developed that remain in the gut, and therefore have no side effects stemming from central actions, these could make major contributions to world health. Other gastrointestinal illnesses for which cannabinoid based therapeutics may be developed include nausea and vomiting, gastric

ulcers, irritable bowel syndrome, Crohn's disease, and gastroesophageal reflux disease.

Intense research has been taking place regarding the neuroprotective properties of cannabinoid chemistry (Mechoulam, Spatz et al. 2002) (van der Stelt and Di Marzo 2005). In part because cannabinoid research in this area is still in its early stages and in part because the pathology underlying many neurodegenerative diseases is still in question, the potential role of cannabinoid-based medications remains speculative and complex. Nonetheless, their potential is very intriguing. To begin with, there is the injury of the ischemic/reperfusion type (e.g., stroke). One area of research involves how changing the balance between activation of CB1 and CB2 receptors alter the outcome following an ischemic episode (Pacher and Hasko 2008). The most striking neuroprotective combination of CB1 and CB2 antagonists and agonists was a combination of a CB1 antagonist with a CB2 agonist (administered to mice experiencing a one hour occlusion of the middle cerebral artery).

This combination elevated the cerebral blood flow during ischemia and reduced infarction by 75% (Zhang, Martin et al. 2008). It appears that stroke patients would receive the most benefit if they could receive the combined effect of CB1 inhibition with CB2 activation. Other studies have shown that ischemia leads to significant increases in the production of endogenous cannabinoids in the area of injury. Pretreatment with the cannabinoid antagonist SR141716 before the ischemia, thereby blocking the impact of the rise in injury-associated cannabinoids, leads to a 50% reduction in infarct volume and a 40% improvement in neurological function (Muthian, Rademacher et al. 2004). Clearly, not all cannabinoid activity is neuroprotective under all conditions.

Other neurodegenerative diseases, e.g., Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS), have drawn the attention of cannabinoid researchers. Not all of the neuroprotective effects of cannabinoids are receptor dependent. In the case of the pathologic changes occurring in basal ganglia in PD and HD, the

receptor-independent antioxidant effects of cannabinoids reduce the oxidative injury of both disorders. In addition, the surrounding microglial reactions are better regulated by increased CB2 stimulation (Micale, Mazzola et al. 2007) (Correa, Docagne et al. 2007). Unfortunately, recent data on multiple sclerosis patients using marijuana has demonstrated decrements on cognitive testing (symbol digit modalities) that injects a cautionary note (Ghaffar and Feinstein 2008).

There are early indications that the immunomodulatory and anti-inflammatory properties of cannabinoids may also provide some neuroprotection to spinal neurons impacted in MS and ALS, both of which receive modulatory influence by both CB1 and CB2 receptors.

Alzheimer's disease is a neurodegenerative disease characterized by deposition of beta-amyloid protein, among other neuroinflammatory changes. Both experimental models of AD and post-mortem brain tissue of AD patients show decrease of CB1 receptors, increase of glial CB2 receptors and over expression of FAAH (the enzyme that metabolizes endocannabinoids) in astrocytes. Whether these changes are part of the pathogenesis or the result of the disease remains an open question. Administration of cannabinoids has been shown to limit amyloidogenesis while reducing neuroinflammation through stimulating microglial CB2 receptors. THC also inhibits acetylcholinesterase, an accepted treatment for slowing progression of the disease (Eubanks, Rogers et al. 2006).

The truth here is that basic research still has many questions to answer before applied research can develop effective medications to treat Alzheimers, multiple sclerosis and other neurodegenerative diseases. We still await an understanding of the basic pathophysiology; and until we have nailed down those details, we cannot be sure whether the abnormalities we see in the endocannabinoid neural system are the cause or the effect of illness. As a result, we can not even be sure whether the administration of cannabinoid medications is palliative or therapeutic. The best we can do at this point, with careful observation of individual patients, is to do no harm.

The role of cannabinoid medication in treating epilepsy is not yet clear. Since endocannabinoids serve as retrograde messengers that enable nerve cells to control the strength of their own synaptic inputs, it makes sense that activation of cannabinoid receptors could potentially protect against the excitotoxicity of seizure activity. In a paradoxical study, induced seizures were reduced not only by a cannabinoid agonist, but also even more by administering a mixture of both an agonist and an antagonist. The only way to make sense of this is to realize that cannabinoids are both anticonvulsant and proconvulsant. Some cannabinoid receptors inhibit the release of excitatory neurotransmitters like glutamate while other receptors inhibit the release of inhibitory neurotransmitters like GABA. The trick in developing effective anticonvulsant medications based on cannabinoid chemistry will be getting the correct effect to the correct place (Wallace, Wiley et al. 2001).

Psychiatric issues have also been advanced as potential targets for potential cannabinoid based pharmacotherapy, but the data here is far more sparse, speculative and conflated with political and personal opinion. With the high rate of PTSD among returning Iraqi veterans, for example, and marijuana frequently being the drug of choice for this population, a lot of attention has recently been paid to research demonstrating that the brain's endocannabinoid chemistry is critical to the process of forgetting aversive memories. On the surface, this seems to suggest that veterans may be effectively self-medicating themselves and that resources should be invested in developing cannabinoid based medications to treat PTSD.

A closer review of the literature, however, reveals the following: CB1 knock-out mice, or mice treated with blockers that completely shut down their endocannabinoid systems do fail to forget learning that came from punishment (Marsicano, Wotjak et al. 2002) (Chhatwal, Davis et al. 2005). Could we hasten the extinction of memories from aversive learning by increasing cannabinoid activity in normal animals? Yes, but not by administering an external cannabinoid, including THC. The only manipulation that enhanced the extinction of aversive memories was to interfere with FAAH, the enzyme which breaks down the body's natural endocannabinoid (Varvel, Wise et al.

2007). In fact, administering THC on a chronic basis only serves to reduce the number of available cannabinoid receptors by 20-60%, which effectively leaves the body's natural endocannabinoids with fewer sites to activate, thereby reducing their impact (Romera, 1997). Finally, the research demonstrating the role of our endocannabinoid system in the forgetting of aversive memories was all conducted on classical conditioning experiments, which are far removed from the experiences that lead to PTSD, in which the stressor is most often seen as being of "human design".

As one critic of medical marijuana observed, "Pot may be medicine, but getting high every day is still getting high every day (Rosin, 1997)," and no amount of numbing the pain of PTSD is likely to help veterans process the deep grief and pain of having participated in the human tragedy of war.

The amygdala, heavily endowed with cannabinoid receptors and endocannabinoid neurotransmitters, is intimately involved with the control of our anxiety/fear. Researchers frequently describe the effect of exogenous cannabinoids as being dose-dependent and bimodal. Low dose diminishes anxiety, while high dose produces anxiety. In naïve humans, most individuals feel relaxation when they first experience marijuana, although a few experience anxiety, fear and even panic or paranoia. Multiple factors beyond a high dose of cannabis may contribute to a negative experience, e.g., an overly rigid personality structure, a threatening setting, fearful expectations or underlying mental illness. Interestingly, over time (often decades), an increasing percentage of individuals who earlier enjoyed the relaxing experience of smoking marijuana gradually are chagrined to find that marijuana begins to produce anxiety instead. Clearly, endocannabinoid chemistry plays an integral role in helping to modulate our ongoing levels of anxiety.

