
# A FRESH LOOK AT THE ENDOCANNABINOID SYSTEM


Cannabinoids hold promise for the treatment of chronic pain.

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The human body is composed of 12 systems. One of these, the endocannabinoid system (ECS; Figure), generally receives less attention than the others, but it is vital to human health and can greatly influence multiple facets of a person's life. The ECS is responsible for linking physiologic systems and maintaining homeostasis for many of the body's main functions. It controls aspects such as appetite stimulation, sleep regulation, mood, stress, memory formation, and pain.[1]

The ECS has three main components: (1) endogenous cannabinoids (CBs), (2) CB receptors, and (3) the enzymes that aid in the regulation of endocannabinoids. CB receptors are located throughout the body, primarily within the central nervous system, but also within peripheral organs, tissues, and immune cells. The receptors are also found within peripheral nerves and central integration sites, which have been shown to induce analgesia in acute and chronic pain models.[2] Interest in CB receptors as a replacement for more traditional routes of pain management has grown, spurred in part by rising rates of opioid overdoses in the United States.

At the same time, research on marijuana is increasing understanding, acceptance, and integration of the ECS in optometric practice. Exogenous CBs such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) target and regulate the ECS. These drugs are being used to treat conditions such as fibromyalgia, migraines, seizures, and Alzheimer disease.[3]

## ENDOGENOUS CBS

The body produces and tightly controls endogenous CBs in response to different environmental factors. Although no specific neurons or pathways are associated with the ECS, all cells are essentially capable of producing endocannabinoids.

The two most notable endogenous CBs identified are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). These lipid-based messengers interact with CB receptors to modulate synaptic function via retrograde signaling.

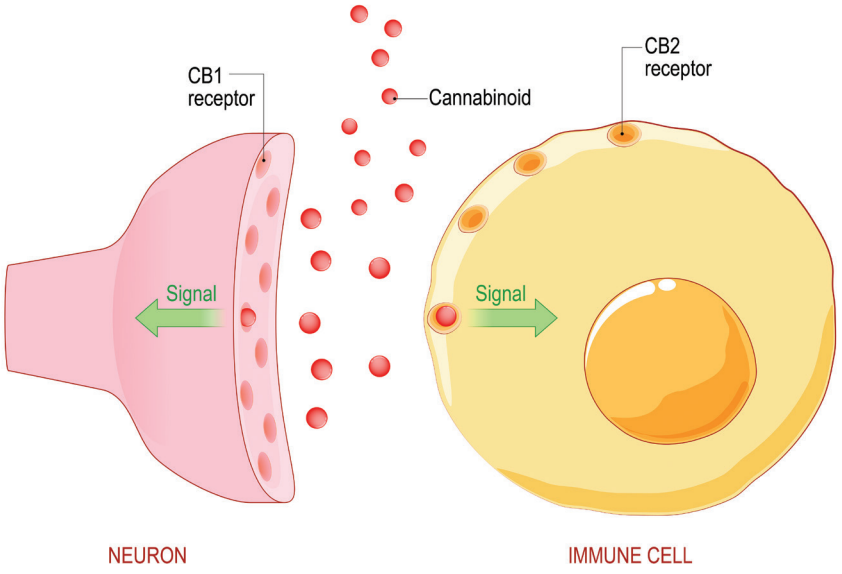


Figure. The endocannabinoid system.

When released from postsynaptic neurons, the messengers target presynaptic CB receptors to downregulate the stimulated neuron and suppress the release of neurotransmitters, ultimately producing a homeostatic effect.[4] AEA acts as a partial agonist to these receptors, whereas 2-AG behaves as a full agonist. The latter is far more abundant within the brain and brainstem, and contributes to appetite, pain, and immunity. AEA is located within the nucleus accumbens and throughout the brain and peripheral tissues. AEA enhances mood through dopamine release and reduces fear and anxiety.[5] A runner's high was previously thought to be due to endorphin release, but recent studies have suggested that the experience may result from increased levels of AEA in people who partake in prolonged and demanding exercise.[6]

The enzymes responsible for breaking down endocannabinoids are another important component of the ECS. Fatty acid amide hydrolase degrades AEA, and monoacylglycerol acid lipase degrades 2-AG.[7]

## AT A GLANCE

- Cannabis has two different subspecies: *Cannabis sativa*, associated with energizing and stimulating properties, and *Cannabis indica*, associated with relaxing and pain-relieving qualities.
- Endogenous cannabinoids induce contraction of the ciliary body, open Schlemm canal, and enhance metalloproteinase function within the trabecular meshwork, causing an increase in outflow through the trabecular meshwork, thus reducing IOP an average of 25%, but the effects last only about 3 to 4 hours, which is not sufficient for glaucoma treatment.

