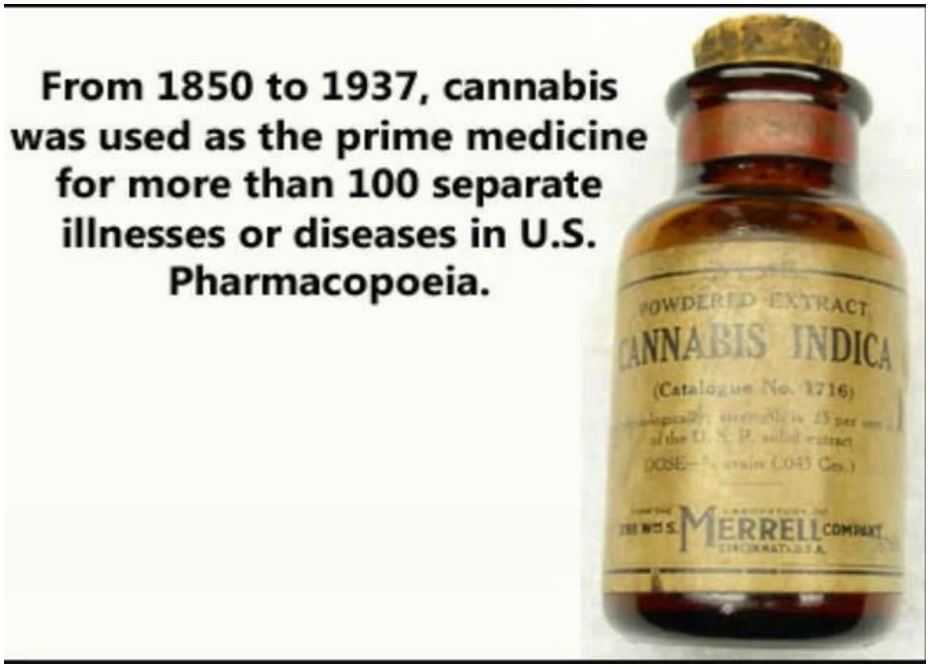
# Why is Cannabis a Medicine? Study of the Endocannabinoid System

**Introduction:** With the huge debate about whether cannabis has medical uses has caused a huge uproar. Even with the many studies and hundreds of stories about the miracle healing power of cannabis it is still considered a dangerous drug to the majority of the medical community. And without the acceptance of physicians it is difficult for many people to go against their doctor. Unfortunately physicians are not properly educated in school about cannabis. Cannabis was made illegal because of propaganda against the advice if the AMA's advice in 1937.

**Objectives:**

1. Brief history of medical cannabis and its uses before illegalization.
2. Learn about the endocannabinoid system and its role in homeostasis.
3. What are endocannabinoids and what do they do?
4. Phytocannabinoids
5. Researched and proven medical uses

## Medical Cannabis Uses In U.S. History

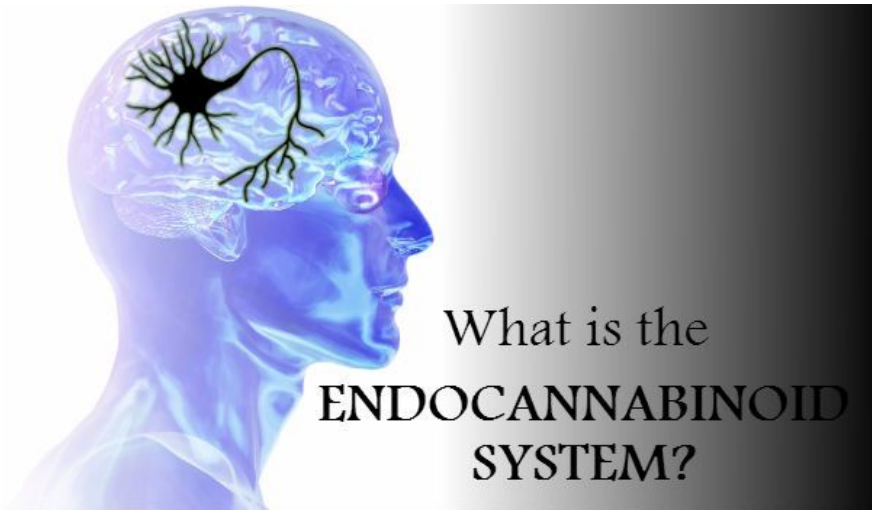


Because medical cannabis history goes back over 5,000 years we are just discussing the U.S. medical uses. We will not discuss any propaganda issues in this class. Just note that cannabis was made illegal to stop the use of hemp for rope, industrial products, food, etc. It was more focused on using timber for paper and nylon for rope and other products. Cannabis is not hemp but was lumped in with hemp because of the difficulty and confusion of THC at the time. I do another class for this.