Does the fact that a chemical temporarily reduces anxiety make it an effective and useful anxiolytic medication? It would appear that the pharmaceutical companies answer this in the affirmative when they get a patent on that chemical, even if that chemical is highly addictive, induces tolerance and often creates a rebound increase in anxiety (even

spiraling into panic attacks) when its effects wear off – i.e., Xanax. In the face of such a poor example of a “legitimate” anti-anxiety medication, it is difficult to argue that marijuana is not equally useful for diminishing anxiety. The primary counter arguments revolve around side effects, including the rebound aggressivity recognized to exist once marijuana has been used often enough to produce tolerance.

Is marijuana an effective antidepressant? Many who have smoked marijuana have experienced a distinct improvement in mood, a gaiety, a lightness, laughter, great pleasure – the very antithesis of the dark mood and anhedonia characteristic of most depression. From this perspective, marijuana looks like an excellent mood elevator. However, many chemicals temporarily grab our mood and elevate it, sometimes to great heights – alcohol, heroin, cocaine, methamphetamine. But few people would seriously consider any of these as legitimate antidepressants. This is in large part because low mood is only one aspect of depression. A much larger part is the profound and pervasive loss of deep regulation that characterizes depression: the sleep-wake cycle is dysregulated, appetite is dysregulated, energy is dysregulated, concentration is dysregulated, emotions are dysregulated, obsessions/compulsions are dysregulated – nothing seems in balance any more. When the modern antidepressants such as Prozac increase serotonin levels, the first things people experience is not an elevation of mood. The first thing they experience is improved balance in the deep regulatory mechanisms governing their sleep, energy, appetites, concentration, impulses, and emotions.

When these basic functions no longer seem as out of control, an improved mood naturally follows. There is no data demonstrating that marijuana brings about the same improvement in regulatory mechanisms that the selective serotonin reuptake inhibitors (SSRI's) accomplish. While there is no doubt that marijuana brings a sense of pleasure and a temporary welcome elevation of mood, it is less certain that it can serve as an effective antidepressant.

Considerable attention has been paid to whether marijuana plays any role in either causing or ameliorating schizophrenia. A sizable number of schizophrenics gravitate toward smoking, both nicotine and

marijuana, and are highly resistant to efforts to get them to abstain. Research is clear that marijuana is neither the necessary nor sufficient cause for developing schizophrenia. However, studies do indicate that marijuana use in adolescence leads to a two to three-fold increase in the relative risk of schizophrenia (Zammit, Allebeck et al. 2002) (Veen, Selten et al. 2004). Although only a minority are at risk, it is estimated that, if marijuana were eliminated from the population, the incidence of schizophrenia would be decreased by 8% (Arsenault et al. 2004).

Of particular interest to the question of whether marijuana can serve as medication for schizophrenia is a study that looked at MRIs of recent onset schizophrenics, with follow-up MRIs five years later. Compared to normal controls, the schizophrenics showed a loss of gray matter (nerve cell bodies) over the five-year period. Those schizophrenics who used marijuana lost gray matter at nearly twice the rate of those who did not. The prudent course would be to suggest that schizophrenics protect their brain's health by adding marijuana to the list of substances, such as nicotine and alcohol, to be avoided (Rais, Cahn et al. 2008).

There is one undeniably powerful medical benefit of marijuana that should not be ignored – its placebo effect. How strong can the placebo effect be? As strong as your mind. For example, a high dose estrogen/progesterone patch to treat menopausal symptoms causes diarrhea in 23% of women; the inactive placebo patch caused diarrhea in 24%. An ADD medication, Strattera, causes upper abdominal pain in 20% of people when given twice a day; but 16% have the same symptom with placebo. Derived from the Latin word for “I shall please,” placebos are tangible symbols of a physician's ability to heal that produce results by mobilizing an individual's expectations.

In the case of marijuana, the substance is hardly inert. Marijuana is a very active placebo, both pharmacologically and sociopolitically. Individuals choosing to treat their illness or discomfort with medical marijuana often feel deeply empowered by the communal action of state voters rising up against federal authorities, overturning a noxious and ineffective War on Drugs. The expectation of experiencing relief

from a host of ills delivered from a natural elixir – the apotheosis of alternative medicine – can be seen as a self administered placebo. “I shall please myself.” The expectation of relief is extremely high; and since marijuana is a very “active” placebo, it appears to deliver on these expectations sufficiently to develop a highly devoted following.

It is here that many physicians have crossed an ethical boundary to the detriment of medicine, and ultimately of the public. In an effort to please the political desires and serve the democratic rights of patients to choose alternative approaches to comfort themselves, some physicians in the medical marijuana movement have forgotten to adhere to the standards of good medical practice. These standards require that medications, especially those with a potential for abuse, damaging side effects or addiction, be prescribed (or recommended) by your physician only within the context of a good faith history and physical, a treatment plan with diagnoses and goals, informed consent (including a full discussion of possible side effects), consultation when needed, periodic reviews of effectiveness of the treatment provided, and proper records. A single appointment with a “pot doc” where the only outcome is a letter of recommendation for medical marijuana, without any follow up appointments, is highly unethical. This is akin to running a Prozac clinic. “Come one, come all, I’ll give you a prescription for Prozac with a year’s worth of renewals for whatever ails you; and you never have to see me again.” The public would rise up and label that doctor as nothing but a shill for the pharmaceutical company, more interested in pushing the drug than actually treating the patient.

To be truly “medicalized,” marijuana needs to take its proper place among other medicines in the over all care of patients. As long as it remains a back door into pulling a fast one on the Feds, its ultimate value will take far longer to be recognized and developed.

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## Toward a New Pain Medicine

Suma Singh, M.D.

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Marijuana (*Cannabis sativa* plant) has been used for more than ten thousand years as folk medicine for many conditions. It was included in the US Pharmacopoeia in 1850 based on cultural experience as a folk medicine, and tinctures were recommended for gout, rheumatism, depression, convulsions, constipation, and malaria. Marijuana was removed from the Pharmacopoeia in the 1940s due to increasing societal concerns over recreational use for its psychoactive properties. Today, “medicinal marijuana” typically refers to marijuana leaves that are smoked, and also to crushed leaves, stems, flowers, and seeds that may be eaten mixed with food.

Before proceeding to describe the potential analgesic benefits of marijuana (specifically, cannabinoids) in this chapter, let me now clearly state that in my view, the risks of smoked “medicinal marijuana” are well documented and do **not** outweigh the analgesic benefits. Cannabis smoke contains carcinogens; in fact, it contains more toxins than tobacco smoke. Smoking cannabis leaves particulate residue inside deep airways and chronic use can damage pulmonary function. Cannabis smoking increases the risk of mouth, throat and lung cancer, and also dramatically worsens any pre-existing lung disease. In my opinion as well as that of most physicians, smoked cannabis has no medical value as a therapy for chronic pain.