## CB RECEPTORS

The two CB receptors of the ECS are the CB1 and CB2 receptors. These transmembrane G protein–coupled receptors are located on presynaptic neurons throughout the central and peripheral nervous system.

CB1 receptors are more abundant and play a greater role in the ECS, which makes them a great target for therapeutic remedies. CB1 receptors are found extensively within the brain and, to a lesser extent, in the spinal cord and dorsal root ganglia. Here, the receptors regulate the release of neuromodulators such as serotonin, acetylcholine, dopamine, opioids, and norepinephrine.[8] The CB1 receptors located within the basal ganglia and cerebellum play a role in sedation and movement, and those located within the spinal cord and brainstem contribute to analgesic effects. CB1 receptors are also found on the hypothalamus, hippocampus, and amygdala, and they contribute to appetite regulation, emotional processing, and memory formation.[9]

CB2 receptors are located predominantly within peripheral organs, specifically the immune system, including the spleen, thymus, and tonsils, and on the surface of macrophages, microglia, and mast cells. CB2 receptors regulate cytokine release, which reduces inflammation and responds to illness. The expression of CB2 receptors is therefore observed mostly during a state of active inflammation.[10]

Both endogenous CBs can bind to either receptor. CB1, however, is a stronger target for AEA, whereas 2-AG more readily binds to CB2 receptors.[10]

## EXOGENOUS CBS

More than 100 constituents, known as phytocannabinoids or exogenous CBs, are derived from the cannabis plant, and they act upon the ECS

**TABLE.** Marijuana Use in the States and Canada

| LEGAL STATUS | UNITED STATES/CANADA |
|---|---|
| Medical Marijuana Only | AL, AR, CT, DE, FL, GA, HI, IN, IA, KS, KY, LA, MD, MN, MS, MO, NH, NM, NY, NC, ND, OH, OK, PA, RI, SC, TN, TX, UT, VA, WV, WI, WY |
| Medical and Recreational Use | AK, AZ, CA, CO, IL, ME, MA, MI, MT, NV, NJ, OR, SD, VT, WA, All Canadian Provinces |
| Not Legalized | ID, NE |

similarly to endogenous CBs. The popularity and legalization of exogenous CBs, most notably delta-9-THC and CBD from the marijuana plant, have increased recently. Like AEA, delta-9-THC is a partial agonist that binds directly to the CB1 and CB2 receptors. Because CB1 receptors are found primarily within the central nervous system and are bound to more readily, delta-9-THC is known for its psychoactive adverse effects. These include analgesia, reduced motor activity, and increased hunger. In addition, delta-9-THC aids in the release of dopamine, leading to euphoria.

It is important to remember that marijuana products sold in a dispensary and online are not regulated by the FDA. Delta-9-THC can be consumed through smoking, edibles, and capsules. When delta-9-THC is smoked, its effects can last from 1 to 4 hours, compared to more than 6 hours with edibles and capsules. The duration of effect also depends on the concentration and the individual.[11] Low doses are recommended at first, after which dosing may be tailored to the individual, but should not exceed 40 mg daily.

CBD cannot bind to CB receptors directly. Instead, CBD indirectly increases the concentrations of 2-AG and AEA by competitively inhibiting fatty acid amide hydrolase and monoacylglycerol acid lipase.[7] This ultimately can confer the therapeutic effects that naturally occurring endocannabinoids offer to the body, including pain relief and anxiety suppression. Unlike delta-9 THC, CBD does not have psychotropic effects because the CB1 receptor is not involved. The therapeutic effects of CBD depend on several factors and generally last from 2 to 6 hours. CBD may be consumed sublingually as an oil droplet, in an edible, or in a supplement; inhaled; or topically applied.[12]

Both delta-9-THC and CBD can be used for a wide variety of medical indications, including but not limited to the treatment of neurodegenerative diseases, mental health issues, and pain.

