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*"With marijuana legislation making headlines almost daily, The Pot Book's timing is impeccable. It takes a candid look at all things cannabis from all angles: history, scientific research, medicinal use, our nation's drug policy, myths, and misconceptions. I recommend this book as a comprehensive must-have guide for any library."*

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*"Consulting with the top experts in the field, Dr. Julie Holland presents the current science and makes a compelling case for the need for further research, unencumbered by anti-drug hysteria, as well as an immediate change to our nation's puritanical drug laws."*

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Exploring the role of cannabis in medicine, politics, history, and society, *The Pot Book* offers a compendium of the most up-to-date information and scientific research on marijuana from leading experts, including Lester Grinspoon, M.D., Rick Doblin, Ph.D., Allen St. Pierre (NORML), and Raphael Mechoulam, Ph.D. Also included are interviews with Michael Pollan, Andrew Weil, M.D., and Tommy Chong as well as an ACLU lawyer and a forensic toxicologist growing cannabis for the U.S. government.

Encompassing the broad spectrum of cannabis knowledge from stoner customs to scientific research, this book investigates the top ten myths of marijuana; its physiological and psychological effects; its risks; why joints are better than water pipes and other harm-reduction tips for users; how humanity and cannabis have co-evolved for millennia; the brain's cannabis-based neurochemistry; the complex politics of cannabis law; its potential medicinal uses for cancer, AIDS, Alzheimer's, multiple sclerosis, and other illnesses; its role in creativity, business, and spirituality; and the complicated world of pot and parenting. As legalization becomes a reality, this book candidly offers necessary facts and authoritative opinions to a society steeped in marijuana myths, misconceptions, and stereotypes.

JULIE HOLLAND, M.D., is a psychiatrist who specializes in psychopharmacology and a clinical assistant professor of psychiatry at NYU School of Medicine. An expert on street drugs and intoxication states, she was the attending psychiatrist in the Psych ER at Bellevue Hospital from 1996 to 2005 and regularly appears on the *Today Show*. The editor of *Ecstasy: The Complete Guide* and the author of the bestselling *Weekends at Bellevue*, she lives in the Hudson Valley.

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HOLLAND

The Pot Book

# The Pot Book

## A Complete Guide to Cannabis

### Its Role in Medicine, Politics, Science, and Culture

EDITED BY
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***Note to the reader:*** This book is intended as an informational guide. The approaches and techniques described herein should not be seen as an endorsement to use marijuana. They also should not be used to treat a serious ailment without prior consultation with a qualified healthcare professional.

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*To the late John Paul Morgan, M.D., chemist, genius, New Yorker, musician, scientist, professor, and friend, who passed away on February 15, 2008. His book* Marijuana Myths/Marijuana Facts: A Review of the Scientific Evidence, *coauthored with Lynn Zimmer, Ph.D., and published by the Lindesmith Center in 1997, helped debunk the following myths:*

Marijuana's harms have been proven scientifically.
Marijuana has no medicinal value.
Marijuana is highly addictive.
Marijuana is a gateway drug.
Marijuana offenses are not severely punished.
Marijuana policy in the Netherlands is a failure.
Marijuana kills brain cells.
Marijuana causes an amotivational syndrome.
Marijuana impairs memory and cognition.
Marijuana can cause permanent mental illness.
Marijuana causes crime.
Marijuana interferes with male and female sex hormones.
Marijuana use during pregnancy damages the fetus.
Marijuana use impairs the immune system.
Marijuana is more damaging to the lungs than tobacco.
Marijuana's active ingredient, THC, gets trapped in body fat.
Marijuana use is a major cause of highway accidents.
Marijuana-related hospital emergencies are increasing, particularly among youth.
Marijuana is more potent today than in the past.
Marijuana use can be prevented

complaints, it is worthwhile to consider the spiritual aspects of its use, the soul-feeding effects.

Many people who are depressed feel overwhelmed and defeated, their souls crushed as they "suffer the slings and arrows" of daily life. Certainly my patients in New York City are weighed down by a barrage of constant worries delivered around the clock via e-mail, voicemail, and to-do lists. If cannabis creates a sense of respite from all that, an oasis of sorts, might that be therapeutic in and of itself? Separating what is therapeutic from what is recreational can become quite murky with regard to treating depression. The euphoria or giddiness that may come from "recreational" use of cannabis may be just what the doctor ordered when the target symptoms are a depressed mood and a pessimistic outlook.

Think of the Dove bar commercial: "My moment. My Dove." Or the Starbuck's Frappuccino ad: "It's 'You' Time." What is being marketed here is the delineation of time, creating a marked boundary, a timeout, giving you permission to relax, perhaps to be alone, where no one can get to you, and there are no responsibilities or chores to be done. Meditation—sitting still, breathing deeply, and clearing the mind—is a therapeutic activity with myriad benefits for mental health and wellness. An herbal medicine to assist "going within," to facilitate psychospiritual exploration, to allow solitude, and, more importantly, comfort in that solitude may likewise have a positive impact on mental health.