Having said so, marijuana is widely used (legally and illegally) for symptom control among certain patient groups with chronic degenerative illnesses (Multiple Sclerosis, HIV/AIDS, Parkinson’s Disease, etc). A 2006 survey in England of 254 multiple sclerosis patients from hospital clinics showed more than 40% had used marijuana for MS symptoms, mainly pain and spasms (Chong, 2006). One third of patients in North America with HIV/AIDS report self-medicating with marijuana for physical symptom relief and stress (Belle-Isle, 2007). Many communities now share this common knowledge and some States have legalized the “compassionate use” of

“medical marijuana” in situations of severe incurable illnesses despite conflict with Federal drug laws. Although marijuana “prescribing” standards vary widely between practitioners, this new open-arms approach for cases of chronic debilitating illness has fostered a climate that is more receptive to therapeutic applications of substances with abuse potential.

Medical science has in fact, been long aware of the therapeutic potential of *Cannabis sativa*. But progress in understanding the nature these effects and potential applications was hindered for decades by social stigma surrounding marijuana and misplaced fears by regulators. As a direct consequence of society’s openhearted willingness to view the possible benefits of “marijuana as medicine”, rigorous scientific exploration was catalyzed. A watershed of discovery of the molecular basis, therapeutic potential, and side effects of active compounds found in marijuana is becoming elucidated.

Marijuana contains approximately 60 chemically similar compounds called “cannabinoids”. Of these, the major psychoactive cannabinoid in marijuana is delta-9 tetrahydrocannabinol, or THC. THC is used in many basic science and clinical studies as a model for the cannabinoid class of therapeutics being developed. A major breakthrough in cannabinoid science was the discovery of 2 specific human cellular receptors (Devane, et al, 1992) for cannabinoids (CB<sub>1</sub> and CB<sub>2</sub>). CB<sub>1</sub> receptors are located mainly in the nerve cells of our brain and spinal cord. Outside the brain, CB<sub>2</sub> receptors are found in the cells of our immune system and gastrointestinal tract.

Discovery of these CB<sub>1</sub> and CB<sub>2</sub> receptors led to an obvious and intriguing question. Assuming it unlikely that our human species evolved cell receptors exclusively for plant compounds in *Cannabis sativa*, why does our body contain cannabinoid receptors? Scientists postulated that humans must harbor natural counterparts for compounds found in marijuana. Mechoulam and others have unequivocally established the presence of a sophisticated internal cannabinoid regulation system that affects a many of our physiological functions. Simply put, we make our own (endogenous) supply of THC-like compounds, now called endocannabinoids. We generate

endocannabinoids that are targeted to bind specifically to CB<sub>1</sub> and CB<sub>2</sub> receptors located in our brain and elsewhere in our body.

CB<sub>2</sub> receptors are located in the cells of our immune system and gut. In the periphery, CB<sub>2</sub> receptors appear to play an important role in modulating the function of the immune system, reducing inflammation, and mediating pain relief. In the gastrointestinal tract, CB<sub>2</sub> receptors and the endocannabinoid system are involved in the regulation of gut motility, secretions, sensation and appetite satiety, vomiting, and inflammation. These complex CB<sub>2</sub> actions are discussed in detail elsewhere in this book.

In the central nervous system, cannabinoids are located in the brain and spinal cord. In the brain, CB<sub>1</sub> receptors are thought to be responsible for the euphoric, sedative, and pain relief effects of cannabinoids. Brain CB<sub>1</sub> receptors are also thought to be involved in the development of physical dependence to cannabinoids. In the spinal cord, cannabinoids appear decrease transmission of pain signals from the periphery acting on the nerve cells in dorsal horn region. In fact, there is now a rigorous body of evidence from various animal studies showing that cannabinoids decrease pain due to inflammation, nerve injury, and cancer. Animal studies with THC shows that this cannabinoid works by decreasing calcium ion flux across the nerve cell membrane by activating the CB<sub>1</sub> receptor, and resultant decrease transmission of pain signals (Strangman, 1998).

Clinical human studies suggest that the pain relief effect of cannabinoids is modest, and similar to that of codeine, a weak opiate agonist. A 2001 review of 20 published human studies indicated a scarcity of well-controlled, scientifically valid data (Campbell, 2001). Eleven studies had to be eliminated due to problems study methodology and lack of scientific validity. From the remaining 9 studies, it appeared that analgesia from 3 cannabinoids was similar to codeine. In these studies, a total of 222 patients were treated with one of 3 cannabinoids (THC, a synthetic nitrogen analogue of THC, and levonantradol) for cancer pain, chronic non-malignant pain, or acute postoperative pain. A 4<sup>th</sup> cannabinoid, benzopyranoperidine, was not more effective than placebo. Side effects were common with all

cannabinoids studied, particularly symptoms of central nervous system depression.

If cannabinoids give only modest pain relief similar to codeine, and are complicated with side effects, then why do scientists/clinicians remain interested in exploring the potential analgesic applications of this class of compounds? The answer may lie in information gleaned from basic science and animal experiments, as well as the unmet clinical need presented by patients suffering from neuropathic pain, fibromyalgia pain, and inflammatory conditions. An example of neuropathic pain for which currently available medications and interventions have only limited effect is central pain from multiple sclerosis.

Central pain (a type of neuropathic pain) a general term used to describe pain that results from direct injury to the brain or spinal cord; in this case, the underlying brain lesions associated with hard plaques. Central pain related to multiple sclerosis occurs most commonly in patients who have suffered with the disease for a long duration, and is frequently described as continuous burning in the legs and feet. Some multiple sclerosis patients also describe sudden lancinating pains that occur without warning, and are sometimes triggered by activity, stress, or weather changes.

Existing treatments for neuropathic pain deliver inadequate pain relief, unacceptable side effects, or both. THC appears to have similar analgesic efficacy to codeine, a weak opiate agonist. But unlike codeine, THC can also produce unpleasant mood effects called dysphoria. Additionally, cannabis and currently marketed cannabinoid medications are associated with central nervous system depression (sedation) that limits utility in chronic pain treatment.

Novel carboxylic acids of cannabinoids with less sedative potential are under clinical investigation by Burstein, Sumariwalla, Mechoulam and others, and may hold therapeutic promise for painful conditions not well treated by standard analgesics. Academic labs and biotechnology firms are simultaneously leading the charge to develop compounds that would target only CB<sub>2</sub> receptors in the peripheral body systems,

and avoid the CNS side effects caused by CB<sub>1</sub> receptor activation in the brain. The unmet medical need for more effective treatment is driving a large volume of research to discover new drugs.

