

Review Article

Review of the neurological benefits of phytocannabinoids

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Abstract

Background: Numerous physical, psychological, and emotional benefits have been attributed to marijuana since its first reported use in 2,600 BC in a Chinese pharmacopoeia. The phytocannabinoids, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (Δ 9-THC) are the most studied extracts from *cannabis sativa* subspecies hemp and marijuana. CBD and Δ 9-THC interact uniquely with the endocannabinoid system (ECS). Through direct and indirect actions, intrinsic endocannabinoids and plant-based phytocannabinoids modulate and influence a variety of physiological systems influenced by the ECS.

Methods: In 1980, Cunha *et al.* reported anticonvulsant benefits in 7/8 subjects with medically uncontrolled epilepsy using marijuana extracts in a phase I clinical trial. Since then neurological applications have been the major focus of renewed research using medical marijuana and phytocannabinoid extracts.

Results: Recent neurological uses include adjunctive treatment for malignant brain tumors, Parkinson's disease, Alzheimer's disease, multiple sclerosis, neuropathic pain, and the childhood seizure disorders Lennox-Gastaut and Dravet syndromes. In addition, psychiatric and mood disorders, such as schizophrenia, anxiety, depression, addiction, postconcussion syndrome, and posttraumatic stress disorders are being studied using phytocannabinoids.

Conclusions: In this review we will provide animal and human research data on the current clinical neurological uses for CBD individually and in combination with Δ 9-THC. We will emphasize the neuroprotective, antiinflammatory, and immunomodulatory benefits of phytocannabinoids and their applications in various clinical syndromes.

Key Words: Cannabidiol, delta-9-tetrahydrocannabinol, endocannabinoid system, neurological disease, phytocannabinoids

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Quick Response Code:**INTRODUCTION**

Numerous physical, psychological, and emotional benefits have been attributed to marijuana since it was first reported in 2,600 BC (e.g., Chinese pharmacopoeia). The phytocannabinoids, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (Δ 9-THC), the most studied extracts from the *cannabis sativa* subspecies, include hemp and marijuana. Recently, it has been

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successfully utilized as an adjunctive treatment for malignant brain tumors, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), neuropathic pain, and the childhood seizure disorders, Lennox-Gastaut and Dravet syndromes. In this review, we provide animal/human research data on the current clinical/neurological uses for CBD alone or with Δ^9 -THC, emphasizing its neuroprotective, antiinflammatory, and immunomodulatory benefits when applied to various clinical situations.

Discovery of the endocannabinoid system

Cannabinoid receptor pharmacology began in the late 1960s when Δ^9 -THC was isolated and synthesized and found to be the primary psychoactive constituent of marijuana.^[40,80,81,105] The discovery in the early 1990s of specific membrane receptors for Δ^9 -THC led to the identification of endogenous signaling system, now known as the endocannabinoid system (ECS). Shortly thereafter, the endogenous cannabinoids, N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), were identified. The ECS consists of two major types of endogenous G protein-coupled cannabinoid receptors (CB1 and CB2) located in the mammalian brain and throughout the central and peripheral nervous systems, including tissues associated with the immune system. CB1 and CB2 receptors can also co-exist in a variety of concentrations in the same locations.^[86] Both phytocannabinoids and endogenous cannabinoids function as retrograde messengers that provide feedback inhibition of both excitatory and inhibitory transmission in brain through the activation of presynaptic CB1 receptors. Manipulations of endocannabinoid degradative enzymes, CB1 and CB2 receptors, and their endogenous ligands have shown promise in modulating numerous processes associated with neurodegenerative diseases, cancer, epilepsy, and traumatic brain injury [Table 1]. In addition, the ECS is known to influence neuroplasticity, apoptosis, excitotoxicity, neuroinflammation, and cerebrovascular breakdown associated with stroke and trauma.^[105]

Phytocannabinoids CBD and Δ^9 -THC

In addition to the phytocannabinoid Δ^9 -THC, it is estimated that the *cannabis* plant consists of over 400 chemical entities, of which more than 60 of them are phytocannabinoid compounds. Some of these compounds

have been identified as acting uniquely on both CB1 and CB2 receptors separately and simultaneously, and/or to inhibit or activate receptor functions. CBD, like Δ^9 -THC, is a major phytocannabinoid accounting for up to 40% of the plant's extract. CBD was first discovered in 1940 more than 20 years before Δ^9 -THC.^[104,105] Until recently, Δ^9 -THC dominated cannabis research. All classes of phytocannabinoid compounds found in marijuana and hemp, including Δ^9 -THC and CBD, are derived from various changes to base molecular structure of cannabigerol-type compounds [Figure 1].^[34,49]

Cannabinoid receptors

Phytocannabinoid compounds and extracts can come from both hemp and marijuana subspecies, including CBD. CBD does not elicit the same psychoactive effects as seen with Δ^9 -THC (i.e., users of CBD do not feel euphoric). The various psychoactive effects generally associated with Δ^9 -THC are attributed to activation of the CB1 cannabinoid receptor found abundantly in the brain. CB1 receptors have the highest densities on the outflow nuclei of the basal ganglia, substantia nigra pars reticulata (SNr), and the internal and external segments of the globus pallidus (a portion of the brain that regulates voluntary movement).^[88] The hippocampus, particularly within the dentate gyrus, and cerebellum