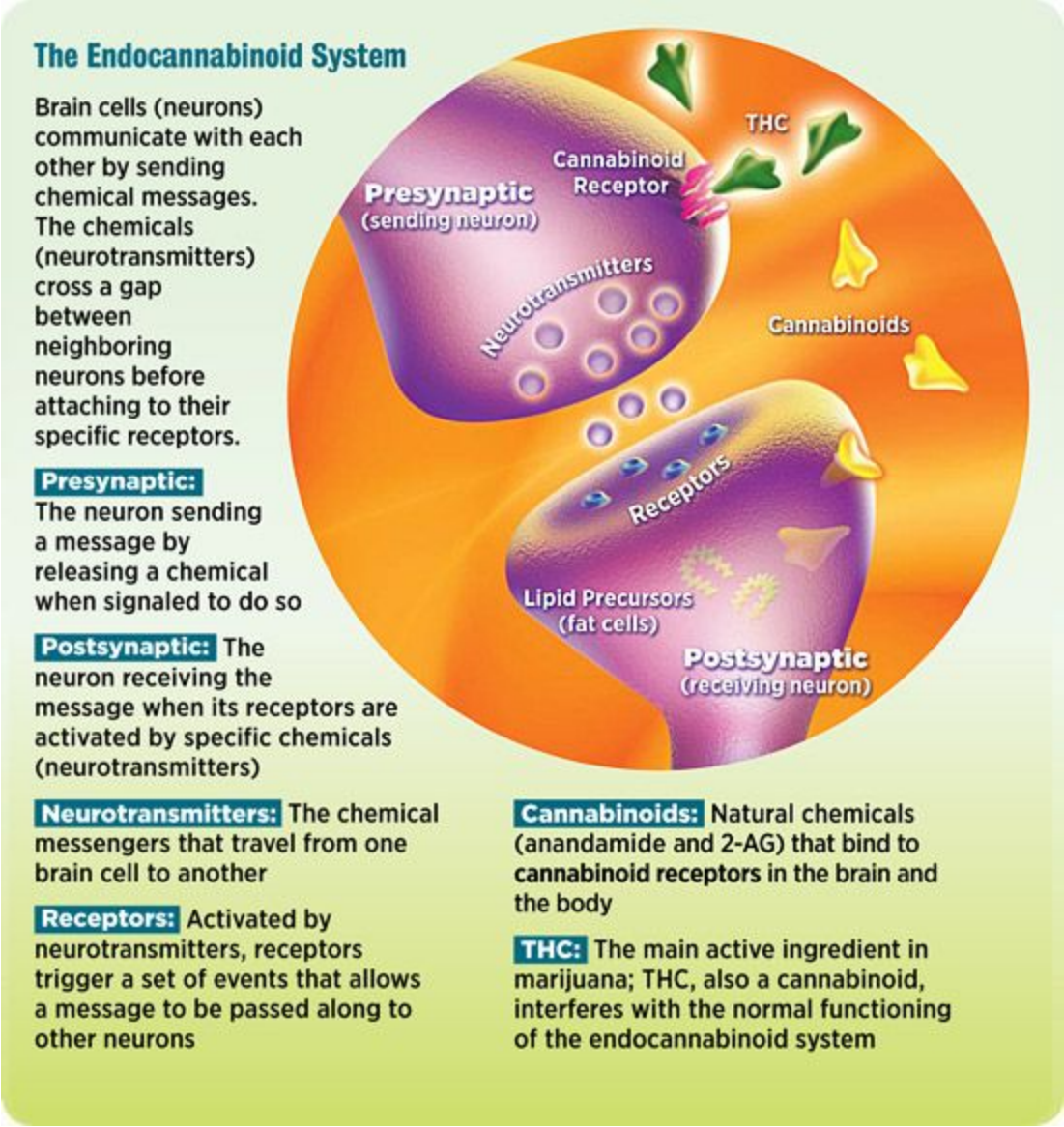
Between the years of 1840-1937 cannabis was also used in medicinal practice throughout North America. During this time, more than one hundred papers were published in the Western medical literature recommending it for various illnesses and discomforts. The first physician to introduce cannabis to Western medicine was W.B. O'Shaunghnessy of Scotland. He introduced cannabis to Western medicine in 1841 after observing its use in India and performing experiments on animals to satisfy himself that it was safe for human use. Soon after its introduction to North America, physicians began to prescribe cannabis for a variety of physical conditions such as rabies, rheumatism, epilepsy, tetanus and as a muscle relaxant. Cannabis became so common in medicinal use that eventually, cannabis preparations were sold over the counter in drug stores.