For multiple sclerosis pain, there are now a number of published studies of cannabinoid medications now available by prescription, and novel cannabinoids that are still in research and development for multiple sclerosis symptoms. In 2004, a double blind, in a pilot study of 24 multiple sclerosis patients with central pain studied the effect of ‘dronabinol’ in doses up to 5 mg twice daily compared to a placebo tablet (Svendson, 2004.). After 3 weeks of treatment, the relative difference in pain reduction between Dronabinol and placebo was around 21%, a small but statistically significant difference. The clinical importance of this small reduction should be considered in context with the clinical scenario.

The longest cannabinoid treatment duration in the published literature is 2 years in length. This study evaluated the long-term tolerability and effectiveness THC/CBD (Sativex) oromucosal spray for relief of central pain associated with multiple sclerosis (Rog, 2007.). Sixty-three patients were enrolled; 34 patients completed > 1 year of treatment, and 28 patients completed 2 years of treatment. Of all patients who used Sativex in this long-term trial, 92% of patients had treatment related adverse events. Roughly half of patient experienced adverse events that were rated as “severe” intensity, and 78% experienced moderate adverse events. The most common adverse events were dizziness and nausea. THC/CBD (Sativex) appeared to remain effective as an analgesic over the long term, with no evidence of tolerance.

HIV/AIDS related neuropathy is another type of neuropathic pain, for which currently available analgesics have limited efficacy or intolerable side effects. Smoked marijuana has been demonstrated in 2 rigorously designed studies to be effective in treating HIV neuropathy pain, which holds promise for development of alternative safer cannabinoid compounds or delivery routes for treatment of sensory neuropathy. In 2005 (Abrams, 2007.), a randomized, placebo controlled trial of cannabis cigarettes smoked three times daily for five

days in 50 patients with painful HIV neuropathy showed statistically and clinically significant reduction in pain compared with placebo cigarettes (mean reduction 34% vs. 17%, percent patients with > 30% pain reduction was 54% vs. 24%).

A second trial conducted by a different group of researchers in 2008 reproduced these results (Ellis, 2008). In this study, 34 patients received both smoked cannabis cigarettes and smoked placebo cigarettes in a blinded crossover fashion. In this study, 46% of patients experienced clinically significant pain relief with cannabis compared to only 18% with placebo. Importantly, daily functioning and mood were similar between both cannabis and placebo. It is possible that an inhaled route of administration may be of therapeutic value as it provides more rapid onset of effect, and as such is being further investigated.

Other models of neuropathic pain have also been used to study the analgesic potential of cannabinoids and some studies yielded contradictory information. In 2008, a large 96 patient study of longer treatment duration (14 weeks) compared an oral synthetic cannabinoid (nabilone) and a weak opiate medication (dihydrocodeine) in patients with chronic neuropathic pain (Frank, 2008). This randomized, double blind, crossover study showed that dihydrocodeine provided better pain relief and had slightly fewer adverse effects than nabilone. There was no placebo arm in this study, so no conclusions can be made about the intrinsic analgesic value of nabilone in chronic neuropathic pain.

Although clinical trials in humans yielded only modest analgesic efficacy, cannabinoids as a class are known to have analgesic properties based on scientifically robust animal data. Researchers are now trying to describe and understand this difference. It may reflect the differences in receptor selectivity (CB<sub>1</sub>, CB<sub>2</sub> vs. some combination of both). It may also reflect dose limiting side effects occurring via brain CB<sub>1</sub> receptors before optimal analgesic effects can be achieved via peripheral CB<sub>1</sub> and CB<sub>2</sub> receptors.

Two interesting studies using an oromucosal cannabinoid preparation in neuropathic pain may illustrate a more targeted and effective

approach to using cannabinoid therapy (Nurmikko, 2007.) . Rather than stand-alone analgesics, cannabinoids may be more useful as adjunctive therapies in cases where currently available treatments are suboptimal. In 2 recently published studies, patients were maintained on existing analgesic regimens even though pain relief was suboptimal. A cannabinoid or placebo treatment was provided as an add-on to existing analgesic regimen. In this five-week clinical study of 125 patients with neuropathic pain due to peripheral nerve injury, patients received either Sativex, (THC: CBD) or placebo in a blinded fashion.

In this robust trial with primary outcome of pain intensity and multiple secondary outcomes, all outcomes improved with the addition of Sativex. Side effects were common, and 18% of patients using Sativex discontinued the study for this reason compared with only 3% of patients taking placebo. An open-label extension study showed that the initial pain relief experienced with Sativex was maintained without dose escalation or further toxicity for 52 weeks.

In addition to using currently available cannabinoid analgesics differently than opioids and other analgesics, we should also consider that novel compounds that bind only to CB<sub>2</sub> receptors should not produce dose limiting CNS effects. Animal model studies confirm that activation of CB<sub>2</sub> receptors inhibits acute pain, inflammatory pain, and neuropathic pain. With this view, Amgen and other biotech companies are rapidly developing libraries of cannabinoid analogues to discover highly potent analogues that are specific and selective only for CB<sub>2</sub> receptors.

Effective pain relief without the risk of sedation, euphoria, abuse, or addiction is the holy grail of analgesic research and development. The concept is applicable not only to cannabinoids, but also opiates and other classes of psychoactive analgesics. Early studies do indicate promise for such compounds currently in development. In the cannabinoid class of selective compounds, a pilot randomized, placebo controlled, double blind, crossover study of CT-3 (a selective, potent synthetic THC analogue) in 21 patients with chronic neuropathic pain showed significant reduction in pain intensity with CT-3 compared to

placebo (Cheng, 2008.). In that study, both CT-3 and placebo were evaluated using the Addiction Research Center Inventory-Marijuana scale, and patients experienced no significant difference between them. In other words, the CT-3 compound seemed to have no abuse or addiction potential.

Such ‘proof of concept’ studies are an exciting development and have fueled tremendous effort in the research community. In fact, recent scientific conventions in pain management and biotechnology sciences are now largely focused in this therapeutic area. Ironically, it may be that our prevailing anguish over legalization (or not) of pot smoking “for compassionate medicinal purpose” may finally yield the necessary sympathetic resonance between science, policy, and society to move forward into a different era of analgesic development.

As inspired and dedicated voices of scientists, clinicians, and patients continue to crescendo above din of “pot politics”, we may yet prevail as we advocate for the availability of safe, effective, and evidence-based treatment for a desperately unmet clinical need – relief of pain and respite from risks of abuse and addiction. The future is promising.

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## Physician Recommendations for Marijuana: Special Populations and Contraindications

Joan E. Zweben, Ph.D. & Judith Martin, MD

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Marijuana use has long been a complex challenge for clinicians. Its effects are more subtle, and except for adolescents, its negative consequences are often more difficult to pin down. Patients in treatment for a variety of conditions can often make a convincing case that their marijuana use is harmless. Indeed, negative consequences may not become visible until there are 2-3 months of abstinence, and many patients are not easily persuaded to conduct this experiment in order to see the downside of their use more clearly. In California, the passage of the Compassionate Use Act in 1996 complicated the issue even further by giving a legal and social stamp of approval to this activity. This obliges clinicians to be more thoughtful about how they address marijuana in the treatment situation. The blurring of the boundaries between a legal and illegal drug requires careful thinking to generate appropriate interventions.