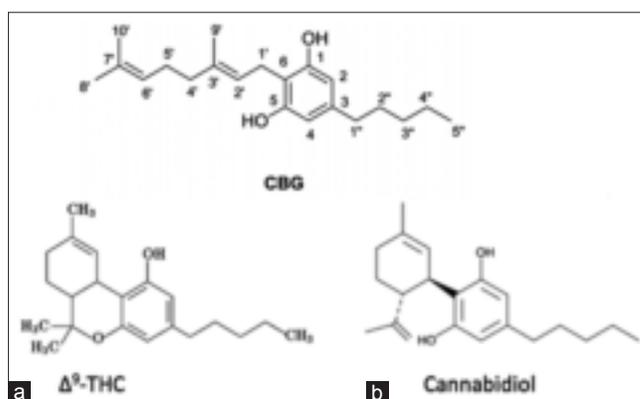


Figure 1: (a) Δ^9 -THC and (b) cannabidiol (CBD) are biosynthesized as tetrahydrocannabinolic acid (THC-A) and cannabidiolic acid (CBD-A) from a common precursor cannabigerolic acid (CBG). These phytocannabinoids in their natural acidic form are considered "inactive". When cannabis grows, it produces THC-A and CBD-A, not Δ^9 -THC and CBD. When cannabis is heated, such as through smoking, cooking, or vaporization, THC-A and CBD-A are decarboxylated into Δ^9 -THC and CBD (i.e. "active" forms)^[44]

Table 1: Conditions and Diseases in Which Activation of The ECS has Shown Benefit^[78]

Emesis	Epilepsy	Obesity	Tourette's syndrome
Pain	Glaucoma	Anorexia	Anxiety
Inflammation	Schizophrenia	Parkinson's disease	Depression
Multiple sclerosis	Cardiovascular disorders	Huntington's disease	Panic
Autism	Stroke (Ischemia)	Insomnia	Prion diseases
PTSD	Cancer	Alzheimer's disease	Psychosis
Obsessive compulsive behavior	Amyotrophic lateral sclerosis	Metabolic syndrome related diseases	

also have higher CB1 receptor densities. Very few CB1 receptors are found in the brainstem. These locations suggest CB1 receptor involvement in the modulation of memory, emotion, pain, and movement.^[37,90] Δ^9 -THC, which targets CB1 receptors, has been shown to reduce nociception in animal models of acute, visceral, inflammatory, and chronic pain. In patient studies with chronic pain and neuropathic pain, the use of marijuana or cannabinoid extracts produced positive and improved symptoms.^[52,95]

Activation of neuronal CB1 receptors

Activation of neuronal CB1 receptors results in inhibition of adenylyl cyclase and decreased neurotransmitter release through blockade of voltage-operated calcium channels.^[46,65,125] The activation of these signaling pathways by CB1 receptors and the high levels of these receptors on presynaptic terminals indicates that endocannabinoid stimulation of CB1 receptors suppresses neuronal excitability and inhibits neurotransmission. These effects have led to the study of phytocannabinoids for the treatment of epilepsy. Several pharmaceutical companies are attempting to develop synthetic high-affinity CB1 antagonists and inverse agonists as therapeutic drugs for diabetes, metabolic syndrome, and drug dependence.^[9,42]

The CB2 receptor

The CB2 receptor, unlike CB1, is not highly expressed in the central nervous system (CNS). Effects of Δ^9 -THC on immune function have been attributed to the CB2 cannabinoid receptor interaction found predominantly in immune cells.^[54] CB2 receptors are distributed widely in the major tissues of immune cell production and regulation, including the spleen, tonsils, and thymus.^[89] These cell lines include B and T lymphocytes, natural killer cells, monocytes, macrophages, microglial cells, and mast cells. Like CB1 receptors, endocannabinoid stimulation inhibits neurotransmission of CB2 receptors.

Cultured microglial cells

A study of cultured microglial cells showed c-interferon and granulocyte macrophage-colony stimulating factor (GM-CSF), known as inflammatory response activators of microglial cell, were accompanied by significant CB2 receptor upregulation.^[73] This suggested that the CB2 receptors play an important role in microglial cell function in the CNS inflammatory response. Activation of CB2 has been implicated in several neurodegenerative diseases such as Huntington's (HD) and AD.^[21,67,98] Increased expression of CB2 in the brain was confirmed with CB2-selective positron emission tomography (PET) tracers in Alzheimer's mice models. This increased expression was concomitant with the formation of amyloid-beta plaques, suggesting a potential utility for CB2 PET tracers as a diagnostic modality for detecting the onset of neuroinflammation.

Unique mechanisms of CBD

The interaction of CBD with CB2 receptors is more complex, but like Δ^9 -THC, CBD is believed to reduce the inflammatory response. CBD's action with the CB2 receptor is just one of several pathways by which CBD can affect neuroinflammation [Table 2]. Because both CBD and Δ^9 -THC modulate the activity of G protein-coupled receptors associated with the endocannabinoid system, and CBD can function as a partial agonist and antagonizes Δ^9 -THC, CBD at higher doses may counter to some extent the psychoactive effects of Δ^9 -THC.^[77] Anecdotally, this effect is noted by many cannabis users who co-ingest CBD.

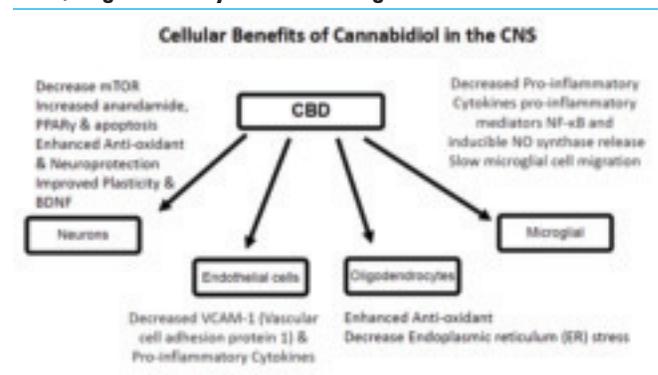
Molecular targets of CBD

Molecular targets of CBD, including cannabinoid and noncannabinoid receptors, enzymes, transporters, and cellular uptake proteins, help to explain CBD's low-binding affinity to both CB1 and CB2 cannabinoid receptors. In animal models, CBD has demonstrated an ability to attenuate brain damage associated with neurodegenerative and/or ischemic conditions outside the ECS. CBD appears to stimulate synaptic plasticity and facilitates neurogenesis that may explain its positive effects on attenuating psychotic, anxiety, and depressive behaviors. The mechanisms underlying these effects involve multiple cellular targets to elevate brain-derived neurotrophic factor (BDNF) levels, reduce microglia activation, and decrease levels of proinflammatory mediators.^[82,122,123]