## The Endocannabinoid System: Why Cannabis work as a medicine

In order to understand why cannabis is a good medicine it's important to first understand why it works. We have a system in our body called the Endocannabinoid System which was discovered in 1992 by a chemist named Raphael Mechoulam from Israel. He actually also discovered the structure of THC in 1964. Endocannabinoids and their receptors interact with a specific neurological network much the way that endorphins do. Important in basic functions as memory, balance, movement, immune health and neuroprotection. Its main objective is to maintain homeostasis. The endogenous cannabinoid system, named after the plant discovery, is perhaps the most important physiologic system involved in establishing and maintaining human health.



**The endocannabinoid system (ECS) is a group of endogenous cannabinoid receptors located in the mammalian brain and throughout the central and peripheral nervous systems, consisting of neuromodulatory lipids and their receptors. Known as "the body's own cannabinoid system",[1] the ECS is involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory, and in mediating the psychoactive effects of cannabis**. (Wikileaf definition)




**We are going over chart above but here are a few more definitions.**

Cannabinoid receptors are also coupled to G-proteins, where a lot of the signaling "magic" happens when a molecule or compound binds to the outer portion of these receptors. The three main ligands that bind to cannabinoid receptors are all lipophilic (fatty or "fat-loving"

compounds), and include endocannabinoids (synthesized within the body), phytocannabinoids (plant-derived, such as from cannabis), and synthetic cannabinoids.

**Endocannabinoids:** Also called cannabinoids. Substances our bodies naturally make to stimulate receptors.. The two most well understood of these molecules are called anandamide and 2-arachidonoylglycerol (2-AG). They are synthesized on-demand from cell membrane.

**Phytocannabinoids:** Phytocannabinoids are plant substances that stimulate cannabinoid receptors. Delta-9-tetrahydrocannabinol, or THC, is the most psychoactive and certainly the most famous of these substances, but other cannabinoids such as cannabidiol (CBD) and cannabinol (CBN) are gaining the interest of researchers due to a variety of healing properties. Most phytocannabinoids have been isolated from *cannabis sativa*, but other medical herbs, such as *echinacea*
*purpura*, have been found to contain non-psychoactive cannabinoids as well.

**Synthetic Cannabinoids:** Laboratories can also produce cannabinoids. Synthetic THC, marketed as dronabinol (Marinol), and nabilone (Cesamet), a THC analog, are both FDA approved drugs for the treatment of severe nausea and wasting syndrome. Paranoia and anxiety are common as the other cannabinoids work to offset that side effects.

**Marinol Lacks Several of the Therapeutic Compounds Available in Natural Cannabis**

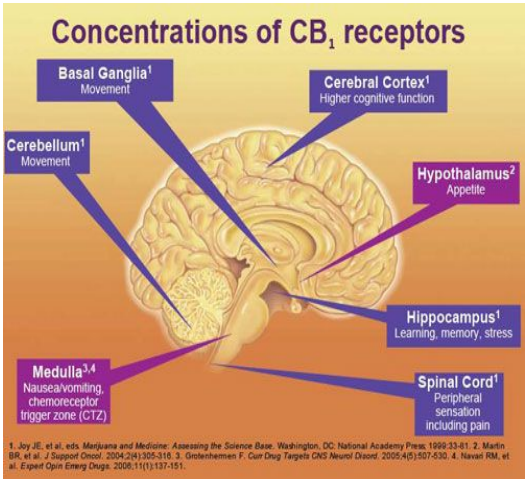
Chemical compounds in cannabis, known as cannabinoids, are responsible for its numerous therapeutic benefits. Scientists have identified 66 naturally occurring cannabinoids. THC. However, several other cannabinoids available in cannabis -- in addition to naturally occurring terpenoids (oils) and flavonoids (phenols) -- have also been clinically demonstrated to possess therapeutic utility. Many patients favor natural cannabis to Marinol because it includes these other therapeutically active cannabinoids. Our bodies receptors are made for a natural plant and the THC analog doesn't have the bioavailability of the whole plant or the ability to process it as well.

## Cannabis Receptors

Sea squirts, tiny nematodes, and all vertebrate species share the endocannabinoid system as an essential part of life and adaptation to environmental changes. By comparing the genetics of cannabinoid receptors in different species, scientists estimate that the endocannabinoid system evolved in primitive animals over 600 million years ago.

Cannabinoid receptors are present throughout the body, embedded in cell membranes, and are believed to be more numerous than any other receptor system. When cannabinoid receptors

are stimulated, a variety of physiologic processes ensue. Researchers have identified two **cannabinoid receptors:**




**CB1:** Predominantly present in the nervous system, connective tissues, gonads, glands, and organs. Anandamide is the primary cannabinoid.

THC is keyed to CB1 and responsible for the euphoric "high" feeling.