## THE STRAINS

Cannabis has two different subspecies—*Cannabis sativa* and *Cannabis indica*. The former is a tall, light green plant with skinny leaves associated with energizing and stimulating properties. Cannabis indica is the darker and shorter plant with more dense leaves that is associated with relaxing and pain-relieving qualities. In terms of medicinal use, indica strains are indicated for pain relief, and sativa strains are used to address psychological conditions such as anxiety and depression. Hybrids are a result of crossbreeding the two plants to create a maximum medicinal effect for patients with conditions such as multiple sclerosis (MS), epilepsy, and lupus. Research, however, has shown that the different strains do not actually determine the effects achieved. Instead, it's the CBs and terpenes within the plants.[13]

## MEDICAL USE

Each state has its own set of qualifying conditions for obtaining a medical marijuana card (Table). Examples include cancer, Crohn disease, MS, amyotrophic lateral sclerosis, Parkinson disease, and fibromyalgia. After gaining approval from their primary care provider, patients may register with their state's medical marijuana registry, request a card, and (likely) pay a fee. Once they receive their medical marijuana card, patients may go to a state-approved dispensary and purchase products such as topical creams, oral medications, oils, and dried-out leaves.[14]

## NEUROLOGIC CONDITIONS

Excitotoxicity secondary to excessive amounts of glutamate is characteristic of many neurologic and neurodegenerative diseases such as migraine, Parkinson disease, schizophrenia, and MS. Cannabis is an emerging therapeutic for these conditions because of its ability to reduce neuropathic pain, muscle spasms, and sleep disturbances. Activating CB1 receptors can block glutamate transmission and enhance corticospinal tract excitability, ultimately reducing spasticity. In addition, CB receptor agonists such as THC implement neuroprotective effects mediated by CB1 receptors to combat neurodegeneration and help slow the progression of MS.[15,16] CBs may also work by slowing nerve impulses within the brain, altering calcium levels at the synaptic cleft, and reducing brain inflammation, all of which are associated with seizures.

## MARIJUANA AND GLAUCOMA

One of the most common questions heard by optometrists regards the use of marijuana to treat glaucoma. There are CB1 receptors

located within the ciliary body, trabecular meshwork, and Schlemm canal. CBs induce contraction of the ciliary body, open Schlemm canal, and enhance metalloproteinase function within the trabecular meshwork, causing an increase in outflow through the trabecular meshwork, thus reducing IOP.[17] Research has shown an average reduction in IOP of 25%, but the effects last only about 3 to 4 hours, which is not sufficient for glaucoma treatment. Moreover, effectivity has been shown only when CBs are administered by inhalation, orally, or intravenously, not topically. CBs have a low aqueous solubility, which does not allow them to enter the anterior chamber when applied in drop form.[18]

## PAIN MANAGEMENT

About 16 million people in the United States experience chronic neuropathic pain characterized by impulsive tingling, shooting, or stabbing sensations. Conditions producing neuropathic pain include but are not limited to fibromyalgia, diabetic neuropathy, and migraine.[19] Nerve damage can provoke hyperexcitability of primary afferent nociceptors, eliciting a decrease in inhibitory neuronal activity within the periaqueductal gray matter of the midbrain and the dorsal horn of the spinal cord. This can eventually lead to persistent and resistant pain. Glial cells also play a role by disrupting inflammation and glutamate signaling.[20]

CB1 receptors are located within these nociceptive modulating regions. CBs are therefore a potential alternative to opioids for the management of chronic pain. Cannabis essentially dampens the pain signal being sent to the spinal cord and brain by acting on GABAergic neurons.[21] In 2010, the United Kingdom approved Sativex oromucosal spray (nabiximols, GW Pharmaceuticals), a drug containing THC and CBD that showed anti-inflammatory and antinociceptive effects in patients with MS and neuropathic cancer pain.

Because of the inflammatory component of pain, CB2 receptors have also shown effectiveness. They can inhibit nonneuronal cells from releasing proinflammatory factors near nociceptive terminals, thereby inducing analgesic effects.[19] CB2 receptors do not induce psychoactive adverse effects, making products such as CBD an attractive option for relieving chronic pain. Conversely, CBs showed negligible outcomes for acute pain relief in several studies that assessed pain after trauma and dental procedures.[22] For delta-9-THC to become a management option, however, further research is necessary to determine proper dosage and guide regulations to ensure safety and efficacy.

## KEEP TABS ON POSSIBLE CANNABINOID TREATMENT

The ECS holds promise for the treatment of neurodegenerative and chronic pain. Further research is necessary before CBs can become a widely accepted and implemented alternative to opioids. ■

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