Very low toxicity of CBD in humans

Unlike the psychoactive properties associated with Δ^9 -THC, CBD has been shown to have very low toxicity in humans and in other species (see Safety section). Ingested and absorbed CBD is rapidly distributed, and due to its lipophilic nature can easily pass the blood-brain barrier. The terminal half-life of CBD is about 9 h and is preferentially excreted in the urine as its free and glucuronide form.^[78]

Table 2: Ongoing research indicates a wide range of cellular mechanisms associated with CBD and the ECS. Specific cellular targets include neurons, endothelial cells, oligodendrocytes and microglial cells [12,78,92,108]



Research on the endocannabinoid system

Research on the ECS is fervently ongoing with wide-ranging discoveries. The roles of endogenous cannabinoid, phytocannabinoids, and synthetic pharmacological agents acting on the various elements of the ECS have a potential to affect a wide range of pathologies, including food intake disorders, chronic pain, emesis, insomnia, glaucoma, gliomas, involuntary motor disorders, stroke, and psychiatric conditions such as depression, autism, and schizophrenia.^[68] Research into ECS's role in the stress response has revealed a significant influence on the hypothalamic–pituitary–adrenal axis, the control of reproduction by modifying gonadotropin release, fertility, and sexual behavior.

The remaining sections will focus on the ECS and the effects of the phytocannabinoids, CBD and Δ9-THC, on neuroinflammation, neuroprotection, and their potential use in the treatment of specific neurological disorders including trauma involving the CNS.^[106] The cited research will include examples of clinical benefits of CBD alone and in combination with Δ9-THC.^[12,84]

Neuroprotective benefits of phytocannabinoids

CBD research in animal models and humans has shown numerous therapeutic properties for brain function and protection, both by its effect on the ECS directly and by influencing endogenous cannabinoids. Broadly, CBD has demonstrated anxiolytic, antidepressant, neuroprotective antiinflammatory, and immunomodulatory benefits. CBD decreases the production of inflammatory cytokines, influences microglial cells to return to a ramified state, preserves cerebral circulation during ischemic events, and reduces vascular changes and neuroinflammation.^[12]

Other effects of CBD

Other effects of CBD include the inhibition of calcium transport across membranes, the inhibition of anandamide uptake and enzymatic hydrolysis, and inhibition of inducible NO synthase protein expression and nuclear factor (NF)-κB activation. CBD increases brain adenosine levels by reducing adenosine reuptake. Increased adenosine is associated with neuroprotection and decreased inflammation after brain trauma.^[7,16] CBD is also known to exert vascular effects, producing vasodilation as well as hypotension that may hold promise as protectant against cerebrovascular damage associated with stroke.^[53,105] CBD has several features that may be exploited for the treatment of AD, including the prevention of glutamate-induced excitotoxicity, reduction of proinflammatory mediators, and the ability to scavenge reactive oxygen species (ROS) and reduce lipid peroxidation.^[16,32,48,59]

Experimental *in vitro* cannabinoid receptor interactions

Experimentally, *in vitro*, cannabinoid receptor interactions with CBD and Δ9-THC, together and separately, have

demonstrated neuronal protection from excitotoxicity, hypoxia, and glucose deprivation; *in vivo*, cannabinoids decrease hippocampal neuronal loss and infarct volume after cerebral ischemia, acute brain trauma, and induced excitotoxicity. These effects have been ascribed to inhibition of glutamate transmission, reduction of calcium influx, reduced microglial activation, and subsequent inhibition of noxious cascades, such as tumor necrosis factor-alpha generation and oxidative stress.^[92]

Delta-9-THC

Δ9-THC can mediate the effects of the neurotransmitter serotonin by decreasing 5-HT₃ receptor neurotransmission. This can contribute to the pharmacological action to reduce nausea. This effect can be reversed at higher doses or with chronic use of Δ9-THC.^[103,117] Synthetic analogs of Δ9-THC, nabilone (Cesamet, Valeant Pharmaceuticals North America) and dronabinol (Marinol-Solvay Pharmaceuticals), are prescribed for the suppression of the nausea and vomiting produced by chemotherapy.^[87] There is limited use for synthetic Δ9-THC due to multiple side effects mediated through activation of CB1 on the CNS in this population.

Brain neuroprotective effects of delta-9-THC

Δ9-THC has also been shown to protect the brain from various neuronal insults and improve the symptoms of neurodegeneration in animal models of MS, PD, HD, amyotrophic lateral sclerosis (ALS), and AD.^[23,35,41] Like CBD, Δ9-THC can offer non-ECS protection by direct effect on neuronal cells, and nonneuronal elements within the brain. Mechanisms include modulation of excitatory glutamatergic transmissions and synaptic plasticity, modulation of immune responses, the release of antiinflammatory mediators, modulation of excitability of N-methyl-D-aspartate receptors and its effect on gap junctions, calcium, and antioxidants.^[70]

Neurodegenerative diseases

Overview

Neurodegenerative diseases include a large group of conditions associated with progressive neuronal loss leading to a variety of clinical manifestations. Histomorphological changes can include gliosis and proliferation of microglia along with aggregates of misfolded or aberrant proteins. The most common neurodegenerative conditions include AD, ALS, HD, Lewy body disease, and PD.