Modulates the perception of pain.Not present in the part of the brain that regulates heart rate and and breathing, making it impossible to overdose on cannabis.

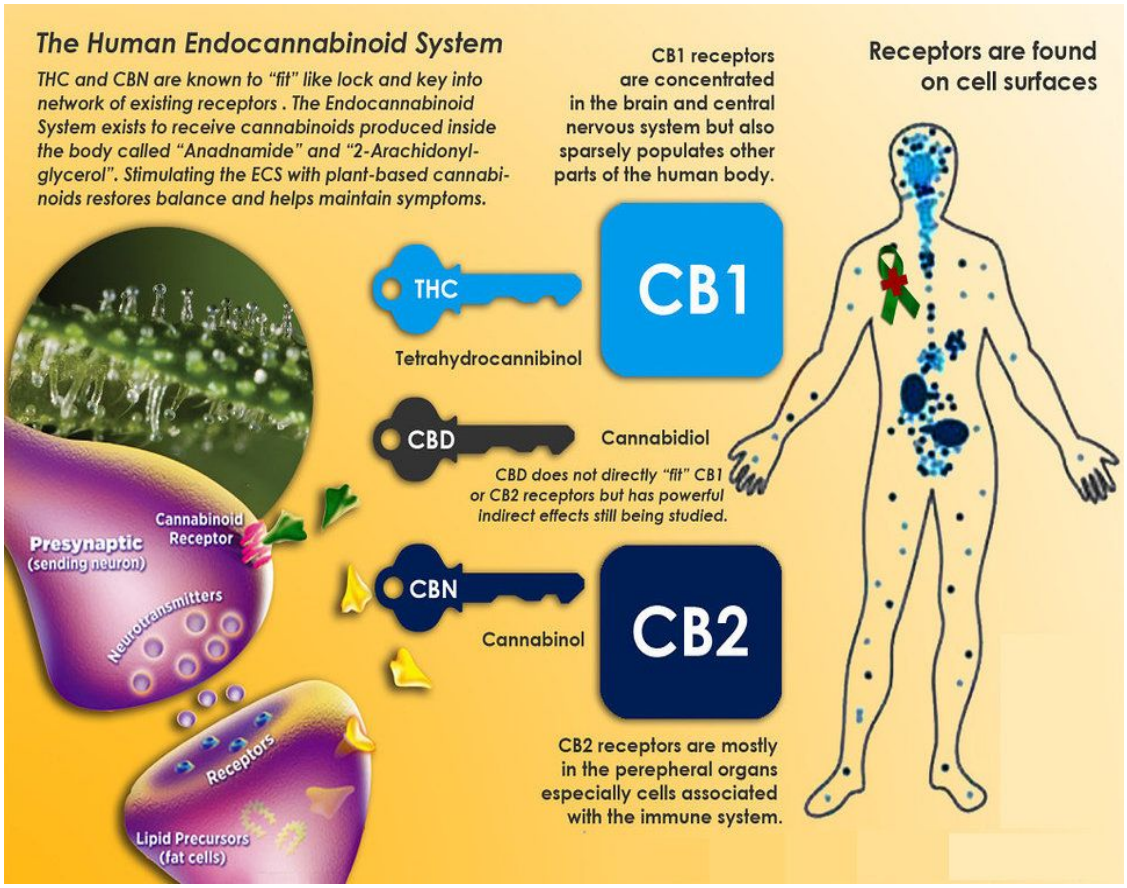
**CB2,** predominantly found in the immune system and its associated structures. Highest concentration in the spleen. 2-Ag is the primary cannabinoid.

The discovery of this receptor helped provide a molecular explanation for the established effects of cannabinoids on the immune system. CB2 receptors are responsible for marijuana's anti-inflammatory effect.

$CB_2$ receptors may have possible therapeutic roles in the treatment of neurodegenerative disorders such as Alzheimer's disease.

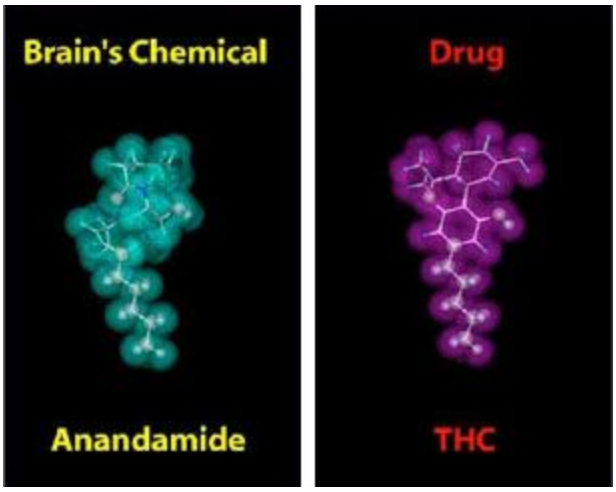
Changes in endocannabinoid levels and/or $CB_2$ receptor expressions have been reported in almost all diseases affecting humans, ranging from cardiovascular, gastrointestinal, liver, kidney, neurodegenerative, psychiatric, bone, skin, autoimmune, lung disorders to pain and cancer.

