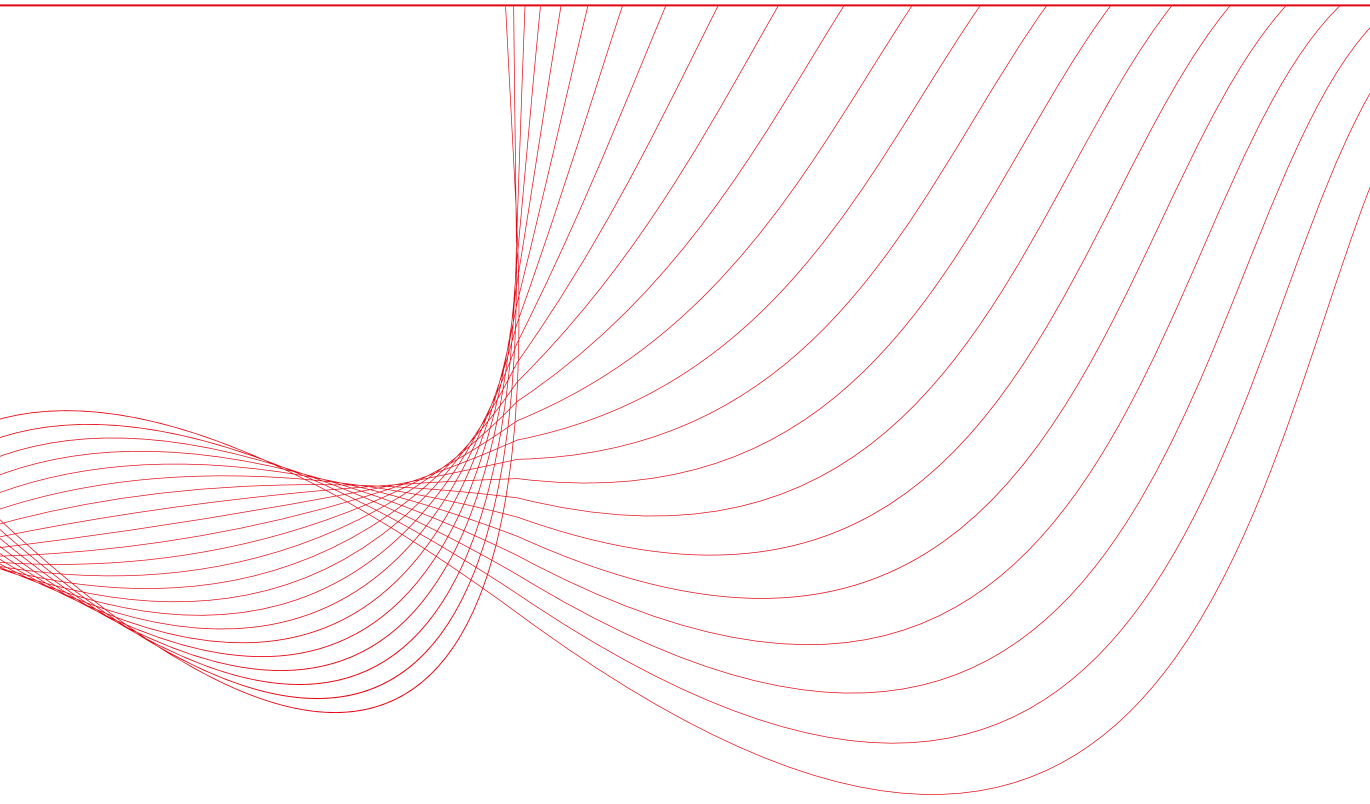
Viola Brugnatelli, MRes | Fabio Turco, PhD

Principles of Clinical Cannabinology

A Comprehensive Guide to Medical Cannabis in Europe

SECOND EDITION

Foreword by Daniele Piomelli, PhD



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Viola Brugnatelli, MRes / Fabio Turco, PhD

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Foreword

by Daniele Piomelli, PhD

For at least ten thousand years, humans have used cannabis as a medicine, a mind-altering ritual plant, an intoxicating substance, a textile, and even a food. Despite this long and varied use, cannabis remains misunderstood, controversial, and stigmatized. After decades of criminalization, its progressive acceptance in many parts of the world—including Canada, and much of the United States and Europe—has posed with increasing urgency the challenge of investigating its potential benefits and risks as well as divulging current knowledge in a balanced and critical manner.