Numerous applications of CBD and delta-9-THC for neurodegenerative diseases

Numerous applications for CBD and Δ9-THC for neurodegenerative diseases are being evaluated for both symptom relief and as treatments for the underlying pathologic changes of neuronal tissue. Both CBD and Δ9-THC can function as agonist and antagonistic on various receptors in the ECS. In addition, a wide

range of non-ECS receptors can be influenced by both endogenous and phytocannabinoids.^[31,92,116]

Neuroprotection for AD

AD is characterized by enhanced beta-amyloid peptide deposition along with glial activation in senile plaques, selective neuronal loss, and cognitive deficits. Cannabinoids are neuroprotective against excitotoxicity *in vitro* and in patients with acute brain damage. In human AD patients, cellular studies of senile plaques have shown expression of cannabinoid receptors CB1 and CB2, together with markers of microglial activation. Control CB1-positive neurons, however, are in greater numbers compared to AD areas of microglial activation. AD brains also have markedly decreased G-protein receptor coupling and CB1 receptor protein expression. Activated microglia cluster at senile plaques is generally believed to be responsible for the ongoing inflammatory process in the disease.

Research with administered cannabinoids for AD

Research with administered cannabinoids for AD in animals has demonstrated CB1 agonism is able to prevent tau hyperphosphorylation in cultured neurons and antagonize cellular changes and behavioral consequences in β -amyloid-induced rodents. CB2 antagonists were protective in *in vivo* experiments by downregulating reactive gliosis occurring in β -amyloid-injected animals. In addition, AD-induced microglial activation and loss of neurons was inhibited. AD-induced activation of cultured microglial cells, as judged by mitochondrial activity, cell morphology, and tumor necrosis factor release, is blunted by cannabinoid compounds.^[60,92] Additionally, Δ 9-THC has been shown to reduce the agitation that is common in patients with severe AD.^[121]

Cannabidiol

CBD is effective in an experimental model of Parkinsonism (6-hydroxydopamine-lesioned rats) by acting through antioxidant mechanisms independently of cannabinoid receptors.^[46] It attenuates PD-related dystonia, but not tremor,^[47] in agreement with a positive correlation between CBD levels measured in the putamen/globus pallidus of recreational users of cannabis.^[50]

In rats lesioned with 3-nitropropionic acid, a toxin inhibitor of the mitochondrial citric acid cycle resulting in a progressive locomotor deterioration resembling that of HD patients, CBD reduces rat striatal atrophy in a manner independent of the activation of cannabinoid adenosine A2A receptors.^[100] In contrast, CBD alone did not provide protection in rats lesioned with malonate.^[99] A clinical study from 1991 using 15 subjects with HD reported an average daily dose of CBD of 10 mg/kg/day per patient for 6 weeks was reported as safe but did not result on any significant symptom relief.^[51] The phytocannabinoid-based medicine Sativex®, a 1:1 combination of CBD and

Δ 9-THC, has produced neuroprotective effects through a CB1- and CB2-mediated mechanism in a model of HD.^[115]

CBD, and to a lesser degree Δ 9-THC, can have both direct and indirect effects on isoforms of peroxisome proliferator-activated receptors (PPARs α , β , and γ). Activation of PPAR, along with CB1 and CB2, mediates numerous analgesic, neuroprotective, neuronal function modulation, antiinflammatory, metabolic, antitumor, gastrointestinal, and cardiovascular effects, both in and outside the ECS. In addition, PPAR- γ (gamma) agonists have been used in the treatment of hyperlipidemia and hyperglycemia. PPAR- γ decreases the inflammatory response of many cardiovascular cells, particularly endothelial cells, thereby reducing atherosclerosis. Phytocannabinoids can increase the transcriptional activity of and exert effects that are inhibited by selective antagonists of PPAR- γ , thus increasing production.^[33]

CBD is further involved in the modulation of different receptors outside the ECS. The serotonin receptors have been implicated in the therapeutic effects of CBD. In a rat model, CBD was observed to stimulate hippocampal neurogenesis. Neuroprotective effects of CBD in hypoxic-ischemic brain damage model involve adenosine A2 receptors. CBD activation of adenosine receptors can enhance adenosine signaling to mediate antiinflammatory and immunosuppressive effects. In a rat model of AD, CBD blunted the effects of reactive gliosis and subsequent β -amyloid-induced neurotoxicity.

Delta-9-THC

In an animal model of AD, treatment with Δ 9-THC (3 mg/kg) once daily for 4 weeks with addition of a COX-2 inhibitor reduced the number of beta-amyloid plaques and degenerated neurons. Δ 9-THC has been used for AD symptom control. Treatment with 2.5 mg dronabinol (a synthetic analog of Δ 9-THC) daily for 2 weeks significantly improved the neuropsychiatric inventory total score for agitation and aberrant motor and nighttime behaviors.^[121]

Multiple sclerosis

CBD and delta-9-THC

MS is an autoimmune disease that promotes demyelination of neurons and subsequent aberrant neuronal firing that contributes to spasticity and neuropathic pain. The pathologic changes of MS include neuroinflammation, excitotoxicity, demyelination, and neurodegeneration. These pathological features share similarities with other neurodegenerative conditions, including AD and cerebral ischemia. The combination of antiinflammatory, oligoprotective, and neuroprotective compounds that target the ECS may offer symptomatic and therapeutic treatment of MS.^[44,120]

Use of cannabis-based medicine for neurodegenerative conditions

The use of cannabis-based medicine for the treatment of MS has a long history and its interaction with the ECS shares many of the same pathways of other neurodegenerative conditions.^[55] In models of experimental MS, stimulation of CB1 and CB2 receptors has been shown to be beneficial against the inflammatory process, lending support to early findings showing that individuals with MS experience a reduction in the frequency of relapses when smoking marijuana.^[22]

