

The Endocannabinoid System (ECS)

A Physician's Guide

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Summary

The existence of the endocannabinoid system (ECS) and its role in maintaining whole body homeostasis have become widely accepted. The ECS can be modulated by **(1)** endocannabinoids, endogenous lipid-based signalling molecules produced by the body; **(2)** phytocannabinoids and terpenes from cannabis and other plants; and **(3)** synthetic cannabinoids. Patients who are using cannabis for symptom relief should be advised to “start low and go slow”. Further elaboration of the ECS can be expected now that cannabis is both legal and widely available in Canada and companies with a Cannabis Research License are able to conduct human studies with Canadian regulatory approval and oversight.



The endocannabinoid system is an important signalling pathway

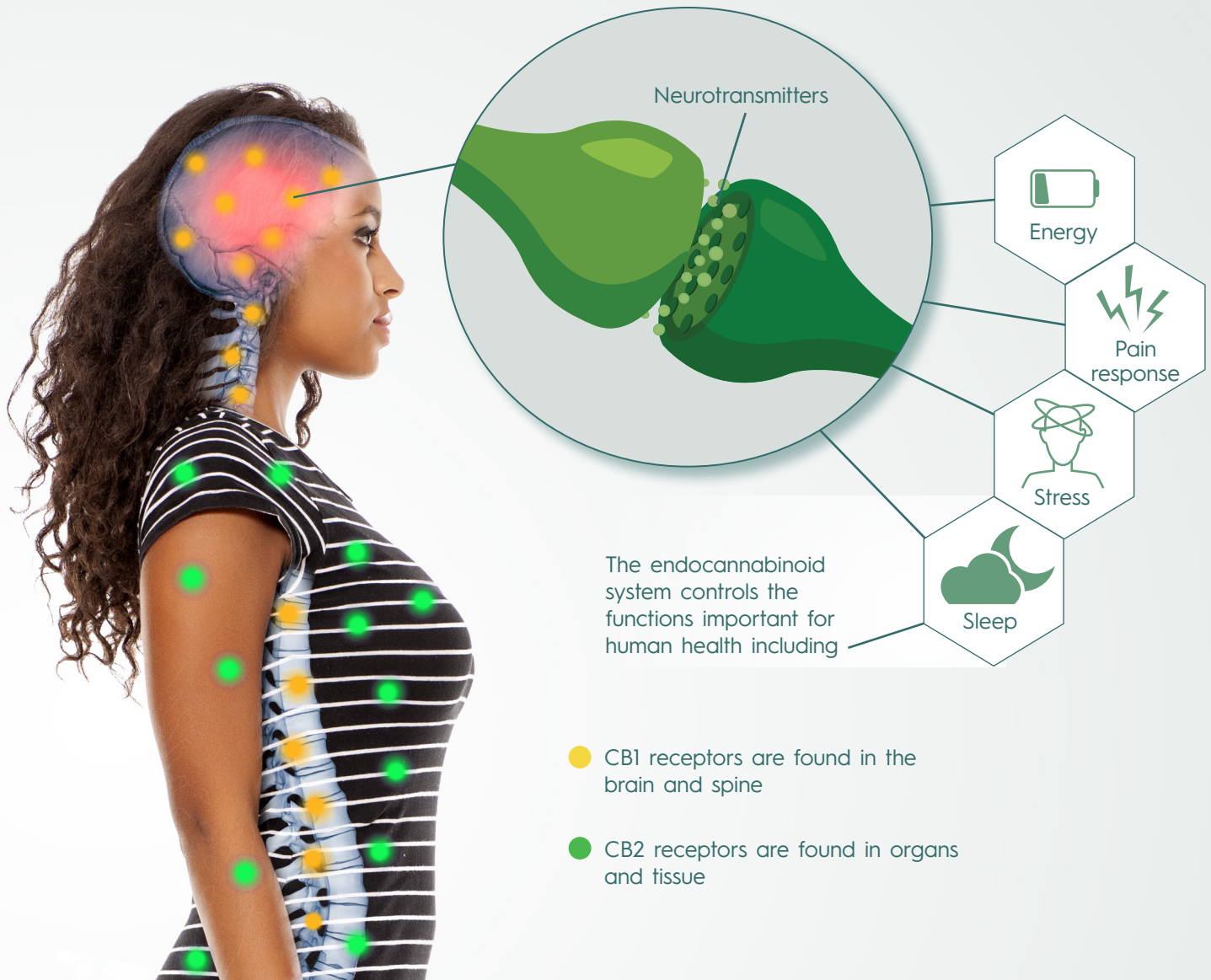
The endocannabinoid system (ECS) is part of a complex and integrated regulatory homeostatic system. It was first discovered in 1988 when scientists identified the CB1 (Cannabinoid Receptor 1) as the main target for *Cannabis sativa* in humans. The core ECS consists of the following:

- **Two naturally occurring endocannabinoids:** *N*-arachidonoyl-ethanolamine (**anandamide** or **AEA**) and 2-arachidonoylglycerol (**2-AG**). These lipid-based signalling molecules act on the cannabinoid receptors, as well as other receptor targets in the body.
- **Two G-protein coupled cannabinoid receptors:** **CB1** and **CB2 (Cannabinoid Receptor 2)**. These are highly conserved throughout evolution and present in all vertebrates.¹ Although the main ligands for the cannabinoid receptors are anandamide and 2-AG, they have other endogenous agonists and antagonists.

Knowledge about the ECS has broadened to include the “expanded endocannabinoid system”² or the “endocannabinidome”.³ The expanded ECS includes a wide array of signalling molecules, receptors and pathways that interact and integrate with the ECS and are well described elsewhere.²⁻⁴

The endocannabinoid system regulates homeostasis

The accepted role of the ECS is to regulate homeostasis, the state of internal stability that is maintained despite changes to the external environment.⁶ The ECS is involved in a broad range of processes including neurological development, pain response, the regulation of stress and emotion, sleep-wake cycle regulation, appetite and digestion, and immune function.^{1,4} The important role of the ECS in maintaining homeostasis makes it a prime therapeutic target; some common drugs including acetaminophen are thought to affect the ECS.³ ECS dysregulation or malfunction can lead to a range of conditions including pain, inflammation, anxiety, sleep disturbance, low energy, and depression.^{1,4}



The endocannabinoid system helps to maintain health and internal balance

CB1 receptors are expressed at high levels in the central nervous system (CNS), at lower levels throughout the peripheral nervous system, and in many other organs and tissues.^{1,4,5} The CB2 receptor is expressed in organs and cells involved in immune function, but its presence in the healthy CNS is controversial.^{1,2,4,5}



The ECS can be modulated by endocannabinoids, phytocannabinoids, and synthetic cannabinoids

In vivo, the ECS is primarily influenced by the endocannabinoids, anandamide and 2-AG. The ECS can also be targeted by phytocannabinoids, defined as *“plant-derived natural products capable of either directly interacting with the cannabinoid receptors or sharing chemical similarity with endocannabinoids or both.”*⁷ The consumption of raw flower or non-decarboxylated cannabis oil does not lead to psychotropic effects or a “high”, because phytocannabinoids exist in their inactive acid form in plants. Heat is required to decarboxylate the acid forms into the active forms, which is why cannabis was traditionally smoked, vaped or cooked. The most widely known phytocannabinoids, Δ^9 -tetrahydro-cannabinol (**THC**) and cannabidiol (**CBD**), are derived by decarboxylation of their acid precursors, tetrahydrocannabinolic acid (**THCA**) and cannabidiolic acid (**CBDA**).

THC, best known for its psychoactive properties, mimics endocannabinoids by acting as a partial agonist on CB1 and CB2 receptors. CBD is nonintoxicating and has low affinity for both CB1 and CB2 receptors.^{2,4} Studies have demonstrated that THC and CBD work together, but the full nature of this interaction is not yet determined.²

Cannabis contains over 100 other active compounds including cannabigerol (**CBG**), cannabichromene (**CBC**), cannabinol (**CBN**), Δ^9 -tetrahydrocannabivarin (**THCV**), cannabidivarin (**CBDV**), as well as numerous terpenes, fatty acids, and polyphenols.^{7,8} Many non-psychotropic phytocannabinoids and terpenes are believed to simultaneously and synergistically modulate the ECS, contributing to a phenomenon known as the “entourage effect”.^{8,9} The entourage effect is the reason that products containing multiple cannabis components are

thought to be more effective than products that include single purified components, although this is unproven and controversial.^{10,11}