## CONCLUSION

Mental health disorders, like most physical ailments, are multifactorial. Psychiatric ailments have their basis in a triad of psychological, sociological, and biological underpinnings. If an herbal remedy can offer substantial relief, it makes sense to take advantage of that first and foremost, either as a substitute for other psychiatric medications, or as a complement to allow lower doses or enhanced compliance with a current regimen.

The bottom line is that we need to know more. More research needs to be performed so we can all adequately understand whether cannabis can be a useful adjunct to psychiatric healing and another "weapon in the armamentarium" of psychopharmacologists to combat psychiatric illnesses. This observation by Marian Fry, M.D. (quoted in O'Shaughnessy 2007), sums it up nicely: "Health is a state of mind, body, and spirit. By restoring their connection to nature, cannabis helps patients on all three levels."

# 25
# Cannabinoids and Neuroprotection

Sunil K. Aggarwal, M.D., Ph.D., and
Gregory T. Carter, M.D.

"Scientific" information disseminated by governmental organizations that promote and enforce cannabis prohibition laws would have you believe that consuming cannabis has no benefit for your brain and nervous system, and in fact has severely detrimental effects, with no exceptions. This must be the case, right? After all, how else can we account for the draconian penalties meted out for some violators of the cannabis prohibition laws? Clearly cannabis use must insidiously "rot" away one's brain, right? Wrong. Nothing could be further from the truth.

Although inhaling cannabis smoke may acutely stimulate the brain's natural "forgetting faculty," by no means does this imply that cannabis is causing "brain damage." Rigorous, peer-reviewed scientific work has consistently demonstrated that chemicals in marijuana, especially the cannabinoids, are actually neuroprotective and can be used to prevent and treat neurotoxicity and neuroinflammation. As your head begins to stop spinning, prepare to be startled by many other ground-shaking discoveries coming out of the emerging field of cannabinoid medicine.

In this chapter, we will review the importance of neuroprotection and the role that cannabinoids play in facilitating it. Let's begin by developing a basic understanding of the molecular signaling system in your body known

as the endocannabinoid, or endogenous cannabinoid, system. The discovery of an endogenous cannabinoid system with specific receptors and ligands has taken our understanding of the actions of cannabis from folklore to valid science (Pacher, Batkai, and Kunos 2006). It now appears that the cannabinoid system evolved with our species and is intricately involved in normal human physiology, specifically in the control of movement, pain, appetite, memory, immunity, and inflammation, among others. The detection of widespread cannabinoid receptors in the brain and peripheral tissues suggests that the cannabinoid system represents a previously unrecognized ubiquitous network in the nervous system. Dense receptor concentrations have been found in the cerebellum, basal ganglia, and hippocampus, accounting for the effects of cannabis on motor tone, coordination, and mood state (Hollister 1986, 1988; IOM 1982). Low concentrations are found in the brainstem, accounting for the remarkably low toxicity of cannabis. Notably, lethal doses for cannabis in humans have not been described (Di Marzo, Bisogno, and De Petrocellis 2000; FDA 1992; Pertwee 2000).

One way to think of a drug that works via a receptor system is to think of a lock and key, where the receptor is the lock and the drug is the key. A perfect fit is required for the key (drug) to open the lock (receptor), which then triggers a cellular response when opened. So far we know of at least two molecular receptor proteins (CB1 and CB2) and two endogenously produced lipid cannabinoids, AEA and 2-AG (anadamide and 2-acylglycerol, respectively), found in numerous tissues throughout the body, including neural and immune tissues. The cannabinoid system helps regulate the function of other systems in the body, making it an integral part of the central homeostatic modulatory system, the check-and-balance molecular signaling network in our bodies that keeps us at a healthy "98.6."

However, as we all know, due to wear and tear, insult and injury, homeostasis can be thrown off-kilter by loads that the body's systems cannot rally from on its own. This is where cannabis botanical medicine is a boon. Modern medical science has confirmed the findings of millennia-old traditional healing systems—that dried cannabis flowers contain compounds that can treat and prevent disease. When cannabinoids found in the resin produced by flower glands of the cannabis plant are administered, they interact structurally and functionally with the body's cannabinoid system.

We will focus here on two well-studied phytocannabinoids (or plant-derived cannabinoids): tetrahydracannabinol (THC) and cannabidiol (CBD). Research has shown that what makes these molecules neuroprotective is their ability to influence brain and immune function at the molecular level, their powerful intrinsic antioxidant activity, and their actions on various other targets, known and unknown.



Why is neuroprotection important? Neuroprotection refers to mechanisms and strategies used to protect against neuronal injury, degeneration, or death in the central nervous system (CNS), especially following acute disorders such as stroke or traumatic brain injury or as a result of chronic neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and multiple sclerosis (MS) (Hill 2006). Neuroprotection has been proposed as a potential strategy to prevent the onset of neurodegenerative diseases (Carter and Weydt 2002; Carter et al. 2003). One common pathway of numerous neurodegenerative diseases is known as excitotoxicity.

