

CANNABIS AND NEUROLOGICAL DISORDERS

Neurodegenerative diseases and movement disorders, which are sometimes interlinked, are among the many conditions that cannabis and cannabinoids may be particularly well suited to treat. Cannabinoids can protect the brain and central nervous system from the damage that leads to various neurological disorders. More than 100 research articles have been published on how cannabinoids act as neuroprotective agents to slow the progression of neurodegenerative diseases that disproportionately affect veterans. Researchers have also established that cannabinoids can alleviate the damage caused by strokes, as well as traumatic brain injury, spinal cord injury, and multiple sclerosis. No other medication offers the combination of anti-oxidative, anti-inflammatory and neuroprotective qualities of cannabis and cannabinoids. The therapeutic use of cannabis for treating neurological disorders has been known to western medicine for nearly two centuries. In 1839, Dr. William B. O'Shaughnessy wrote about cannabis that doctors had "gained an anti-convulsive remedy of the greatest value." In 1890 Dr. J. Russell Reynolds, physician to Queen Victoria, noted in an article in *The Lancet* that for "organic disease of a gross character in the nervous centers . . . India hemp (cannabis) is the most useful agent with which I am acquainted."

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

Research published in 2013 shows the active chemicals in cannabis are uniquely suited to fighting neurodegenerative diseases that can result from trauma, such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS). The neuroprotective effects of cannabis, based on the combination of anti-inflammatory and anti-oxidant properties of the primary cannabinoids THC and CBD, is undergoing intense preclinical research for treating numerous neurodegenerative disorders. Recent research has revealed that chemicals similar to those in cannabis can also reduce the effects of serious brain injury and keep badly head-injured people alive.

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

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

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

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

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

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

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

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

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

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

Few clinical trials have looked at cannabinoids and Parkinson's disease. However, research has shown that 25 percent of Parkinson's patients smoke cannabis, and 46 percent of these patients report improvement of side effects from long-term levodopa treatment.[248] A randomized placebo controlled study using extracts of cannabis produced significant improvements in patients' cognition. The authors note that they did not see improvements in pain or sleep disorders. They speculate that the oral route (versus inhaled) of cannabis ingestion leads to too much variability of cannabinoids in blood.

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

Oxidative stress in the brain is a major hallmark of neurological disorders such as Parkinson's and Alzheimer's disease. Cannabinoids have well-established antioxidant properties that protect neurons from oxidative damage. Alzheimer's disease, characterized in part by a decrease in the production of new

neurons, is associated with oxidative stress due to the membrane action of beta-amyloid peptide aggregates. A laboratory study published in 2004 indicates that one of the cannabis plant's primary components, cannabidiol (CBD), exerts a combination of neuroprotective, anti-oxidative and anti-apoptotic effects by inhibiting the release of the toxic beta-amyloid peptide.[251]

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

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

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

How Cannabis Compares to Other Treatments

Neurologic Medications

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

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

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

Baclofen (Lioresal) has been widely used for spasticity since 1967. It is a GABA agonist. Tolerance to the medication may develop. Baclofen must be slowly weaned to prevent withdrawal effects such as seizures, hallucinations and increased spasticity. It must be used with care in patients with renal insufficiency as its clearance is primarily renal. Side effects are predominantly from central depressant properties including sedation, ataxia, weakness and fatigue. May cause depression when combined with tizanidine or benzodiazepines.

Dantrolene Sodium (Dantrium) acts peripherally at the level of the muscle fiber and works best for cerebral palsy and traumatic brain injury. Because the action of dantrolene sodium is not selective for spastic muscles, it may cause generalized weakness, including weakness of the respiratory muscles. The side

effects include drowsiness, dizziness, weakness, fatigue and diarrhea. In addition, hepatotoxicity (liver damage) occurs in < 1 percent of patients who take dantrolene sodium.

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

Cannabis vs. Other Medications

Cannabis: By comparison, the side effects associated with cannabis are typically mild and are classified as "low risk." Euphoric mood changes are among the most frequent side effects. Cannabinoids can exacerbate schizophrenic psychosis in predisposed persons, though it can also provide symptomatic relief in refractory schizophrenia. Cannabinoids impede cognitive and psychomotor performance, resulting in temporary impairment. Chronic use can lead to the development of tolerance. Tachycardia and hypotension are frequently documented as potentially adverse events in the cardiovascular system. A few cases of myocardial ischemia have been reported in young and previously healthy patients. Inhaling the smoke of cannabis cigarettes induces side effects on the respiratory system. Cannabinoids are contraindicated for patients with a history of cardiac ischemias. In summary, a low risk profile is evident from the literature available. Serious complications are extremely rare and are not usually reported during the use of cannabis.

THE EXPERIENCE OF PATIENTS

Vollie Rutledge, Jr. — Neurological Disorder

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

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

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

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