Many plants besides cannabis contain ECS-modulating compounds. For example, β -caryophyllene is a terpene that is widespread in plants including hops, black pepper, clove, rosemary, and balsam.^{6-9,11} Many of these plants have proven anti-inflammatory, antioxidant, analgesic, antidepressant, anti-anxiety, and neuroprotective effects.^{7,11} Some of these molecules interact directly with cannabinoid receptors, while others interact with multiple targets including other G-protein coupled receptors and transient receptor potential ion channels. Some molecules work indirectly to influence the synthesis or breakdown of endocannabinoids and others influence wider networks including the arachidonic acid cascade and nitric oxide signalling pathways.^{2,3,7,9}

In addition to endocannabinoids and phytocannabinoids, synthetic cannabinoids have been developed for a variety of indications. Some are already approved by Health Canada, including Cesamet® (nabilone), a prescription medication containing synthetic THC for the prevention of severe nausea and vomiting in cancer patients.³

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Other cannabis-containing prescription medications include Sativex® and Epidiolex®. Sativex® (nabiximols) is a prescription medication containing a combination of THC, CBD, and terpenoids that is approved for the treatment of spasticity and neuropathic pain in multiple sclerosis and pain in cancer patients.^{1,2} Epidiolex® is a purified form of plant-based CBD, prescribed to treat seizures caused by Lennox-Gastaut syndrome and Dravet syndrome. It is not

yet approved for use in Canada. The potential therapeutic applications of phyto- and synthetic cannabinoids are extensive. Promising indications include the prevention or alleviation of pain, social anxiety and depression, sleep disorders, and low energy.^{3,9} Although THC and CBD are being tested individually and in combination for many indications, the contributions of terpenoids and the acid forms of THCA and CBDA may contribute to the effects.¹²

Table 1 – Route of administration, onset and duration.

For more information, please refer to the Health Canada documents¹ and website.¹³

Route of administration	Examples	Average time of onset	Average duration
Inhalation	Smoking or vaping at 160-230 degrees celcius	5 to 15 minutes ¹²	2 to 4 hours ¹²
Oral	Capsules, edibles, teas, juices, tinctures, oils, lozenges	60 to 180 minutes ¹²	6 to 8 hours ¹²
Oromucosal/ intranasal / sublingual	Sprays, films, tablets	15 to 45 minutes ¹²	6 to 8 hours ¹²
Topical	Ointment, creams, balms, salves, patches	Variable ¹²	Variable ¹²



Cannabis for symptom relief: “Start low and go slow”

The Cannabis Act permits patients to access cannabis for medical purposes through their health care practitioner. Health Canada provides patient information at Canada.ca/cannabis.

Common administration methods along with some examples, and their time of onset of effect and duration are shown in **Table 1**. Recreational formulations including “shatter”, “dabs”, “hash”, and “kief” are generally considered to be inappropriate for most medical applications as they deliver highly concentrated amounts of THC.¹²

Absorption of cannabis products is variable and depends on the route of administration, formulation/preparation, lipophilicity, and bioavailability. The experienced effect(s) are influenced by product concentration and dose, previous experience, and presence of other prescription and non-prescription drugs.¹² Cannabinoids are lipophilic and when ingested orally are absorbed to a greater extent in the presence of fat or oils.¹²

Precise doses or dosing schedules for most cannabis products are not yet established. Evidence from patients’ surveys and clinical studies demonstrate that most people using smoked or orally ingested cannabis for medicinal purposes ingest between 1-3 grams of dried cannabis per day, although patients generally obtain benefits with lower doses.¹ Legal producers are required to state an equivalency factor on all their products. A ‘high’ is not necessarily required for symptom control.¹²

It is important for new patients to “start low and go slow” and to increase dose slowly to avoid or control undesired effects. Higher doses of THC and CBD are associated with an increased risk of side

effects including drowsiness/fatigue, dizziness, dry mouth, anxiety, nausea, and cognitive impairment.¹² Combining THC with CBD can help mitigate some side effects. Health Canada advises starting with products containing ≤ 2.5 mg THC or $\leq 10\%$ THC (100 mg/g), combined with equal or higher amounts of CBD.¹³





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About Emerald Health Therapeutics

Emerald Health Therapeutics is led by a team of life science professionals that are dedicated to advancing health and wellness through science. Specifically, we have focused on harnessing the power of the endocannabinoid system and the cannabis plant with the goal of delivering better, more controlled outcomes for consumers seeking to enhance health and wellness. Our team is here to assist you every step of the way with any questions or queries you may have.

Please visit www.emeraldhealth.ca for more information, or contact info@emeraldhealth.ca.