Excitotoxicity refers to a process by which nerve cells are damaged and killed by glutamate, the major excitatory neurotransmitter in the mammalian brain, and other substances. Toxicity occurs due to overactivation of cellular glutamate receptors, leading to a pathological influx of calcium ions, which in turn activates cell-damaging enzymes. Another common mechanism of neurodegeneration that is often interlinked with excitotoxicity involves unchecked production of free radicals. Free radicals are atoms and molecules with unpaired electrons that are normally produced through oxidative processes in the body. When they are not scavenged and are allowed to accumulate, they can cause oxidative damage in cells through a process called oxidative stress. Cannabinoids can modulate both these processes and have been shown to be neuroprotective in several major human diseases, which we will now overview.

## THE THERAPEUTIC ROLE OF CANNABIS IN NEURODEGENERATIVE DISORDERS

### *Amyotrophic Lateral Sclerosis*

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a rapidly progressive, usually fatal disorder characterized by the ongoing loss of motor neurons in the brain, spinal cord, and peripheral nervous system. The vast majority of ALS cases occur sporadically, with unknown etiology. ALS affects men more commonly than women, with a male-to-female ratio of approximately 1.5:1. ALS typically affects adults aged forty to sixty years, with a mean onset age of fifty-eight years (Krivickas and Carter 2005).

ALS is more common in urban areas, possibly due to environmental factors. Considerable geographic clustering has been seen in association with

ALS, most notably in the Western Pacific region of the world, but more recently in Gulf War veterans. Despite clustering, environmental or causal factors remain to be determined (Krivickas and Carter 2005). Young males with ALS have the best prognosis and may have a longer life expectancy.

A notable example of this is theoretical astrophysicist Stephen Hawking, who was diagnosed with ALS while in graduate school in his early twenties. He has now survived over four decades with the disease and continues to lecture all over the world, using a speech synthesizer activated by eye movement. Unfortunately, the typical prognosis for ALS is grim: about half of all ALS patients die within two-and-a-half years after the onset of symptoms (Krivickas and Carter 2005). Survival rates vary somewhat, depending on the patient's decision to use a feeding tube and assisted ventilation. Nonetheless, five years after being diagnosed, only 25 percent of ALS patients are still alive (Carter and Miller 1998).

An estimated 10 percent of all ALS cases are familial, usually inherited as an autosomal dominant trait. About 15 percent of these cases result from a gene defect on chromosome band 21q12.1, which leads to a mutation in the antioxidant enzyme Cu/Zn superoxide dismutase (SOD1) (Carter and Miller 1998). Emerging evidence suggests that this mutation results in increased oxidative stress for the motor neurons, which is presumably related to free radical toxicity, leading to cell death. ALS is not a rare condition; there are an estimated thirty thousand Americans living with it, and population studies indicate that the prevalence is increasing (Carter and Miller 1998; Krivickas and Carter 2005).

Studies suggest that excessive glutamate, an excitatory neurotransmitter in the CNS, is involved in the disease process. Serum, spinal fluid, and brain tissue of patients with ALS contain excessive levels of glutamate, which is apparently due to reduced clearance of glutamate from the motor cortex and decreased activity of glutamate transport proteins (Weiss 2004). Studies done in animal models of glutamate-induced neurotoxicity have shown that cannabinoids afford protection against oxidative damage induced by free radicals produced by glutamate (Hampson 2002; Hampson et al. 1998, 2000; Mechoulam and Shohami 2006; Raman et al. 2003; Van der Stelt et al. 2001). Administration of delta-9-THC both before and after the onset of ALS symptoms slowed disease progression and prolonged survival in animals compared to untreated controls (Abood et al. 2001).

Other trials in animal models of ALS have also shown that naturally occurring and synthetic cannabinoids slow down the progression of ALS (Bilsland et al. 2006; Weydt et al. 2005). Another recent study showed that blocking the CB1 cannabinoid receptor extended the lifespan of mice with ALS (Bilsland et al. 2006). This suggests that some abnormality within our internal cannabinoid system may be part of the underlying disease mechanisms in ALS. It is clear that cannabinoids are able to slow down the progression of ALS in mice, likely by acting as an antioxidant, among other mechanisms (Eshhar, Striem, and Biegon 1993; Hansen et al. 2001). This would limit the amount of damage done by free radicals produced by excess glutamate.



There are several other studies published using mice with a model of ALS that clearly show a significant benefit from cannabinoids, including delta-9-THC (Abood et al. 2001; Akinshola, Chakrabarti, and Onaivi 1999; Weydt et al. 2005). This same beneficial effect has also been shown in spinal neurons taken from these mice and cultured in nutrient gel (Weydt et al. 2002).

Based on these promising preclinical findings, some experts in this field are now recommending cannabis for their ALS patients (Greene 2007). In addition to the neuroprotective effect, patients also report that cannabis helps in treating symptoms of the disease, including alleviating pain and muscle spasms, improving appetite, diminishing depression, and helping manage sialorrhea (excessive drooling) by drying up saliva in the mouth (Amtmann et al. 2004). Indeed, in a large survey it was noted that ALS patients who were able to obtain cannabis found it preferable to prescription medication in managing their symptoms. However, this study also noted that the biggest reason ALS patients were not using cannabis was their inability to obtain it, due to either legal or financial reasons or lack of safe access (Amtmann et al. 2004).