In *Principles of Clinical Cannabinology*, Fabio Turco and Viola Brugnatelli provide a comprehensive and easy-to-read guide to the clinical use of cannabis, covering its history, pharmacology, therapeutic applications, and potential benefits and drawbacks. They have in mind as readers healthcare professionals, students, researchers, and patients who seek to understand the science behind cannabis-based medicine and its possible roles in treating a wide range of medical conditions.

The book is organized in several chapters, each followed by a useful list of references to primary articles and reviews. The first chapter provides an overview of the endogenous cannabinoid system, the ubiquitous signaling complex that is hijacked by D9-tetrahydrocannabinol (THC) in cannabis. The second explores the plant's pharmacology, mainly focusing on its two

most abundant constituents—THC and cannabidiol (CBD)—but also covering less well-known compounds, such as D8-THC and D10-THC, which have recently attracted attention due to their contentious use as substitutes for D9-THC. The third chapter examines potential medicinal uses of cannabis, covering a long list of pathologies—such as chronic pain, epilepsy, multiple sclerosis, and others—for which various levels of evidence of efficacy exist in the medical literature. The last chapter tackles the regulatory landscape surrounding the medicinal use of cannabis in Europe and describes in detail currently available products. The last two sections will be especially useful to practicing physicians, who often struggle not only with cannabis' inherent complexities but also with the vast amount of conflicting information that can be found online.

Throughout *Principles of Clinical Cannabinology*, the authors draw on the latest scientific research and extensively on anecdotal evidence to present a view of cannabis that strives to be both balanced and objective. There is much still to learn about this complex plant, but this clear and well-written book will serve as a valuable resource for those seeking to understand it better.

Daniele Piomelli, PhD

Irvine, California.

April 9th, 2023

Introduction

In recent years, numerous European nations have adopted legislation to permit and regulate the use of Medical Cannabis. Despite these advancements, a substantial knowledge gap persists among both patients and healthcare professionals regarding the therapeutic potential of cannabis and the legal frameworks that regulate its use. This textbook has been developed to bridge this gap, providing a detailed update on the field of Medical Cannabis. It is specifically designed for physicians and healthcare professionals who are keen to broaden their understanding and expertise in this evolving area.

The first chapter of the book focuses on the Endocannabinoid System (ECS), a crucial regulatory system that helps maintain body homeostasis. To enhance understanding of how cannabis and its derivatives impact health, this section offers a detailed analysis of the ECS and the role of endocannabinoids. It specifically examines their functions in relation to various pathological conditions, demonstrating how these mechanisms may contribute to therapeutic benefits. This foundational knowledge prepares readers to further explore the medical applications of cannabis in the following chapters of the textbook.

The second chapter of the book examines the therapeutic properties of the *Cannabis Sativa L.* plant, focusing on its pharmacologically active components. Primarily, it highlights phytocannabinoids such as tetrahydrocan-

nabinol (THC) and cannabidiol (CBD), among others. This section provides a detailed overview of each component, explaining their effects, potential health benefits, and the mechanisms through which they interact with the human body. This analysis aims to equip healthcare professionals with a comprehensive understanding of the medicinal properties of cannabis.

The third chapter presents the latest data from scientific research on the efficacy of Medical Cannabis across a variety of diseases and medical conditions. It aims to assist physicians and healthcare professionals in making more informed decisions about the use of cannabis as a therapeutic option. Additionally, the manuscript features practical insights from prescribers around the world, sharing their experiences and approaches to treating various clinical conditions with Medical Cannabis. This global perspective enriches the guidance provided, helping practitioners understand diverse approaches and best practices in the application of cannabis therapies.

The fourth chapter is focused on a detailed examination of European countries where legislation supporting the use of medical cannabis has been enacted.