Many tissues contain both CB1 and CB2 receptors, each linked to a different action. Researchers speculate there may be a third cannabinoid receptor waiting to be discovered. This is just a beginning of what is discovered every day.




## Endocannabinoids

**Anandamide**: (The Bliss Receptor)  Plays a role in pain, depression, appetite, memory, and fertility. Its name comes from *ananda*, the Sanskrit word for "bliss". Anandamide's discovery may lead to the development of an entirely new family of therapeutic drugs. Eventually,




anandamide was found to do a lot more than produce a state of heightened happiness. It's synthesized in areas of the brain that are important in memory, motivation, higher thought processes, and movement control.

It plays an important role in pain, appetite, and fertility. It also helps put the brakes on cancer cell proliferation.

By increasing neurogenesis — the formation of new nerve cells — anandamide exhibits both anti-anxiety and antidepressant properties. Anandamide, like all neurotransmitters, is fragile and breaks down quickly in the body which is why it doesn't produce a perpetual state of bliss.

**2-Arachidonoylglycerol (2-AG):** The other main endocannabinoid, that along with anandamide, has an effect on the CB receptors in the central and peripheral nervous system. Specifically, 2-AG is a full agonist of both CB receptors, and is the primary ligand (binding molecule) for the CB2 receptor.

Plays a complex and important role in various bodily processes including immunity and inflammation.

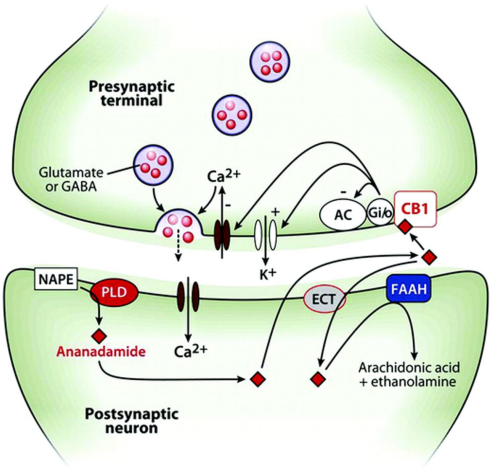
2-AG is the most abundant endocannabinoid found in the body, and like anandamide, is thought to play an important role in the regulation of appetite, immune system functions and pain management.

It is also thought that 2-AG may also play a role in the inhibition of cancer cell proliferation.

## Key Concepts

We are going to concentrate on learning two and then discuss other concepts.
**Brain cells (neurons) communicate with each other and with the rest of the body by sending chemical "messages."** These messages help coordinate and regulate everything we feel, think, and do. Typically, the chemicals (called **neurotransmitters**) are released from a

neuron (a presynaptic cell), travel across a small gap (the synapse), and then attach to specific receptors located on a nearby neuron (postsynaptic cell). This spurs the receiving neuron into action, triggering a set of events that allows the message to be passed along.




But the EC system communicates its messages in a different way because it works “backward.” When the postsynaptic neuron is activated, cannabinoids (chemical messengers of the EC system) are made “on demand” from lipid precursors (fat cells) already present in the neuron. Then they are released from that cell and travel ***backward*** to the presynaptic neuron, where they attach to cannabinoid receptors.