It is common to hear patients say: “I have a *prescription* for marijuana,” and staff may use this description as well. To maintain conceptual clarity, it is useful to preserve the distinction between a physician recommendation and a prescription. In the U.S., there is a long and careful process of determining safety and efficacy before a medication is approved for general clinical use. The term “prescription” refers to drugs that have the approval of the Food and Drug Administration. The California legislation states that a physician can “recommend” marijuana. The term “prescription” is often used to refer to smoked marijuana, but it is important to preserve the distinction between prescription and recommendation, as the two have quite different implications.

### Addiction Treatment

Abstinence-based addiction treatment holds that once a person has passed the boundary into uncontrolled use, he or she cannot return to controlled use. This includes not only the primary drug of abuse, but

all intoxicants. There are two main rationales for this position: 1) drug substitution is common; 2) the use of one intoxicant often precedes relapse to the primary drug of abuse. Studies have confirmed this connection for a number of drug combinations, for example, an elevated rate of relapse in stimulant users who smoke marijuana. However, many clinicians see alcoholic patients who remain sober and stable for many years, yet smoke marijuana. Recent studies found that cannabis use is not related to treatment outcome or the abuse of other drugs in methadone patients (Epstein & Preston, 2003; Weizman, Gelkopf, Melamed, Adelson, & Bleich, 2004). An older longitudinal study of youth from preschool through age 18 found that adolescents who had engaged in some experimentation, primarily with marijuana, were the best-adjusted in the sample (Shedler & Block, 1990). These relationships are complex and too little guidance exists to identify who can safely smoke marijuana, and too little systematic research has been devoted to this topic.

### Medical Marijuana and Addiction Treatment Programs

Within addiction treatment programs, it is especially important to have clear thinking on this topic. The California Society of Addiction Medicine (CSAM) (California Society of Addiction Medicine News, 1997) recommends that all physicians who recommend cannabis should adhere to the accepted standards of practice, as cited in their January 1997 issue of Action Report:

- History and physical examination of the patient
- Development of a treatment plan with objectives
- Provision of informed consent, including discussion of side effects
- Periodic review of the treatment's efficacy
- Proper record keeping that supports the decision to recommend the use of marijuana

In the case of smoked marijuana by physician recommendation, there is conflict between two principles:

- 1) Abstinence is defined as no abuse of psychoactive substances, **and** taking properly prescribed medication as directed. (this principle is also known as 'don't play doctor.')

- 2) Addiction treatment programs provide environments that are safe for recovering patients, and avoid known triggers to relapse.

A flexible approach includes getting a release to talk with the prescribing physician and determining, if possible, whether acceptable standards of care were followed. This includes a request for records. Unfortunately, issuing of recommendations based on a phone call is common in some communities and feeds the cynicism about “marijuana as medicine.” It can be useful to ask the prescribing physician if there is a substitute medication that the patient could use during his/her stay in the program.

When the recommendation is based on reasonable grounds, the program can arrange off-site smoking, with no exposure to recovering staff or patients to the marijuana smoke or smell. Marijuana should not be kept on site at treatment facilities that have addicted patients. Other forms of cannabinoid that are standardized in pill or spray, etc. would be more manageable and would minimize any cued reactivity to other patients.

### Mental Health Patients

The impact of marijuana smoking has been difficult to unravel, in part because most consumers are polydrug users. Recent studies and systematic analyses offer findings that merit thoughtful consideration. A recent review of observational studies supports the view that cannabis use could increase the risk of psychotic illness (Moore et al., 2007). This review reported an increase in risk of psychosis of about 40% in a pooled analysis of participants who had ever used cannabis. All the studies that examined the increase in risk in relation to cannabis exposure showed a dose-response relationship, with a 50% - 200% increase in risk. Although the individual lifetime risk of psychotic disorders is less than 3%, the authors conclude that there is now enough evidence to inform cannabis users of the increase in risk because exposure to this drug is so common.

Some older European studies suggest marijuana may interfere with the action of neuroleptics (Knudsen & Vilmar, 1984). This study

describes ten schizophrenic patients on verified adequate depot neuroleptic treatment whose condition was acutely aggravated following cannabis use. The authors hypothesize that cannabis acts as an antagonist to these medications. A recent Australian study reported that a higher frequency of cannabis use was predictive of psychotic relapse after controlling for medication adherence, other substance use and duration of untreated psychosis (Hides, Dawe, Kavanagh, & Young, 2006).

Evidence exists that cannabis worsens affective symptoms, but confounding variables are numerous. A follow-up of participants in the Baltimore Epidemiological Catchment Area Study (approximately 15 years later) found that cannabis smokers with no baseline depressive symptoms were four times more likely than those with no cannabis use diagnosis to have depressive symptoms at follow up (Bovasso, 2001). Suicide ideation and anhedonia were common symptoms. Subsequently, data from the National Comorbidity Survey suggested a possible causal role in the development of Major Depressive Episode (MDE) (Chen, Wagner, & Anthony, 2002). The report that the risk of a first MDE was moderately associated with more advanced stages of marijuana use.

Veterans and others with PTSD have long claimed that marijuana helps them manage their symptoms better than existing medications. However, newer medication studies indicate stronger benefits for those with intrusive symptoms.

### Adolescents

Concern about marijuana use in this age group has always been great because of the potential impact of any drug on the developing brain, and because of the distortions of self-concept that can take hold when marijuana use is frequent. Disturbances in attention and concentration bring many adolescents to conclude they are not interested in school, or are not very intelligent, or both. This feeds a cycle in which they seek a social group with similar attitudes and behaviors, and a downward spiral begins.

In 1999, the California Society of Addiction Medicine published a review and a position statement (Cermak, 1999) that remains solid in its conclusions despite a great deal of work published in the intervening years. Separating out the cause and effect relationships between an adolescent's use of marijuana and specific problems is difficult due to the presence of a large number of variables. Adolescents who use cannabis also use tobacco and alcohol at young ages and more often. They have psychiatric problems, especially conduct disorders and ADHD, as well as difficult family environments. Because of this, CSAM recommended that prevention efforts encourage adolescents to avoid or delay use of marijuana, alcohol, and tobacco. An effective strategy depends on engaging parents and the larger community in identification of high-risk youth and offering attractive alternative social activities for them.

### Clinical Vignette

The following illustrates the clinical challenges in working with patients who use marijuana:

John was a gay male methadone patient who had recently lost his partner of 20 years to AIDS. They had a close and harmonious relationship, and tended to "cocoon" rather than socialize with others. John was HIV positive, and during his period of grieving, lost weight and was barely able to go to work. He did manage to keep his job, but came home from work and vegetated in front of the television for the evening. He regularly attended a recovery group in which he received a great deal of affection and support. Group members shared the goal of achieving a satisfying life without the use of intoxicants, but group leaders did not discharge for drug use unless a group member declared he or she no longer had this commitment.