In summary, there is strong scientific basis to support the use of marijuana in the pharmacological management of ALS. Moreover, further investigation both at the clinical and basic science level into the usefulness of cannabionoids in treating ALS is warranted.

### *Multiple Sclerosis*

Multiple sclerosis (MS) is a chronic relapsing neuro-degenerative disease that produces widespread demyelination (loss of myelin, the insulative sheath that covers nerve cells to speed the transmission of signals) of nerve cells in the brain and spinal cord, leading to muscular weakness and a loss of coordination. In some cases the disease can be fatal. According to the U.S. National Multiple Sclerosis Society, about two hundred people are diagnosed every week with the disease, typically in the range of twenty to forty years of age.

Reports of the ability of cannabis to reduce MS-related symptoms including pain, muscle spasticity, depression, fatigue, and incontinence are now well established in the medical literature (Baker et al. 2000; Brady et al. 2004; Chong et al. 2006; Cosroe et al. 1997; DeSanty and Dar 2001; Greenberg, Weiness, and Pugh 1994; Meinck, Schonle, and Conrad 1989; Rog et al. 2005; Ungerleider et al. 1987; Wade et al. 2004a, 2003; Zajicek et al. 2003). This has led many MS patient organizations, including the MS Societies of Britain and Canada, to now stand in favor of the use of cannabis to treat MS (Page et al. 2003; Wade et al. 2004b).

Not only is MS-related symptomatology treatable with cannabis, but recent clinical and preclinical studies also suggest that cannabinoids may inhibit the disease progression. Investigators at the London Institute of Neurology reported that administration of the synthetic cannabinoid agonist WIN 55,212-2 provided significant neuroprotection in an animal model of multiple sclerosis (Pryce et al. 2003). The results of this study are important because they suggest that in addition to symptom management, cannabis may slow the progression of MS in a similar fashion to its reported effects in ALS. In both ALS and MS, cannabis and cannabinoid medicine may slow the neurodegenerative processes enough that it may ultimately limit the degree of chronic disability in these diseases.

Investigators at Vrije University Medical Center in the Netherlands reported in 2003 that administration of oral delta-9 THC boosts immune function in patients with MS (Killestein et al. 2003). These results suggest the possibility that cannabis may be a disease-modifying treatment for MS. More recently, clinical data from an extended open-label study (a study where there is no placebo, and the study participants know they're getting the active drug) of 167 multiple sclerosis patients reported that orally administered whole-plant cannabis extracts relieve pain, spasticity, and bladder incontinence, with effects lasting for an extended period of treatment (mean duration of treatment for study participants was 434 days) without requiring subjects to increase their dose (Vaney et al. 2004). These results demonstrate that cannabis, unlike other drugs to treat pain and spasticity, does not rapidly induce tolerance. Moreover, these results suggest that the cannabinoid therapy was actually slowing the disease progression, since the same dose remained equally effective over the course of this extended study.

The British government is now sponsoring a three-year clinical trial to assess the long-term effects of cannabinoids on MS-associated symptom management as well as disease progression. Moreover, Health Canada also



recently approved the prescription use of a cannabis-based medicinal extract (Sativex, nabiximols) for the treatment of MS-associated neuropathic pain. Similar approval of cannabis extracts is pending or regionally approved in Britain and other European countries.

### *Alzheimer's Disease*

Alzheimer's disease (AD) is also a progressive, neurodegenerative disorder of unknown etiology. However, beyond that, all similarity to ALS stops. AD is characterized by a progressive deterioration of memory and overall cognitive functioning. Other symptoms of AD include aggressive behavior and agitation, depression, appetite loss, and, occasionally, in advanced cases, difficulty walking. The disease is estimated to affect about 5 million Americans. In 2006 the worldwide prevalence was 26.6 million. By 2050, prevalence is expected to quadruple, by which time one in eighty-five persons worldwide will be living with the disease (Brookmeyer et al. 2007). Alzheimer's usually begins after age sixty, though some younger people may very rarely have early-onset Alzheimer's. The risk of developing Alzheimer's goes up with age. Around 5 percent of men and women ages sixty-five to seventy-four have Alzheimer's, and nearly half of those age eighty-five and older may have the disease, though Alzheimer's is not a normal part of aging.

There are a number of physiological and anatomical changes that occur in the brains of AD patients. Nerve cells die in parts of the brain that are vital to memory and other functions, and connections (synapses) between nerve cells are broken. This disruption in synaptic connections within the brain lead to impaired thinking and memory problems. Alzheimer's starts with mild memory problems and can end with severe brain damage. How fast the disease works and the course the disease takes vary from person to person. Average Alzheimer's patients live from eight to ten years after they are diagnosed, though they can live as long as twenty years. Biopsies of the brains of AD patients show numerous amyloid plaques—hardened protein deposits that are thought to directly cause most of the central nervous system dysfunction seen in AD.

Sometimes the term *dementia* is used to describe the symptoms caused by these changes in brain function. Some symptoms may include asking the same questions repeatedly; becoming lost in familiar places; being unable to follow directions; getting disoriented about time, people, and places; and neglecting personal safety, hygiene, and nutrition. There is no set schedule or rate at which people with dementia develop symptoms. While dementia

is certainly part of AD, there are also many other conditions, reversible and permanent, that can cause dementia.