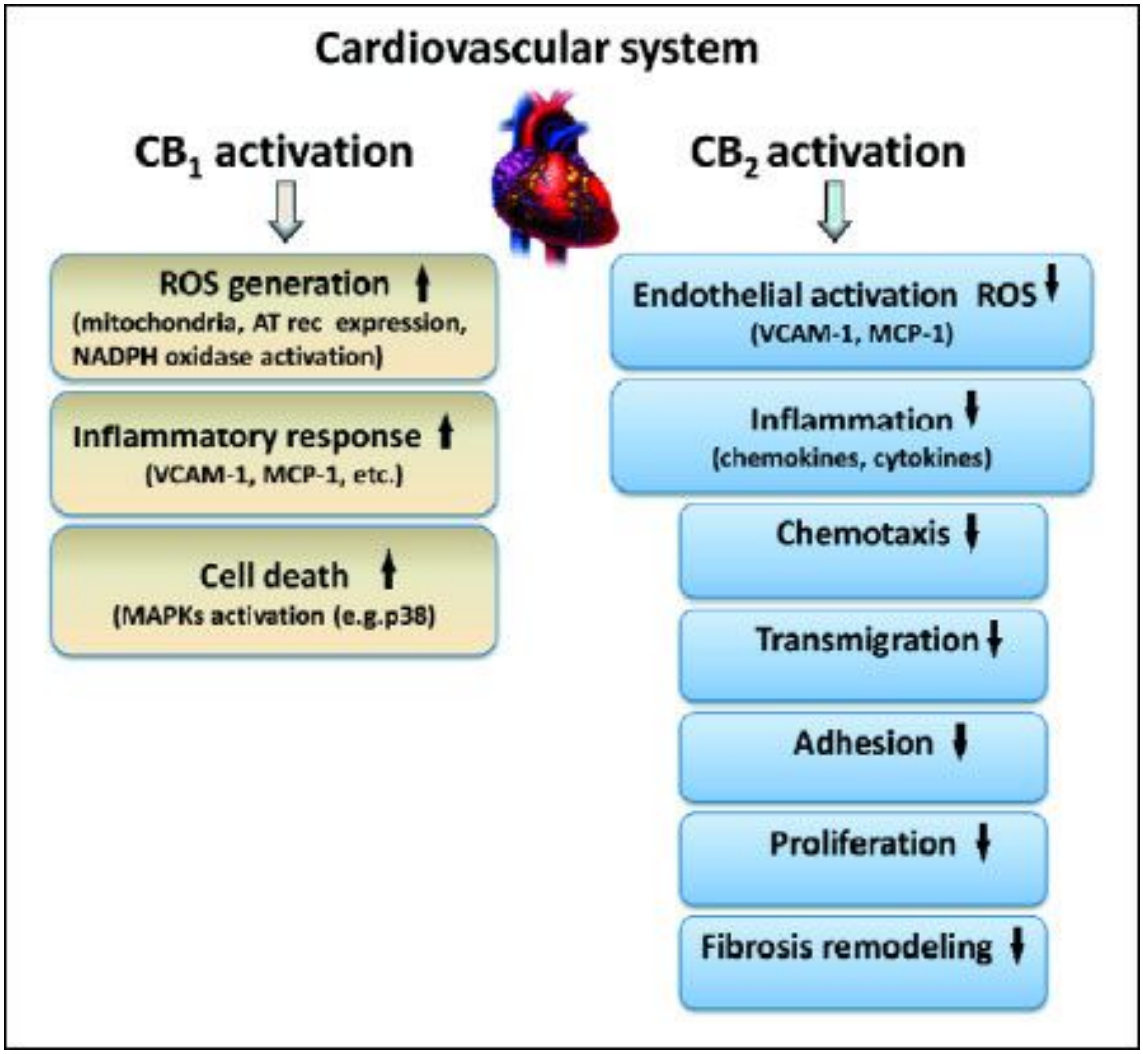
**So why is this important?** Since cannabinoids act on presynaptic cells, they can control what happens next when these cells are activated. In general, cannabinoids function like a “dimmer switch” for presynaptic neurons, limiting the amount of neurotransmitter (e.g., dopamine) that gets released, which in turn affects how messages are sent, received, and processed by the cell.

The nature of the endocannabinoids are functionally much like neurotransmitters.These signaling cannabinoids keep track of metabolic systems all over the body. This information is shared with the nervous system and the immune system so that any imbalance is attended to. If the body is in chronic disease or emotional stress, the immune system can fall behind and lose control of compromised systems. It is here that phytocannabinoids can pitch in to support the stressed body in a return to health. The cannabis plant provides analogues of the body's primary signaling cannabinoids. Tetrahydrocannabinol (THC) is mimetic to anandamide, and cannabidiol (CBD) is mimetic to 2-AG, and has the same affinity to CB1 and CB2 receptors; providing the body with additional support for the immune and endocannabinoid systems.

**Endocannabinoids are usually produced ‘on demand’ following elevation of intracellular Ca2+ concentrations**. Owing to their lipophilic nature, the

endocannabinoids act locally and are not synthesized until needed.

- **Endocannabinoids possess immune-modulatory functions** and usually inhibit cytokine release from immune cells and regulate the migration of the latter. Slows the rate of inflammation.
- **Endocannabinoids are key regulators of food intake, gastrointestinal function, energy storage in the adipose tissue and energy processing by the liver and the skeletal muscle**
- **Endocannabinoids are deeply involved in pain processing** at peripheral, spinal and *supra*-spinal sites.
- **Endocannabinoids regulate both male and female reproduction.**
- **Endocannabinoid can differentially affect cell fate in healthy and cancer cells by regulating differentiation, proliferation and apoptosis.** It can help kill cancer cells and save healthy ones.
- **Endocannabinoids, and anandamide in particular, also directly interact with non-CB1, non-CB2 receptors,** the most studied of which is the transient receptor potential vanilloid type-1 (TRPV1) channel.
- **Dysregulation of the ECS underlies several neurological, immune and metabolic disorders,** and therapeutic strategies manipulating the ECS are being developed.