American Academy of Neurology statement on medical marijuana

In 2014, the American Academy of Neurology (AAN) published a review article of 34 studies investigating the use of medical marijuana (as extracts, whole plants and synthetic phytocannabinoids) for possible neurological clinical benefits. They found strong support for symptoms of spasticity and spasticity-related pain, excluding neuropathic pain in the research using oral cannabis extracts. They reported inconclusive support for symptoms of urinary dysfunction, tremor, and dyskinesia. This study was subsequently used to form a consensus statement for their society. In the article they concluded their results based on the strength of the reported research [Table 3].^[66]

MS animal models utilizing delta-9-THC

MS animal models using autoimmune encephalomyelitis (EAE) have been used that demonstrate demyelination, neuroinflammation, and neurological dysfunction associated with infiltration of immune cells into the CNS consistent with the human disease. In certain types of mouse models of MS spasticity, Δ^9 -THC has been

shown to ameliorate spasticity and tremors.^[114] Activation of the ECS system in MS (and EAE) appears to limit neuronal damage by downregulation of cannabinoid receptors inhibiting GABA synapses as a protective action to reduce neuronal excitotoxic damage. Upregulation of endocannabinoid tone protects neurons from excitotoxicity in parallel with a therapeutic effect in a mouse model of MS.

Human trials using Δ^9 -THC for MS

Thus far, human trials with MS patients have been mixed using only 9-THC. In a 15-week trial with a tolerated dose of 9-THC, subjects had reduced urinary incontinence, and a 12-month follow-up demonstrated an antispasticity effect.^[3,36] However, subsequent clinical trials did not demonstrate any effect on disease progression following long-term treatment with 9-THC.^[126,127]

CBD acts specifically to enhance adenosine signaling which increases extracellular adenosine, not AG-2. Neuroprotective effects of CBD in hypoxic-ischemic brain damage also involve adenosine A2 receptors. Specifically, CBD diminishes inflammation in acute models of injury and in a viral model of MS through adenosine A2 receptors.^[15,18,72,76] CBD also ameliorates the severity of the disease by attenuating neuroinflammation and axonal damage through an effect on oligodendrocyte progenitor cells (OPC) that can be used to differentiate into new myelinating oligodendrocytes. OPCs are highly vulnerable to inflammation and oxidative stress. Inflammation contributes to demyelinating diseases such as MS. Synthetic cannabinoids studies have shown they can protect OPCs possibly by controlling endoplasmic reticulum (ER) stress response that modulates the response to inflammatory stimuli.^[79]

Table 3: Conclusions from Subcommittee of the American Academy of Neurology (AAN) systematic review on medical marijuana in neurologic diseases published in 2014^[66]

Neurologic Disorder:

Spasticity:

Oral cannabis extract (OCE) is effective, and Sativex[®] and tetrahydrocannabinol (THC) were probably effective for patient reported symptoms.

OCE and THC are effective for reducing both patient reported symptom and objective measures at 1 year.

Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain)

OCE is effective;

THC and Sativex[®] are probably effective.

Urinary dysfunction:

Sativex[®] is probably effective for reducing bladder voids/day.

THC and OCE are probably ineffective for reducing bladder complaints.

Tremor:

THC and OCE are probably ineffective;

Sativex[®] is possibly ineffective.

Other neurologic conditions:

OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease.

OCE are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy

Table 3. Note the authors reported numerous confounding factors when comparing studies due to many formulations and doses used to make comparative analysis of cannabinoid efficacy were markedly different. In addition, most studies were significantly underpowered.

This 2014 AAN systemic review medical marijuana in neurologic diseases evaluated research using plant-based oral cannabis extract (OCE), specifically, THC, CBD, other plant components, as well as, Marinol[®], Cesamet[®] and Sativex[®].^[66]

Positive human clinical trials by GW Pharmaceuticals have permitted the pharmaceutical, Sativex® to be marketed for MS spasticity in 16 countries outside the U.S. It is an oral-mucosal spray containing a 1:1 ratio of plant extracted Δ^9 -THC and CBD, having antispasmodic and analgesic properties shown to be effective for MS patients. The ability to modify pain may be attributed to a CB receptor-mediated regulation of supraspinal GABAergic and glutamatergic neurons. The results of these studies were cited in the AAN review.^[22]

A meta-analysis in 2007 reported that CB receptor-based medications were superior to placebo in the treatment of MS-related neuropathic pain.^[58,78,93,94,121] This analysis evaluated 18 studies that included Sativex® ($n = 196$), CBD ($n = 41$), and dronabinol, Marinol®, Δ^9 -THC only ($n = 91$). Sativex® was reported to have the greatest effect to reduce neuropathic pain at 1.7 ± 0.7 points ($P = 0.018$), in a scale of 0 to 10. CBD 1.5 ± 0.7 ($P = 0.044$), dronabinol 1.5 ± 0.6 ($P = 0.013$) were slightly less and all cannabinoids pooled together 1.6 ± 0.4 ($P < 0.001$) and placebo 0.8 ± 0.4 points ($P = 0.023$). Dizziness was the most commonly observed adverse event with a slightly greater incidence in the Sativex® CBD/THC buccal spray. Overall, the analgesic response to cannabinoids was generally retained over time, at least for the 6–10 weeks follow-up period.^[58] Several preclinical studies have used CBD, for both spasticity and neurogenic pain, to augment existing pharmacological treatments. Further human clinical studies using CBD for MS are needed.