There are currently no Food and Drug Administration (FDA)–approved treatments or medications available that actually modify the disease course of AD. There are only a few drugs (Aricept [donepezil] and Namenda [memantine]) that have been FDA-approved to treat symptoms of the disease, but these drugs do not actually improve the long-term prognosis. None of these drugs halt the formation of plaques in the brains of AD patients.

There is now ample evidence in the medical literature to indicate that cannabis may provide not only symptomatic relief to patients afflicted with AD, but it also actually limits the formation of new plaques in the brain. Thus, it appears that cannabis may actually slow down the progression of the disease. In a study done at Scripps Research Institute in California, researchers reported that delta 9-THC, both in the test tube and in computer models, inhibited the enzyme responsible for the aggregation of amyloid plaque, which is the primary marker for AD, in a manner considerably superior to the FDA-approved AD drugs such as donepezil and tacrine (Cognex) (Eubanks et al. 2006).

This study identified a mechanism whereby cannabinoids can directly impact AD pathology. The researchers concluded that cannabinoids, including delta 9-THC, may provide an improved therapeutic treatment for AD that simultaneously treats both the symptoms and the progression of the disease. Other studies, both in vitro and in vivo, have shown that cannabidiol (CBD) and the synthetic cannabinoid WIN-55,212-2 can help prevent brain-cell death that results from exposure to the amyloid plaques and can also improve memory (Iuvone et al. 2004; Marchalant et al. 2008; Marchalant, Rosi, and Wenk 2007).

Other recent studies have shown that injecting the synthetic cannabinoid WIN 55,212-2 directly into the brain significantly decreased neurotoxicity and helped prevent cognitive impairment in rats injected with amyloid-beta peptide (a protein that induces AD in rats) (Ferraro et al. 2001; Ramirez et al. 2005). The cannabinoid appeared to reduce the neuroinflammation associated with AD. Previous preclinical studies have demonstrated that cannabinoids can prevent cell death by antioxidation (Hampson et al. 1998). In addition to potentially modifying the progression of AD, recent clinical trials also indicate that cannabinoid therapy reduces agitation and improves appetite and weight gain in patients with AD.

Daily administration of 2.5 mg of synthetic THC over a two-week



period reduced nocturnal motor activity and agitation in AD patients in an open-label pilot study (Walther et al. 2006). Improved weight gain and mood state were also noted among AD patients administered cannabinoids in a separate study previously published (Volicer et al. 1997). Thus far, at least two chemicals in cannabis, THC and CBD, have been shown to be effective against AD-related pathology. Additional studies using cannabis to treat AD are clearly warranted, as we face a looming global epidemic of Alzheimer's disease as the population ages. Any advances in therapeutic and preventive strategies that lead to even small delays in Alzheimer's onset and progression can significantly reduce the global burden of the disease (Brookmeyer et al. 2007).

### *Tourette's Syndrome*

Tourette's syndrome (TS) is a complex neurological disorder, the cause of which remains essentially unknown. The disease is characterized by tics, which are involuntary repeated movements or verbal expressions that occur spontaneously and without warning. The severity of this disease is variable, but in its worst expression, it can be quite disabling. As with ALS and MS, there is no cure for TS. However, unlike ALS and MS, the condition often improves with age.

TS is estimated to affect approximately 100,000 people in the United States (Tourette's Syndrome Association, www.tsa-usa.org). There have been numerous studies published investigating the use of cannabinoids for the treatment of TS. Starting in the late 1990s, Muller-Vahl and colleagues published a number of papers clearly showing the efficacy of cannabis in treating TS. Cannabis appears to decrease the tic severity score, or TSS. This is a reliable, reproducible, standardized rating scale to describe tic frequency and magnitude of the movements.

The patients also experienced an overall improvement in global functioning (Muller-Vahl 2003a; Muller-Vahl et al. 2001, 2002, 2003b, 2003c). In one case report, a single oral dose of 10 mg of delta-9-THC in a twenty-five-year-old man with severe, uncontrolled TS dropped the subject's total TSS from 41 to 7, an 84 percent improvement, within two hours following ingestion of the cannabinoid (Muller-Vahl 2003). The improvement was observed for a total of seven hours. A similar effect was also seen in patients following inhalation (smoking) of marijuana, confirmed again using the TSS rating scale.

The results continued to be positive even in a randomized, double-blind

placebo-controlled crossover single-dose trial of THC in twelve adult TS patients. The investigators reported a significant improvement in TSS as well as a decrease in obsessive-compulsive behavior (OCB) after treatment with delta-9-THC compared to placebo (Muller-Vahl et al. 2002). Investigators reported no cognitive impairment in subjects following THC administration, concluding, "THC is effective and safe in treating tics and OCB in TS" (Muller-Vahl et al. 2003b).

In a second randomized, double-blind, placebo-controlled trial (Muller-Vahl 2003a) involving twenty-four patients who were administered daily doses of up to 10 mg of THC over a six-week period, researchers reported that subjects experienced a significant reduction in TSS following long-term cannabinoid treatment with no impairment of learning, recall, or verbal memory. There was actually a statistically significant improvement in verbal memory span both during and after cannabinoid therapy.