- 


**Summary:** The ECS is a very complex body system that research is barely started on. It is too complicated to even begin to explain in this class but I am hoping to start an understanding of the concept and how if our cannabinoids are deficient by chronic stress and disease then cannabis can supplement by interacting with the receptors in our body. It is all about understanding **WHY** cannabis is an effective medicine.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**Sanjay Gupta, MD, Chief Medical Correspondent for CNN, wrote the following in an Aug. 8, 2013 article titled "Why I Changed My Mind on Weed," published on CNN.com:**
**"I had steadily reviewed the scientific literature on medical marijuana from the United States and thought it was fairly unimpressive. Reading these papers five years ago, it was hard to make a case for medicinal marijuana. I even wrote about this in a TIME magazine article, back in 2009, titled 'Why I would Vote No on Pot.'**

**Well, I am here to apologize.**

**I apologize because I didn't look hard enough, until now. I didn't look far enough. I didn't review papers from smaller labs in other countries doing some remarkable research, and I was too dismissive of the loud chorus of legitimate patients whose symptoms improved on cannabis...**

**I mistakenly believed the Drug Enforcement Agency listed marijuana as a schedule 1 substance because of sound scientific proof. Surely, they must have quality reasoning as to why marijuana is in the category of the most dangerous drugs that have 'no accepted medicinal use and a high potential for abuse.'**

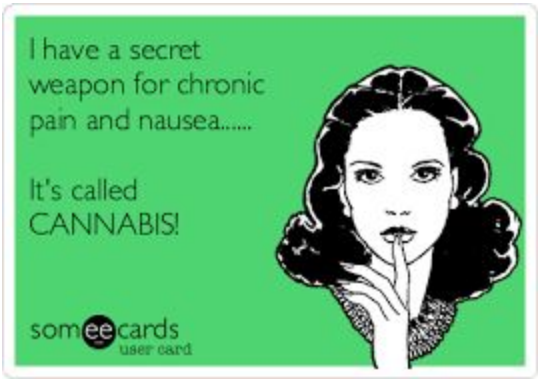
**They didn't have the science to support that claim, and I now know that when it comes to marijuana neither of those things are true. It doesn't have a high potential for abuse, and there are very legitimate medical applications. In fact, sometimes marijuana is the only thing that works...**

**We have been terribly and systematically misled for nearly 70 years in the United States, and I apologize for my own role in that."**

# A Few Common Medical Issues


**Chronic Pain: Arthritis, Pain with chronic conditions, Neuropathy, Cancer, and Migraines are just a few.**

Cannabinoids have shown significant promise in basic experiments on pain. Peripheral nerves that detect pain sensations contain abundant receptors for cannabinoids, and cannabinoids appear to block peripheral nerve pain in experimental animals. Even more encouraging, basic studies suggest that opiates and cannabinoids suppress pain through different mechanisms. If that is the case, marijuana-based medicines could perhaps be combined with opiates to boost their pain-relieving power while limiting their side effects.Survey data indicates that the use of cannabis is common among patients with chronic pain and a majority of patients who use it for this indication report it as being effective. In addition to anecdotal claims, several recent FDA-designed clinical trials report that inhaled inhaled marijuana can significantly alleviate neuropathic pain.




- **Nausea, Vomiting, Appetite and Eating Disorders:** When activated by the anti-nausea drug dronabinol, which is also a synthetic version of THC and approved in 1985 for AIDS and Cancer patients, CB1 prompts the release of hunger-promoting hormones. And suppressing the receptors activity is thought to aid in weight loss. But the mechanism by which the receptor kills or kindles appetite is not entirely understood**. Below are a just a few places that CB1 receptors accumulate:**
    - The sections of the hypothalamus and hind brain that regulate food intake;
    - The reward centre of the brain – helping food make us feel better;
    - From within stomach and intestinal tissue – helping us know when we are hungry;
    - The limbic forebrain – helping food seem more palatable**.**

The United Patient's Group, a resource for alternative medicine, on its page titled "Nausea and Vomiting," available at www.unitedpatientsgroup.com (accessed Mar. 18, 2015), state: ***"There is strong evidence that the cannabinoids naturally produced in the body play a role in suppressing nausea in normal circumstances, and intake of cannabinoids from medical marijuana during episodes of nausea can also effectively relieve symptoms...***