Neuropsychiatric and brain trauma

Cannabidiol

CBD is recognized as a nonpsychoactive phytocannabinoid. Both human observational and animal studies, however, have demonstrated a broad range of therapeutic effects for several neuropsychiatric disorders. CBD has positive effects on attenuating psychotic, anxiety, and depressive-like behaviors. The mechanisms appear to be related to the CBD's benefit to provide enhanced neuroprotection and inhibition of excessive neuroinflammatory responses in neurodegenerative diseases and conditions. Common features involving neuroprotective mechanisms influenced by CBD—oxidative stress, immune mediators, and neurotrophic factors—are also important in conditions such as posttraumatic stress disorder (PTSD), postconcussion syndrome, depression, and anxiety. Many studies confirm that the function of the ECS is markedly increased in response to pathogenic events like trauma. This fact, as well as numerous studies on experimental models of brain trauma, supports the role of cannabinoids and their interactions with CB1 and CB2 as part of the brain's compensatory and repair mechanisms following injury. Animal studies indicate that posthead injury administration of exogenous CBD reduces short-term brain damage by improving brain metabolic activity, reducing

cerebral hemodynamic impairment, and decreasing brain edema and seizures. These benefits are believed to be due to CBD's ability to increase anandamide.^[109]

Treatment with CBD

Treatment with CBD may also decrease the intensity and impact of symptoms commonly associated with PTSD, including chronic anxiety in stressful environments.^[11] Exposure to stress can trigger anxiety in PTSD patients and remind them of traumatic experiences. In human studies, subjects introduced to fearful contexts exhibited decreased posttest anxiety when treated with CBD.^[5] A human case report demonstrated that therapy with cannabis resin containing CBD helped to induce a significant reduction of symptoms of anxiety and depression in a teenage patient suffering from PTSD.^[96] By reducing induced anxiety, CBD may help to regulate the negative effects associated with PTSD. In rodent models, CBD effectively blocked the formation of fearful memories.^[112,113] CBD may be an effective strategy to combat PTSD fear memory acquisition because of its direct effects diminishing the severity of traumatic memory. Rat trials also show CBD's potential in fear memory extinction, demonstrated through a significant decrease in freezing time when re-exposed to an anxiety-inducing situation.^[91] Treatment with CBD has also been shown to attenuate contextual memories associated with past experience in murine experiments, showing CBD's ability to disrupt harmful memories.^[1]

Antidepressant and neuroprotective properties

Antidepressants, used for the treatment of depression and some anxiety disorders, also possess numerous neuroprotective properties, such as preventing the formation of amyloid plaques, elevation of BDNF levels, reduction of microglia activation, and decreased levels of proinflammatory mediators.^[82] Similarly, CBD decreases the production of inflammatory cytokines, the activation of microglial cells, and brain leucocytes infiltration.^[79]

Rat models; efficacy of CBD in neurobehavioral disorders

In rat models of neurobehavioral disorders, CBD demonstrated attenuation of acute autonomic responses evoked by stress, inducing anxiolytic and antidepressive effects by activating 5HT1A receptors in a similar manner as the pharmaceutical buspirone that is approved for relieving anxiety and depression in humans.^[114] CBD experimentally attenuates the decrease in hippocampal neurogenesis and dendrite spines density induced by chronic stress and prevents microglia activation in a pharmacological model of schizophrenia. A double-blind, randomized clinical trial with CBD reported a significant clinical improvement similar to the antipsychotic amisulpride, but with less side effects.^[69] Modulation of autophagy and enhanced neuronal survival have been reported using CBD in neurodegenerative experimental

models, suggesting benefits of CBD for psychiatric/cognitive symptoms associated with neurodegeneration.^[10]

Human imaging studies correlated with CBD

Human imaging studies have demonstrated CBD affects brain areas involved in the neurobiology of psychiatric disorders. A study has showed that a single dose of CBD, administered orally in healthy volunteers, alters the resting activity in limbic and paralimbic brain areas while decreasing subjective anxiety associated with the scanning procedure.^[24,39] CBD reduced the activity of the left amygdala–hippocampal complex, hypothalamus, and posterior cingulate cortex while increasing the activity of the left parahippocampal gyrus compared with placebo. In healthy volunteers treated with CBD and submitted to a presentation of fearful faces, there was a decrease of the amygdala and anterior and posterior cingulate cortex activities and a disruption in the amygdala–anterior cingulate cortex connectivity. In healthy humans, CBD reversed the anxiogenic effects of $\Delta 9$ -THC and reduced anxiety in a simulated public-speaking task.^[5,24,39]

Tetrahydrocannabinol

Interestingly, THC, administered prior to a traumatic insult in human case studies and animal models has had measurable neuroprotective effects. In a 3-year retrospective study of patients who had sustained a traumatic brain injury (TBI), decreased mortality was reported in individuals with a positive $\Delta 9$ -THC screen. In mouse models of CNS injury, prior administration of $\Delta 9$ -THC provided impairment protection.^[105]

Anxiety relief in humans

For anxiety relief in humans, variability in the responses to cannabis depends on multiple factors, such as the relative concentrations of $\Delta 9$ -THC and other phytocannabinoids. Studies have found $\Delta 9$ -THC facilitates fear extinction.^[2,45] The $\Delta 9$ -THC disrupts the reconsolidation of a fear memory in a manner dependent on activation of CB1.^[19] In humans, oral dronabinol (synthetic $\Delta 9$ -THC) prevents the recovery of fear. In general, conditions associated with chronic stress appear to be positively responsive to phytocannabinoids. Studies in rat models reported that cannabinoids prevented the effects of acute stress on learning and memory and improved neuroplasticity, behavioral, and neuroendocrine measures of anxiety and depression.^[1,8,17,91,96,107,112,123,128]

Cancer

CBD and THC

Cancer is a disease characterized by uncontrolled division of cells and their ability to spread. Novel anticancer agents are often tested for their ability to induce apoptosis and maintain steady-state cell population. In the early 1970s, phytocannabinoids were shown to inhibit tumor growth and prolong the life of mice with lung adenocarcinoma. Later studies have demonstrated cannabinoids inhibited tumor

cell growth and induced apoptosis by modulating different cell signaling pathways in gliomas, lymphoma, prostate, breast, skin, and pancreatic cancer cells as well.^[26,76]