### *Gliomas*

Gliomas are rapidly growing malignant brain tumors that usually result in death within two years after diagnosis. Gliomas arise from glial cells, or glia, which are the major support structures of the brain and are the only non-neuronal cells of the CNS. In humans they outnumber actual nervous tissue (neurons) by a factor of about ten to one. However, because of their small size, they account for only about 50 percent of the cellular volume of the brain. Glia are ubiquitous in the nervous system and are critical in maintaining the extracellular environment. This includes supporting as well as coating (myelinating) the neurons.

Currently there are no known cures for gliomas. The best available standard treatments provide only minor symptom relief. However, there are numerous basic science studies and one pilot clinical trial demonstrating the ability of cannabis and cannabinoids to inhibit the growth of gliomas. One might wonder, why would cannabis inhibit the growth of a glioma? Here's a possible answer: glia are involved, actively or passively, in virtually all disorders or insults involving the brain. This makes them very important cells within the CNS, and we are now discovering that they are largely regulated by endogenous (internal) cannabinods.

We now know that there are at least two cannabinoid receptor subtypes. Subtype 1 (CB1) is expressed primarily in the brain, whereas subtype 2 (CB2) is expressed primarily in the periphery (Bouaboula et al. 1995; Di Marzo et al. 1994, 2000; Puffenbarger et al. 2000). Cannabinoid



receptors constitute a major family of receptors within the central nervous system, similar to the receptors of other major neurotransmitters such as dopamine, serotonin, and norepinephrine (Di Marzo et al. 1994). There is considerable evidence that glial cells, from which gliomas form, are regulated through cannabinoid signaling systems. This provides further insight into understanding how the emerging therapeutic effects of cannabis actually work. Normally, glial cells express CB1 receptors, taking in and degrading the endogenous cannabinoid anandamide (Bouaboula et al. 1995). However, gliomas appear to express CB2 receptors. This may be an indicator of tumor malignancy (Sanchez et al. 1998, 2001).

The most recent therapeutic role for cannabinoids in the CNS evolved from the discovery that cannabinoids selectively induce cell death (apoptosis) in glioma cells in vitro and that THC and other cannabinoids lead to a spectacular regression of malignant gliomas in immune-compromised rats in vivo (Esposito et al. 2001; Galve-Roperh et al. 2000; Sanchez et al. 1998; Sinha et al. 1998). The mechanism underlying this is not yet clear, but it appears to involve both CB1 and CB2 receptor activation (Recht et al. 2001). A recent study comparing the antiproliferative effects of cannabinoids on C6 glioma cells suggests the involvement of vanilloid receptors (VRs) (Jacobsson, Wallin, and Fowler 2001), indicating that cannabinoids that stimulate both CB receptors and VR receptors would be better suited for glioma chemotherapy.

A nonpsychoactive cannabinoid found in cannabis, cannabidiol (CBD), inhibited the growth of various human glioma cell lines in vivo and in vitro in a dose-dependent manner. CBD produces significant antitumor activity both in the whole animal and in test tube cells, thus suggesting an application of CBD as an antineoplastic agent (Molina-Holgado, Lledo, and Guaza 1997). Another study showed that cannabinoids inhibited glioma tumor growth in animals and in human glioblastoma multiforme (GBM) tumor samples (Guzman 2003; Sanchez et al. 1998; Waksman et al. 1999).

More recently, the administration of THC to human glioblastoma multiforme cell lines decreased the proliferation of malignant cells and induced tumor cell death more rapidly than did the administration of WIN 55,212-2, a synthetic cannabinoid agonist (Guzman et al. 2006). Researchers also noted that THC selectively targeted malignant cells while ignoring healthy ones in a more profound manner than the synthetic alternative. A recent landmark human clinical trial demonstrated tumor volume shrinkage with intratumor THC injections in several patients with

recurrent glioblastoma multiforme (Guzman 2006). It should be noted that a diagnosis of glioblastoma mulitforme is a virtual death sentence, with a five-year survival rate of fewer than 5 percent and with few treatment options; anything that slows its progression is extraordinary and should be vigorously pursued.

Compared to other traditional chemotherapeutic agents, the safety profile of THC is remarkably good. Taken together with its apparent antiproliferative action on tumor cells noted here, the basis is set for future trials aimed at evaluating the potential antitumor activity of cannabis. It is worth noting that, in addition to the ability of various cannabinoids to moderate glioma cells, there is an emerging body of evidence that demonstrates cannabinoids and endocannabinoids have the ability to inhibit the proliferation of other cancer cell lines, including breast, prostate, colorectal, lung, and uterine carcinomas, as well as gastric and pancreatic adenocarcinomas, leukemia, and various forms of lymphoma (Caffarel et al. 2006; Carracedo et al. 2006; Klein, Newton, and Friedman 1998; Ligresti et al. 2006). As a result, experts now believe that cannabinoids represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis (the formation of new blood vessels that feed tumor growth), and the metastatic spread of cancer cells (Chen and Buck 2000; Guzman 2003; Kogan 2005).