John was very open about his regular marijuana use, and his group gently challenged this behavior. He was in such pain that no one wanted to put a great deal of pressure on him, but continued to encourage him to work through his feelings and begin to generate a picture of a satisfying life ahead. Gaining and maintaining his weight was one key reason he gave for continuing to use marijuana. However, he was able to enter a university study on using human growth hormone for wasting syndrome, and this was very successful at restoring him to normal weight.

In time, he became ready to face the future, and it became clearer that marijuana interfered with mobilizing to generate a new social network. He was quite anxious about entering the social scene. Upon inquiry, he agreed

that once he smoked a joint after work, the likelihood that he would move far from his couch was small. Gradually, he began to tackle small social forays, and his marijuana smoking diminished markedly.

In summary, the legal status of marijuana has created complex challenges for clinicians. Despite some findings that marijuana may be relatively benign for some populations, there is clear evidence of high risk for certain vulnerable populations. Our role is to promote thoughtful self-examination, devoid of casualness or hysteria about use. As treatment providers, we can gear our recommendations to promoting the widest margin of safety while remaining flexible in how we address current dilemmas.

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## Why Most Physicians Will Never Prescribe Joints

Keith Humphreys, Ph.D.

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It wasn't just women with breast cancer who were excited in late 2007 when scientists at California Pacific Medical Center Research Institute showed that a compound found in marijuana may be able to block the growth of aggressive tumors. This finding also cheered activists who hope that mainstream medicine will soon embrace marijuana cigarettes as a treatment. For a range of reasons, that's extremely unlikely.

Effective medicines can of course be derived from plants. Digoxin from foxglove, atropine from belladonna and quinine from cinchona are only a few examples. The marijuana plant likewise contains potentially therapeutic compounds known as cannabinoids, one of which, cannabidiol, was examined in the breast cancer study. Other research has examined tetrahydrocannabinol (THC) - the cannabinoid in marijuana that is primarily responsible for the plant's psychoactive effects (e.g., feeling "high," mild hallucinations, changes in mood). THC has been shown to benefit at least some patients with a range of problems, including chemotherapy-induced nausea and the tremors and muscles spasms associated with multiple sclerosis.

Nonetheless, don't expect organized medicine to race to hand out reefers. Citations that the rate of support among the general public of California is 70-75% fade to insignificance when one realizes that this is at least double the level of endorsement among physicians (i.e., those who would actually do the prescribing and be responsible for the results).

Only about one third of physicians want medical prescription of marijuana to be legal (even including those who not be willing to write such prescriptions themselves), according to multiple studies including a survey of 960 physicians conducted by Brown University

researchers. For anyone who has worked in the medical field, this lack of enthusiasm for a new practice right is striking, given that in general medicine fiercely guards its autonomy and is usually eager to have unfettered access to new practice domains. What are the sources of doctors' reluctance?

Older members of the field remember vividly the era when most physicians smoked tobacco cigarettes and cheerfully rated Camel their favorite brand. The tobacco industry built on this foundation with deceptive advertisements linking doctors with smoking in the public mind, which damaged medicine's credibility.

These bitter historical experiences, supplemented by decades of subsequent research evidence that smoke inhalation of all forms (even wood smoke) can cause acute and long-term respiratory damage, make many physicians wary of recommending a smoked medicine. Anti-smoking values are so well-established in medicine that one could safely revise the adage to read "Where's there's smoke – there's a worried doctor". Indeed, to take a local example, it is impossible to imagine that Stanford Medical Center, which recently banned smoking anywhere on the grounds, would start to stock joints in its pharmacy.

A smoked plant has the further disadvantage from a medical perspective of not being pure (e.g., what if the plant had been sprayed with pesticide?) or of a standardized dose. This exposes the patient to risk of side effects, and the physician to risk of malpractice.

As the California Pacific research team noted, for example, obtaining the correct dose of cannabidiol through smoking marijuana would be virtually impossible. It would also of course cause THC's intoxicating effects (cannabidiol does not produce a high), which some patients find aversive. Will all the therapeutic components of marijuana one day be available in pure, standardized forms that can be safely administered without combustion?

Liquid THC, known as dronabinol, has been available by prescription for years and has some evidence of effectiveness, but its slow absorption after ingestion makes it unappealing to some patients. At

least one company (Solvay Pharmaceuticals) is working to make a dronabinol mist that could be taken in a standardized dose with an inhaler, such as is done with medicines for asthma. An alternative approach is to heat marijuana in a vaporizer and have patients inhale the fumes. Recent research conducted at the University of California at San Francisco indicates that this method allows THC to be inhaled without the carcinogens found in marijuana cigarettes.

These technologies may eventually make some physicians more comfortable with prescribing THC. But others will have the opposite reaction because purified, inhalable (and therefore fast-acting) THC could carry more addictive risk than marijuana itself. Addiction medicine specialists are aware of this possibility, which may be why the Brown University survey showed that they were less sanguine about medical marijuana than doctors in any other specialty.

In general, as plant-based compounds are processed and purified (e.g., from coca leaf to cocaine or opium poppy to morphine) or are administered through a more rapid, efficient route (e.g., from ingesting to smoking), their power to produce addiction increases. In other words, the very dosing technologies that could make THC more pure, potent and fast-acting as a medicine may also make it more likely to produce dangerous dependence.

There may be no way to cut this Gordian knot, but one English company is trying. G.W. Pharma breeds and grows marijuana plants under controlled conditions designed to maximize the plant's therapeutic potential and minimize its intoxicating and dependence-producing effects. Their product, a nasal spray, is approved for medical use in Canada under the trade name Sativex. Because Sativex is a botanical (i.e., composed of plant matter rather than synthetic), U.S. Food and Drug Administration approval would historically have been impossible, but the agency recently developed guidelines in this area and has approved one botanical (Veregen, composed of green tea leaves) for medical use.

Whether Sativex will produce good results – including not being addictive -- in all the required clinical trials and then clear FDA

regulatory hurdles remains to be seen. In any event, its makers have clearly grasped something important about medicine: You can't become associated with the status and trust society bestows on doctors without at the same time accepting the scientific and ethical rigor to which doctors are subject. Too many advocates of reefer as medicine want medicine's legitimacy without its accompanying responsibility, and that's why marijuana deservedly remains a bit player in mainstream medicine practice.

## Appendix

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### The Road to FDA Approval of Drugs

The Food and Drug Administration (FDA) is part of the Department of Health and Human Services. It is charged by the Federal Food, Drug and Cosmetic Act to approve the entry of drugs into the American market. To gain approval, a sponsor must prove that the drug is both safe and effective in controlled clinical trials.

In most instances, sponsors are pharmaceutical corporations who make a large investment in order to secure a substantial share of a lucrative market. It is a long and expensive venture with an uncertain outcome.