Utility for glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most frequent class of malignant primary brain tumors. Both animal and human studies have demonstrated both $\Delta 9$ -THC and CBD, combined and separately, have significant antitumor actions on GBM cancer cell growth. The mechanism of $\Delta 9$ -THC antitumoral action is through ER stress-related signaling and upregulation of the transcriptional coactivators that promote autophagy.^[13,14,101,102]

CBD reduces growth different tumor xenografts

CBD has also been shown to reduce the growth of different types of tumor xenografts including gliomas. The mechanism of action of CBD is thought to be increased production of ROS in glioma cells, thereby inducing cytotoxicity or apoptosis and autophagy.^[71,74-76] CBD is able to inhibit cancer cell invasion and metastasis mediated by inhibition of epidermal growth factor, NF- κ B, and mTOR pathways. mTOR signaling pathway acts as the central regulator of cell metabolism, growth, proliferation, and survival, and is critical for tumor suppression. CBD also reduces angiogenesis through actions on both tumor and endothelial cells.^[111] The combined administration of THC and CBD is currently being therapeutically explored in human studies.^[26,71,110,111]

In Feb 2017, GW Pharmaceuticals announced positive results from a phase 2 placebo-controlled clinical study of their proprietary drug combining of $\Delta 9$ -THC and CBD in 21 patients with recurrent GBM. The results showed 83% one-year treatment group survival rate compared with 53% for patients in the placebo cohort ($P = 0.042$). Median survival was greater than 550 days compared with 369 days in the placebo group. GW Pharmaceuticals has subsequently received Orphan Drug Designation from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for their $\Delta 9$ -THC and CBD combination for the treatment of malignant glioma.^[47]

Intractable epilepsy

Cannabidiol

Reports of cannabis use in the treatment of epilepsy appear as far back as 1800 BC. Scientific reports appear in 1881 from neurologists using Indian hemp to treat epilepsy with dramatic success.^[104] The use of cannabis therapy for the treatment of epilepsy diminished with the introduction of phenobarbital and phenytoin and the passage of laws prohibiting marijuana use in the U.S.

Experiments with $\Delta 9$ -THC have demonstrated a rebound hyperexcitability in the CNS in mice, with enhanced neuronal excitability and increased sensitivity to convulsions and has not been used on most trials

of intractable epilepsy. CBD, however, produces antiepileptiform and anticonvulsant effects in both *in vitro* and *in vivo* models.^[64,51,61-63,85]

More recently in 1980, Cunha *et al.*, published a double-blind study that evaluated CBD for intractable epilepsy in 16 patients with grand-mal seizures. Each patient received 200–300 mg daily of CBD or placebo along with antiepileptic drugs for up to 4 months.^[25] They found in the treatment group 7 of 8 responded with fewer seizures. In the placebo group 1 of 8 responded with fewer seizures.^[25,124,129] Since this report was published, there has been renewed interest in medical marijuana for clinical use, but most studies are isolated case reports and small clinical trials. These all suggest that CBD, the nonpsychoactive compound of cannabis, potentially can be helpful for controlling medication refractory seizures.

As with most cannabinoid research to date, conducting studies can be difficult due to limited legal access to medical grade marijuana and phytocannabinoid extracts. Hemp-derived CBD, however, has recently experienced less regulation and as a result research using CBD for refractory epilepsy has experienced a resurgence.

CBDs reduce neuronal hyperactivity in epilepsy

CBD's overall effect appears to result in reduction of neuronal hyperactivity in epilepsy.^[20,56] As discussed earlier, the CB1 receptor is a presynaptic, G-protein-coupled receptor that activates voltage-gated calcium channels and enhances potassium-channel conduction in presynaptic terminals. While $\Delta 9$ -THC binds directly to CB1 receptors, CBD has indirect effects by increasing endogenous anandamide expression. Anandamide affects excitability in neuronal networks by activating the transient receptor potential (TRP) cation channel. CBD regulation of Ca^{2+} homeostasis via several mechanisms may contribute to these actions, particularly for partial or generalized seizures.^[62]

Endogenous cannabinoids

Endogenous cannabinoids appear to affect the initiation, propagation, and spread of seizures. Studies have identified defects in the ECS in some patients with refractory seizure disorders, specifically having low levels of anandamide and reduced numbers of CB1 receptors in CSF and tissue biopsy.^[97] Additionally, the ECS is strongly activated by seizures, and the upregulation of CB1 receptor activity has antiseizure effects.^[27]

The pharmaceutical company, GW Pharmaceuticals, is currently developing the CBD drug, Epidiolex® that is a purified, 99% oil-based CBD extract from the cannabis plant. Results of a recent 2015 open-label study (without a placebo control) in 137 people with treatment-resistant epilepsy indicated that 12 weeks of Epidiolex® reduced the median number of seizures by 54%.^[29,30] Notably, subjects in this study ranged from 2 to 26 years old with

an average age of 11. The dosing for CBD (Epidiolex®) was 2–5 mg/kg per day, titrated until intolerance or up to a maximum dose of 25 mg/kg or 50 mg/kg per day (dependent on study site). Although this study exclusively looked for effects on seizure incidence, no evidence suggests that the antiseizure effects of CBD are limited to the treatment of this condition. Other open-label studies of Epidiolex® are ongoing in the U.S. Currently, The U.S. FDA has given permission to use this drug for “compassionate use” for a limited number of subjects with treatment-resistant epilepsy syndromes such as Lennox-Gastaut syndrome (a childhood-onset, treatment-resistant epilepsy characterized by multiple types of seizures and developmental delay) in children and adults and Dravet syndrome (a severe myoclonic epilepsy of infancy) in children. Development of synthetic forms of CBD is also in progress to treat seizure and other disorders responsive to the phytocannabinoid CBD.