### *Stroke, Alcoholic Damage, and Other Forms of Brain Injury*

Recent studies have demonstrated the neuroprotective effects of synthetic, nonpsychotropic cannabinoids, which appear to protect neurons from chemically induced excitotoxicity (Hamelink et al. 2005; Hampson 2002; Hampson et al. 2000; Jiang et al. 2005; Nagayama et al. 1999; Mechoulam and Shohami 2002; Valjent, Pages, and Rogard 2001; Van der Stelt et al. 2001). Direct measurement of oxidative stress reveals that cannabinoids prevent cell death by antioxidation. The antioxidative property of cannabinoids is confirmed by their ability to antagonize oxidative stress and consequent cell death induced by the powerful oxidant retinoid anhydroretinol. Cannabinoids also modulate cell survival and growth of B-lymphocytes and fibroblasts, as demonstrated in these studies.

The neuroprotective actions of cannabidiol and other cannabinoids were examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate. Glutamate toxicity was reduced by both CBD (nonpsychoactive) and THC (Eshhar, Striem, and Biegon 1993). The



neuroprotection observed with CBD and THC was unaffected by a cannabinoid receptor antagonist, indicating it to be cannabinoid-receptor independent. CBD was more protective against glutamate neurotoxicity than either ascorbate (vitamin C) or alpha-tocopherol (vitamin E).

Cannabinoids have shown efficacy as immune modulators in animal models of neurological conditions such as experimental allergic encephalomyelitis (a common animal model for MS) and neuritis (El-Remessy et al. 2006; Friedman et al. 1995). These data suggest that cannabinoids might modify the presumed autoimmune causes of other neurological diseases, such as MS. Current data suggests that cannabidiol may have a potential role as a therapeutic agent for neurodegenerative disorders produced by excessive cellular oxidation, such as ALS, a disease characterized by excess glutamate activity in the spinal cord (Carter 1999; Panikashvili et al. 2001). This may have implications in treating pain in neuromuscular diseases (Jensen et al. 2005).

It is not yet known how excess glutamate affects cannabinoid homeostasis in the body, including endogenous levels of the endocannabinoids AEA (anadamide) and 2-AG (2-acylglycerol), as well as other constituents of their lipid families such as N-acylethanolamines (NAEs) and 2-monoacylglycerols (2-MAGs). Hansen and colleagues used three in vivo neonatal rat models characterized by widespread neurodegeneration as a consequence of altered glutamate neurotransmission and assessed changes in endocannabinoid homeostasis (Hansen et al. 2001). A forty-six-fold increase of cortical NAE concentrations (AEA, thirteen-fold) was noted twenty-four hours after intracerebral NMDA injection (a method for activating a class of glutamate receptors with the molecule N-methyl-D-aspartate), while less severe insults triggered by mild concussive head trauma or NMDA receptor blockade produced a less pronounced NAE accumulation.

By contrast, levels of 2-AG and other 2-MAGs were unaffected by the insults employed, rendering it likely that key enzymes in biosynthetic pathways of the two different endocannabinoid structures are not equally associated with intracellular events that cause neuronal damage in vivo. Cortical subfields in the brain exhibited an up-regulation of cannabinoid CB1 receptor mRNA expression and binding capacity following mild concussive head trauma and exposure to NMDA receptor blockade. This may suggest that mild to moderate brain injury may trigger elevated endocannabinoid activity via concomitant increase of anandamide levels, but not 2-AG, and CB1 receptor density.

Panikashvili and colleagues were able to show that 2-AG has an important neuroprotective role (Panikashvili et al. 2001). After closed-head injury (CHI) in mice, the level of endogenous 2-AG was significantly elevated. After administering synthetic 2-AG to mice after CHI, they found a significant reduction of brain edema, better clinical recovery, reduced infarct volume, and reduced hippocampal cell death compared with controls. When 2-AG was administered together with additional inactive 2-acyl-glycerols that are normally present in the brain, functional recovery was significantly enhanced. The beneficial effect of 2-AG was dose-dependently attenuated by SR-141761A, an antagonist of the CB1 receptor, implying a receptor-based mechanism of action for this neuroprotective effect.

Ferraro and colleagues looked at the effects of the synthetic cannabinoid receptor agonist WIN 55,212-2 on endogenous extracellular GABA levels in the cerebral cortex of an awake rat using microdialysis (Ferraro et al. 2001). GABA (gamma-aminobutyric acid) is a common inhibitory neurotransmitter in the mammalian brain. WIN 55,212-2 was associated with a concentration-dependent decrease in dialysate GABA levels. WIN 55,212-2-induced inhibition of GABAergic activity was counteracted by the CB1 receptor antagonist SR141716A, which by itself was without effect on cortical GABA levels. These findings suggest that cannabinoids decrease cortical GABA levels, an important neuromodulatory action, given that excessive GABAergic activity has been shown to be neurotoxic.