In a few exceptions, institutions like the National Institutes of Health have sponsored clinical trials for drugs targeted for the treatment of cancer, AIDS, addiction, and epilepsy. They then collaborate with pharmaceutical companies for manufacturing and marketing.

To begin the process, the sponsor must have a purified compound, usually synthesized in their own laboratories, and sometimes licensed from another entity such as a foreign company. They must provide scientific evidence of the safety and efficacy in laboratory animals that will predict a similar outcome in human beings having a clearly defined medical condition. This constitutes the *preclinical phase* of the process and often takes as long as five to ten years.

When this has been completed, the sponsor can file an application for an Investigation New Drug (IND). The application must provide a detailed plan for human clinical trials which includes the number of patients to be studied, the number and names of the institutions to be involved, the comparison vehicle, (e.g. a placebo) or an already approved drug, and the structures for oversight of safety and statistical analysis. The study end-points and the indications requested must be carefully defined. Only about twenty percent of drugs successfully complete this process and achieve approval for marketing.

The *clinical phase* of testing is divided into three phases. Phase I determines preliminary safety and proper dose. Phase II evaluates effectiveness and looks for adverse reactions which can stop the process. Phase III enlarges the study group and prolongs the assessment of long-term side effects. These three phases typically require more than five years to complete.

The FDA monitors the clinical phases very carefully and will alert for any suggestions of adverse reactions. At any hint of serious problems, the FDA will intervene and terminate or suspend the trial pending clarification.

Upon successful completion of the clinical phases, the sponsor submits a New Drug Application (NDA) to the FDA. The document must contain all the data from the clinical phases as well as information on the drug's pharmacology, and the data on the bioavailability and toxicology. Detailed descriptions of the manufacturing and its controls must be provided including data on drug's shelf-life.

The total cost to a sponsor for the development of a new drug has been estimated to be anywhere from three hundred million dollars to more than one billion dollars, depending on the complexity of the drug and the size of trials required. Some of this money is paid to the clinical investigators and their institutions, usually medical schools, for overhead and support.

The FDA relies on the review and analysis of experts in the field to serve on advisory panels to recommend approval or not. There has been recent controversy about this process since members of advisory panels have been permitted to serve despite their close financial relationships with the sponsors.

Once the sponsor has achieved approval, they can market the drug for the approved indication. If the sponsor wants the drug to be used for other types of indications, they must submit supplemental applications supported by additional clinical trial data. The time for approval of supplemental applications can be lengthy since they are given lower priority than new drug applications.

New formulations of the drug must also be approved. For example if a drug was initially approved for oral administration, a formulation for an inhalant-type version of the product would have to be supported by clinical trials and approved.

There are two additional categories that deserve mention. One is the orphan drug program that provides incentives for manufacturers to develop drugs to treat diseases, which effect two hundred thousand or fewer U.S. patients. The other is the Treatment IND program, which permits persons with the disease targeted by an IND to obtain access to the drug while it is still in Phase III trials.

In addition to the FDA approval, The Drug Enforcement Administration (DEA), a part of the Justice Department, is charged by the Controlled Substances Act (CSA) to assign drugs with potential for abuse to schedules that limit their access and use. For example, Schedule I includes heroin, LSD and marijuana because they have high potential for abuse, they have no currently accepted medical use in treatment. Schedule II includes Marinol, methadone, methamphetamine, and cocaine, all of which have high abuse liability but do have currently accepted medical uses, albeit with severe restrictions.

The marijuana plant is considered a botanical substance that cannot be approved by the FDA because of contains a complex mixture of substances that are not uniform or purified. Botanicals can be marketed as “dietary supplements” but the marijuana plant still falls under the restrictions of the CSA and the DEA as a Schedule I entity that cannot be marketed.



## *About the Authors*

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### **DONALD R. AVOY, M.D.**

Donald R. Avoy is a graduate of the University of Colorado and Stanford Medical School where he also did postdoctoral training in Internal Medicine and a fellowship in Hematology. Following that training he was in private practice and also served as Medical Director of the regional Red Cross Blood program in this area. He also spent several years as Medical Director of Syntex Diagnostic Division (SYVA). He has published many articles in scientific journals and is also the author of "Descent" a novel about heroin addiction. Dr. Avoy is also the editor of the book, "Professional Perspectives on Addiction Medicine: Understanding Opioid Addiction and the Function of Methadone Treatment".

Since 1997, Dr. Avoy has been with the Santa Clara Valley Health & Hospital System Department of Alcohol & Drug Services Addiction Medicine Division.

### **TIMMEN L. CERMAK, M.D.**

Timmen L. Cermak studied philosophy as an undergraduate at Ohio Wesleyan University, before graduating from Case Western Reserve Medical School in 1972. After 2 years with the Indian Health Service, he entered his psychiatry residency at Stanford, where he assisted Dr. Stephanie Brown in creating the first therapy group for adult children of alcoholics. Following a post-doctoral fellowship in neurophysiology under Dr. Karl Pribram, he served as medical director of the alcohol inpatient unit at the San Francisco V.A. hospital from 1982-85. During this time he helped found the National Association for Children of Alcoholics (NACoA), serving first as president and then chairman of the board. He currently has private practice offices in San Francisco and Mill Valley, CA.

Dr. Cermak is Board Certified in Psychiatry, with a Certificate of Added Qualification in Addiction Psychiatry. He is also certified by

the American Society of Addiction Medicine (ASAM). He serves on the Executive Council of the California Society of Addiction Medicine (CSAM), chaired CSAM's task force on medical marijuana and is editor of the society's newsletter. He is currently President-Elect of CSAM and co-chairs the subcommittee on Screening, Intervention and Referral for the Governor's Prevention Advisory Council. Dr. Cermak is also a member of the American Academy of Psychiatrists in Alcohol and Addictions (aaPaa).

He is the author of *A Primer on Adult Children of Alcoholics, Diagnosing and Treating Co-dependence, A Time to Heal, Evaluating and Treating Adult Children of Alcoholics*, and *A Time To Heal Workbook*. His most recent work, *Marijuana: What's a Parent to Believe?*, was published by Hazelden in August of 2003.

## **ROBERT GARNER**

Robert Garner is the Director of the Santa Clara Valley Health & Hospital System, Department of Alcohol & Drug Services. For over thirty years, he has been the driving force behind the development of innovative and effective quality systems of care. As a recognized leader in the substance abuse health care profession, Robert Garner brings the most current research-based methods to efficiently coordinate services and operate a large County Department. As the Director, his Department was the first County in the State to develop a managed and coordinated system of care for adult treatment. His Department was also the first to fund a psychiatrist to provide for dually diagnosed clients in the treatment system and the first County to fund a network of transitional housing services to support clients in recovery.

Recognizing that continuing education is key to maintaining a high standard of care, Mr. Garner developed the Learning Institute and the Research Institute focusing on implementing evidence – based best practices in the County and bringing nationally renowned experts to provide on-going training to the provider groups that comprise the County's system of care. Robert Garner has brought forth the gold standard for others to follow on how to blend high quality standards

into an integrated system of care that is strategic, evidence-based and financially responsible

Robert Garner is also the Founding member and past President of the California Association of County Drug and Alcohol Administrators where he is currently the Chairman of the Youth Committee.