***Inhaled medical marijuana achieves superior results in reducing nausea and vomiting over synthetic alternatives...***

Gil Bar-Sela, MD, DirectRambam Health Care Campus, Haifa, Israel, et al., stated in their June 2013 study "The Medical Necessity for Medicinal Cannabis: or of the Integrated Oncology and Palliative Care Unit at the Prospective, Observational Study Evaluating the Treatment in Cancer Patients on Supportive or Palliative Care" published in *Evidence-Based Complementary and Alternative Medicine*: ***"We followed patients with a medicinal cannabis license to evaluate the advantages and side effects of using cannabis by cancer patients… All cancer or anti-cancer treatment-related symptoms, including nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, and pain had significant improvement... There were no significant side effects to the cannabis except for memory lessening in the 106 patients who continued cannabis use."***

**Movement and Neurodegenerative Disorders: Including chronic illness that may present with spasticity, chronic pain, tremors, and paraplegia. Examples: Rheumatoid Arthritis, MS, Strokes, Spinal cord injuries, Parkinson's, Cerebral Palsy, Dystonia, Alzheimer's and many more.**


A neurological study found herbal cannabis provided relief from muscle spasms and ataxia (loss of coordination). They also found that ingesting marijuana improved muscle control and reduced pain significantly. They also discovered an endogenous cannabinoid system in the human body. This system is intricately involved in normal movement of the body. Cannabinoid receptors are densely located in the basal ganglia (part of brain that controls movement). Most movement disorders are caused by a dysfunction in this part of the brain. **Cannabis' properties fight the effects of stroke, as well as brain trauma, spinal cord injuries, and multiple sclerosis. Cannabinoids act as neuroprotective agents to slow the progression of diseases such as: Huntington's, Alzheimer's and Parkinson's disease.**

Extensive modern studies in both animals and humans have shown that cannabis can treat many movement disorders affecting older patients, such as tremors and spasticity, because cannabinoids have antispasticity,

analgesic, antitremor, and antiataxia properties.

**GW Pharmaceuticals, in the UK, has been conducting clinical trials for more than a decade with its cannabis medicine, Sativex® Oromucosal Spray, a controlled-dose whole-plant extract. GW's Phase II and Phase III trials show positive results for the relief of neurological pain related to: multiple sclerosis (MS), spinal cord injury, peripheral nerve injury (including peripheral neuropathy secondary to diabetes mellitus or AIDS), central nervous system damage, neuroinvasive cancer, dystonias, cerebral vascular accident, and spina bifida. They have also shown cannabinoids to be effective in clinical trials for the relief of pain and inflammation in rheumatoid arthritis and also pain relief in brachial plexus injury. Sativex® was approved in Canada for symptomatic relief of neuropathic pain in 2005, in 2007 for patients with advanced cancer whose pain is not fully alleviated by opiates, and in 2010 for spasticity related to multiple sclerosis. As of 2014, Sativex has been made available or approved for named patient prescription use in 24 countries, including the UK, Spain, Italy and Germany.**

**Cancer:**
**For side effects of chemotherapy and radiation:** The medical benefits of cannabis are no secret. In October 2003, the government patented medical marijuana under US Patent # 6630507, which mentions the antioxidant properties of cannabinoids. The patent also identifies the active chemicals in cannabis that cause drug-like effects on the body, and cites their benefits for patients going through chemo, radiation, or other sources of oxidative stress. We already discussed the making of Dronabinol in 1985.

**Anti-Tumor Properties:**
Cannabinoids may **inhibit tumor growth by causing cell death, blocking cell growth**, and blocking the development of blood vessels needed by tumors to grow. Laboratory and animal studies have shown that cannabinoids may be able to kill cancer cells while protecting normal cells.


- Cannabinoids may **protect against inflammation of the colon** and may have potential in reducing the risk of colon cancer, and possibly in its treatment.
- A laboratory study of delta -9-THC in hepatocellular carcinoma

(liver cancer) cells showed it **damaged or killed the cancer cells**. The same study of delta-9-THC in models of liver cancer showed that it had anti-tumor effects. Delta-9-THC has been shown to cause these effects by acting on molecules that may also be found in non-small cell lung cancer cells and breast cancer cells.

- A laboratory study of cannabidiol (CBD) in estrogen receptor positive and estrogen receptor negative breast cancer cells showed that it **caused cancer cell death while having little effect on normal breast cells**. Studies of metastatic breast cancer showed that cannabinoids may lessen the growth, number, and spread of tumors.
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**Other Medical Cannabis uses for another class:**

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| PTSD | Autoimmune Disorders |
| Alcohol Withdrawal | Obesity & Weight Loss |
| Crohn's Disease & IBS | Diabetes & Complications |
| ADD / ADHD / Autism | Hospice |
| Opiate Withdrawal | Hypertension |
| Seizure Disorders | Many More….. |

Thank you for attending!

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