Cannabinoids may also be effective in post-stroke neuroprotective therapy. Sinor and colleagues showed that AEA and 2-AG increased cell viability in cerebral cortical neuron cultures subjected to eight hours of hypoxia and glucose deprivation, conditions that mimic ischemia, or inadequate blood supply, commonly associated with stroke. This effect was observed at nanomolar (very low) concentrations, was reproduced by a nonhydrolyzable analog of anandamide, and was unaltered by CB1 or CB2 receptor antagonists (Sinor, Irvin, and Greenberg 2000). These results imply that cannabinoids can have an important therapeutic role to play in preventing ischemia-induced brain tissue damage. Recently, cannabinoids have also been shown to actually stimulate the genesis of new neurons in the brain, specifically in the rat hippocampus (Jiang et al. 2005; Mishima et al. 2005). Further study is required to elucidate the scope of the neurogenic effects of cannabinoids.

A neuroprotective role for cannabinoids in staving off ethanol-induced neurotoxicity associated with heavy binge drinking has also been demonstrated. When cannabidiol is given concurrently with binge alcohol exposure in rats, they demonstrated a dose-dependent reduction in the normally substantial neurodegeneration observed in the hippocampus and entorhinal cortex (Hamelink et al. 2005). It is also likely that cannabinoids could play a beneficial role in preventing the glumatergic excitotoxcity seen in alcoholic withdrawal.



The leading cause of blindness in the United States occurs due to diabetes—a condition known as diabetic retinopathy. This is believed to be caused by ischemia in retinal tissues leading to excessive glutamate production, nitric oxide and superoxide production, and finally nerve-cell death. In addition, nearby microglia, sensing dysfunction, become activated and start an inflammatory process that often is cytotoxic. A recent study has shown that cannabidol may be used therapeutically to protect the retinal nerve cells that are essential for vision (El-Remessy et al. 2006). They showed that cannabidiol is able to function as an antioxidant that can neutralize toxic superoxides, inhibit the self-destructive process set in motion by the overactive microglia, and help increase the body's innate protective cannabinoid response by inhibiting the enzyme that destroys endocannabinoids.

Many more avenues await exploration in the field of cannabinoid medicine, and the future appears bright. Recently, cannabidiol was shown to be effective in treating neurodegenerative disorders caused by prions—the misfolded protinaceous infectious particles that cause bovine spongiform encephalopathy (mad cow disease), sheep scrapie, and, in humans, Creutzfeldt-Jakob disease, fatal familial insomnia, and other diseases. Russo first documented the possibility of cannabinoid medicine contributing to this area of therapy in 2003. Recently a team of French researchers (Dirikoc et al. 2007) reported that cannabidiol inhibited the accumulation of prion protein in both mouse and sheep cell culture, limited accumulation and resultant neurotoxicity of the aberrant protein in the brains of scrapie-infected mice, and significantly increased infected mouse survival time compared to untreated controls. They noted that cannabinoids' unique mechanism of action in treating tissue spongioform encephalopathies represent a new class of compounds for the treatment of these as yet uncurable diseases.

## CONCLUSION

In this chapter we have attempted to summarize the recent research on cannabis with a primary focus on its emerging therapeutic role in treating neurodegenerative human diseases. We have reviewed many studies on cannabinoids that indicate important progress documenting the neruoprotective

actions of cannabis in treating several major neurodegenerative disorders, including amyotrophic lateral sclerosis, multiple sclerosis, and Alzheimer's disease.

When cannabinoid receptors in the central nervous system are activated, this triggers signaling pathways in the brain that are linked to neuronal repair and cell maintenance, and the release of other compounds that further activate neuroprotective responses. Additionally, it is clear that our own internal marijuana, the endocannabinoids, are released in response to pathogenic events, thus representing a potential compensatory repair mechanism. Enhancing this "on demand" action of endocannabinoids is an important strategy the body uses to help prevent further brain injury as well as promote healing. The neuroprotective activities of both externally administered cannabinoids and the internal endocannabinoids are novel processes that can be effectively exploited to help promote and protect the nervous system in the face of disease or physical and chemical trauma.

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# Cannabis and HIV/AIDS

Mark A. Ware, M.D., and Lynne Belle-Isle

Human immunodeficiency virus (HIV) and/or acquired immune deficiency syndrome (AIDS) affects more than 33 million people worldwide (UNAIDS 2009). In the debate surrounding the medical use of cannabis, one does not need to look far to find the contributions of people living with HIV/AIDS (PHAs). Whether as political activists advocating for greater access to medical marijuana, as participants in surveys of medical cannabis use, or as research subjects in clinical trials evaluating the safety and efficacy of medical cannabis, PHAs have contributed significantly to the ideology of cannabis as medicine as well as the evidence base on which clinical and political decisions are made.

The Canadian AIDS Society was the first national nongovernmental organization to officially adopt a position on HIV/AIDS and the therapeutic use of cannabis (Canadian AIDS Society 2004). This chapter explores the main medical reasons why the HIV/AIDS community is invested in the cannabis debate and illustrates how converging evidence from anecdote to clinical trials have paralleled developments in cannabinoid physiology; the cumulative experience of PHAs with cannabis cannot be ignored.

Despite great advances in the development of pharmacological agents to reduce the impact and severity of HIV infection, the clinical picture of HIV/AIDS is still dominated by debilitating symptoms such as pain, nausea, and loss of appetite. We will review each of these symptoms in turn and consider the evidence for cannabis in each. Cannabis for