### **KEITH HUMPHREYS, PH.D**

Keith Humphreys is a Professor of Psychiatry at Stanford University School of Medicine and Research Career Scientist in the Department of Veterans Affairs (VA). His research center studies treatments and self-help programs for substance abuse and psychiatric disorders. In addition to his scientific projects, he is actively involved in teaching addiction treatment methods to medical students, psychiatric residents, and clinical psychology interns. Professor Humphreys has published more than one hundred scientific articles, has received national and international awards for his work, and has been a consultant to The White House Office on National Drug Control Policy, The White House Office on Faith-Based and Community Initiatives and The National Institutes of Health. He currently serves on the VA Undersecretary for Health's Committee on the Care of Seriously Mentally Ill Veterans and the National Advisory Committee of the Substance Abuse and Mental Health Services Administration. He has also served as a consultant on mental health-related issues to agencies in other nations, including Spain, Bulgaria, Iraq, Ireland, Canada, and South Africa. His opinions on public policy matters do not necessarily reflect official positions of any organization with which he is affiliated

### **JUDITH MARTIN, M.D.**

Judith Martin, M.D. is the Medical Director for the Bay Area Addiction Research and Treatment program. She is the President of the California Society of Addiction Medicine (CSAM) and Chairs the CSAM Committee for the Treatment of Opioid Dependence.

**RAPHAEL MECHOULAM, PH.D.**

Raphael Mechoulam obtained his Ph.D. degree from the Weizmann Institute in Rehovot, Israel, under the supervision of Prof. F. Sondheimer. He is professor of medicinal chemistry (emeritus) at the Hebrew University of Jerusalem where he established the Department of Natural Products. Some of the main achievements of his group include the isolation, identification and synthesis of the major active principle of marijuana ( $\Delta^9$ -tetrahydrocannabinol) and other plant cannabinoids, the isolation and identification of the first endogenous cannabinoids (anandamide and 2-arachidonoyl glycerol), the identification of numerous active plant and mammalian natural products and initial investigations on the biological activities of these compounds. His main research interest is the chemistry, biological activity and clinical applications of natural products and drugs.

Raphael Mechoulam has been awarded numerous prizes for his scientific work and has published more than 350 scientific articles. He is a member of the Israel Academy of Science.

**MAXIMILIAN PETERS, B.Pharm. M.Sc.**

Maximilian Peters is a graduate of the Ludwig-Maximilians-University of Munich, Germany. His M.Sc. thesis was on the chemistry and anticancer properties of novel cannabinoid derived drugs. He is currently doing research on the actions of cannabinoids on Transient Receptor Potential ion channels under the supervision of Prof. Raphael Mechoulam and Prof. Baruch Minke at the Hebrew University of Jerusalem, Israel.

**SUMA SINGH, M.D.**

Suma Singh completed primary medical training at Boston University Medical School, and subspecialty training in Anesthesiology at Brigham & Women's Hospital/Harvard Medical School. During a Pain Management Fellowship at Stanford University Medical Center, she was introduced to Addiction Medicine while learning how to treat Chronic Pain in Addicted Patients at the Stanford Hospital Inpatient

Psychiatric Unit. Upon completion of her Fellowship, she began full-time clinical research in development of chronic pain medications with reduced abuse liability.

Dr. Singh began working with patients in Methadone Maintenance almost 10 years ago, while still engaged in full-time clinical research. Over the years, balance of patient care & clinical research shifted such that she currently works full-time as Medical Director for Department of Alcohol and Drug Services for Santa Clara Valley Health and Hospital System and provides teaching to VMC HHS physicians-in-training on the management of patients with addiction and chronic pain. She also intermittently provides clinical research consulting to other research teams in these areas.

### **MARK STANFORD, PH.D.**

Mark Stanford is the Senior Manager of Medical and Clinical Services for the Santa Clara Valley Health & Hospital System Department of Alcohol & Drug Services - Addiction Medicine and Therapy Division. He has direct clinical experience working in every modality of addictions treatment including inpatient, residential, day treatment, outpatient and medication-assisted treatment programs.

Dr. Stanford is a clinical research educator in the behavioral neurosciences. He has taught psychopharmacology throughout the Bay Area including a 20-year history with UC Berkeley Extension Department of Biological and Behavioral Sciences and Mathematics, and as a lecturer at Stanford University Department of Family and Community Medicine. He also teaches Treatment and Clinical Considerations of Substance Abuse Disorders for LCSW's, MFT's and Psychologists for their CEU licensing requirements.

He is the author of numerous materials in behavioral neuroscience including the textbook, *Foundations in Behavioral Pharmacology – An Introduction to the Neuroscience of Drug Addiction and Mental Disorders*. He is also the Chief editor of the book, *Professional Perspectives on Addiction Medicine: Understanding Opioid Addiction and the Function of Methadone Treatment*.

**NORA D. VOLKOW, M.D.**

Nora D. Volkow became Director of the National Institute on Drug Abuse (NIDA) in May, 2003. Dr. Volkow came to NIDA from Brookhaven National Laboratory (BNL), where she held concurrent positions including associate director for life sciences, director of nuclear medicine, and director of the NIDA/Department of Energy Regional Neuroimaging Center. In addition, Dr. Volkow was a professor in the Department of Psychiatry and associate dean of the medical school at the State University of New York-Stony Brook.

At Brookhaven, Dr. Volkow was the first to use imaging to investigate neurochemical changes that occur during drug addiction. Her primary focus was on mechanisms underlying the reinforcing, addictive, and toxic properties of drugs of abuse in the human brain.

Dr. Volkow received her B.A. from Modern American School, Mexico City, Mexico, her M.D. from the National University of Mexico, Mexico City, and her postdoctoral training in psychiatry at New York University. In addition to BNL and SUNY-Stony Brook, Dr. Volkow has worked at the University of Texas Medical School and Sainte Anne Psychiatric Hospital in Paris, France.

**JOAN ZWEBEN, PH.D.**

Joan Ellen Zweben, Ph.D. is a clinical psychologist with over thirty-five years' experience in treating addiction, and training treatment practitioners. These practitioners include peer counselors, social workers, marriage and family counselors, psychologists, probation officers, nurses and physicians. She has a broad based background in both alcoholism and drug dependence, and has experience with both residential and outpatient modalities. She has a long-standing commitment to building treatment resources through networking activities.

Dr. Zweben is the founder and Executive Director of The East Bay Community Recovery Project and The 14th Street Clinic & Medical Group and has steadily developed the medical and psychosocial

services of these affiliated organizations. Her activities as an author, teacher, and consultant keep her informed of new developments in the field. She is the author of 3 books, over 55 articles or book chapters and editor of 15 monographs on treating addiction.

Dr. Zweben is a Clinical Professor of Psychiatry; University of California, San Francisco.



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