Despite the preclinical data by GW Pharmaceutical and anecdotal reports on the efficacy of cannabis in the treatment of epilepsy, a 2014 Cochrane review concluded that “no reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy.” This report noted this conclusion was mostly due to the lack of adequate data from randomized, controlled trials of $\Delta 9$ -THC, CBD, or any other cannabinoid in combination.^[28,38,43,83]

Safety

A comprehensive safety and side effect review of CBD in 2016 on both animal and human studies described an excellent safety profile of CBD in humans at a wide variety of doses. The most commonly reported side effects were tiredness, diarrhea, and changes of appetite/weight.^[57] In studies comparing other medicinal drugs used for the treatment of these medical conditions, CBD also had a very favorable side effect profile. CBD does have interactions with common hepatic (drug)-metabolizing enzymes, belonging to the cytochrome P450 family. Therefore, interactions with drug transporters and interactions with drugs must be considered.^[6]

CBD – better safety profile vs. other cannabinoids

CBD also has a better safety profile compared to other cannabinoids, such as THC. For instance, high doses of CBD (up to 1500 mg/day) are well tolerated in animals and humans. In contrast to THC, CBD does not alter heart rate, blood pressure, or body temperature, does not induce catalepsy, nor alter psychomotor or psychological functions.^[92] This improved safety profile may be a result of its lack of direct agonist properties at cannabinoid receptors.^[4]

Synthetic analog nabilone

A synthetic analog of $\Delta 9$ -THC, nabilone (Cesamet™; Valeant Pharmaceuticals North America), was approved in 1981 for the suppression of the nausea and vomiting

produced by chemotherapy. Synthetic Δ^9 -THC, dronabinol (Marinol®; Solvay Pharmaceuticals), was subsequently licensed in 1985 as an antiemetic and in 1992 as appetite stimulant. The capability of Δ^9 -THC for stimulating the CB1 receptor is paradoxically both the main reason for, and drawback against, its therapeutic use. In fact, as discussed below, psychotropic effects, and the potential risk of cardiac side effects, tolerance, and dependence, limit the application of Δ^9 -THC as a synthetic or from a plant source in many therapeutic applications.^[87]

Adverse effects

The 2014 AAN review of 34 articles on MS using cannabinoids of various forms noted several adverse effects. Reported symptoms included nausea, increased weakness, behavioral or mood changes (or both), suicidal ideation or hallucinations, dizziness or vasovagal symptoms (or both), fatigue, and feelings of intoxication. Psychosis, dysphoria, and anxiety were associated with higher concentrations of THC. However, no direct fatalities or overdoses have been attributed to marijuana, even in recreational users of increasingly potent marijuana possibly due to lack of endocannabinoid receptors in the brainstem.^[66]

In a recent rule change by the World Anti-Doping Agency or WADA, CBD will no longer be listed as a banned substance for international sport competition for 2018. The agency noted that Δ^9 -THC will still be prohibited. WADA issued with this ruling that noted CBD extracted from cannabis plants still may contain varying concentrations of THC.^[119] CBD extracted from the hemp plant has by definition <0.3% Δ^9 -THC.

Dosing

It is beyond the scope of this review to provide any meaningful dosing recommendations for CBD or Δ^9 -THC. Like other cannabinoids, CBD produces bell-shaped dose–response curves and can act by different mechanisms according to its concentration or the simultaneous presence of other cannabinoid-ligands.^[11,70] In general, due to significant psychoactive properties of Δ^9 -THC, the therapeutic dose range is limited by side effects. With a currently estimated 850 brands of marijuana-derived CBD products and 150 hemp-derived products on the market and an even greater number of various extracts of Δ^9 -THC and marijuana plants cultivated to produce maximum Δ^9 -THC concentration, universal dosing recommendations are nearly impossible.

Prescribing medical marijuana

Ultimately, prescribing medical marijuana either as a primary treatment or adjunctive therapy will require extreme care and knowledge about the patient's goals and expectations for treatment. States that have allowed medical marijuana have generally required competency

trainings and certification prior to prescribing. There are general screening questions that should be considered before recommending marijuana to a patient. At minimum, these questions should include the following:^[118]

- Is there documentation that the patient has had failure of all other conventional medications to treat his or her ailment?
- Have you counseled the patient (documented by the patient's signed informed consent) regarding the medical risks of the use of marijuana—medical, psychological, and social (such as impairment of driving or work skills) and habituation?
- Does your patient have a history of misused marijuana or other psychoactive, addictive prescription and illegal drugs?
- Will you want periodic drug testing?
- Will you know the standardization and potency content of the medical marijuana to be used and whether it is free of contaminants?

FDA approvals

The FDA has approved the synthetic drugs Cesamet®, Marinol®, and Syndros® for therapeutic uses in the U.S. FDA-posted indications include nausea and the treatment of anorexia associated with weight loss in AIDS patients. Marinol® and Syndros® include the active ingredient dronabinol, a synthetic delta-9-THC. Cesamet® contains the active ingredient nabilone that has a chemical structure similar to THC and is also synthetically derived. Although these medications are often cited in human clinical research, their general use is limited based both on side effects and indication constraints.

CONCLUSION

Although federal and state laws are inconsistent about the legality of cannabis production, its increasingly documented health benefits make it once again relevant in medicine. Current research indicates the phytocannabinoids have a powerful therapeutic potential in a variety of ailments primarily through their interaction with the ECS. CBD is of particular interest due to its wide-ranging capabilities and lack of side effects in a variety of neurological conditions and diseases.

Legalization of marijuana in many states: Need for education
Because of the rapid legalization of medical marijuana by the majority of state legislatures in the U.S., physicians are faced with a lack of formal education and basic knowledge as to the possible indications, side effects, interactions, and dosing when prescribing medical marijuana. Because of federal restrictions on human research in the U.S., we lack the number and quality of human trials typically used when prescribing a medication. This review of the neurological benefits

of phytocannabinoids has demonstrated significant benefits for neuroprotection and disease reductions in a wide variety of neurological diseases and conditions in humans.

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