The countries covered include:

- Austria;
- Belgium;
- Croatia;
- Czech Republic;
- Denmark;
- Finland;
- France;
- Germany;
- Greece;
- Ireland;

- Italy;
- Lithuania;
- Luxembourg;
- Malta;
- Netherlands;
- North Macedonia;
- Norway;
- Poland;
- Portugal;
- Slovenia;
- Spain;
- Sweden;
- Switzerland;
- United Kingdom.

For each country, this chapter will analyze relevant laws, variations between public and private healthcare systems, which medical professionals are authorized to prescribe cannabis, the pathologies that can be treated, and the specific cannabis preparations and varieties available for prescription.

The structure of this handbook is designed to offer a comprehensive view of the botanical, therapeutic, legislative and market aspects of the *Cannabis Sativa L.* plant. Although the chapters and sub-chapters are arranged to provide a sequential overview, each sub-chapter is also crafted as a standalone article with references.

This format allows for quick reference and ease of access, enabling readers to explore specific topics independently from the rest of the text.

By integrating the most up-to-date scientific evidence, clinical experience, and regulatory insight, this manuscript aspires to serve as both a practical guide and a source of inspiration for those working at the intersection of medicine and cannabis science. Whether you are a seasoned practitioner or just beginning to explore this field, we invite you to engage with the chapters ahead with curiosity and critical thought. The journey into the therapeutic potential of Cannabis Sativa L. is one of both ancient wisdom and cutting-edge research—and it begins here.

Ad Maiora!

CHAPTER **1.**

PHYSIOLOGY OF THE ENDOCANNABINOID SYSTEM

1.1. Introduction to the Endocannabinoid System

Exploring the Endocannabinoid System: History and Discoveries

The exploration of the Endocannabinoid System represents a fascinating journey from the ancient roots of a plant to its profound implications in human physiology.

Image 1. Dr. Raphael Mechoulam, PhD.

"By using a plant that has been around for thousands of years, we have discovered a new physiological system of immense importance."
These are the words of Raphael Mechoulam, PhD, considered to be the father of the international cannabinoid research community: "We wouldn't have been able to get there if we hadn't examined the plant."[1]

In the two decades following the identification and synthesis of tetrahydrocannabinol (THC)—the psychoactive compound in cannabis—by scientists Raphael Mechoulam and Yoel Gaoni in 1964 in Israel, substantial knowledge has been accumulated regarding the pharmacology, biochemistry, and clinical effects of cannabis. However, no one yet really knew how this plant worked, the profound mechanisms through which this plant influences the brain (on a molecular level) to alter consciousness, stimulate appetite, decrease nausea, inhibit epileptic seizures, and relieve pain. No one understood why consuming cannabis could block muscle spasms in Multiple Sclerosis patients; no one knew why it improved mood.

It was not until the late 1980s that researchers discovered the presence of receptor sites in the mammalian brain—specialized proteins embedded in cell membranes—that respond pharmacologically to molecules found in cannabis resin.[2]

An Overview of How Cannabinoid Receptors were Discovered

On 18 July 1990, Dr. Lisa Matsuda and her team at the National Institute of Mental Health (NIMH) made a groundbreaking announcement. They successfully pinpointed the exact DNA sequence responsible for encoding THC-sensitive receptors within the mouse brain. The same research team also successfully cloned the receptor, naming it CB1.[3] Humans also possess the same receptor, a string of 472 amino acids in a chain that traverses the cell membrane seven times.

A potent THC-like molecule synthesized by Pfizer (CP55,940) allowed researchers Allyn Howlett and William Devane to begin mapping the precise locations of cannabinoid receptors within the brain, following the signals emanating from a radioactive tag ‘bound’ to this molecule.[4]

It was unsurprising to discover the regions with the highest receptor concentrations were identified in the following areas of the brain:

- Hippocampus (memorCerebral cortex (cognition);
- Cerebellum (motor coordination);
- Basal ganglia (movement);
- Hypothalamus (appetite);
- Amygdala (emotions);
- Periaqueductal grey matter (pain).

These sites represent the areas where some of the main effects of cannabis on the brain are explored.

In contrast, cannabinoid receptors are not present in the brain regions that control cardiovascular and respiratory functions. This absence aligns with the non-lethality of a THC overdose, unlike, for example, high doses of opioids, which can be fatal.[5];[6]

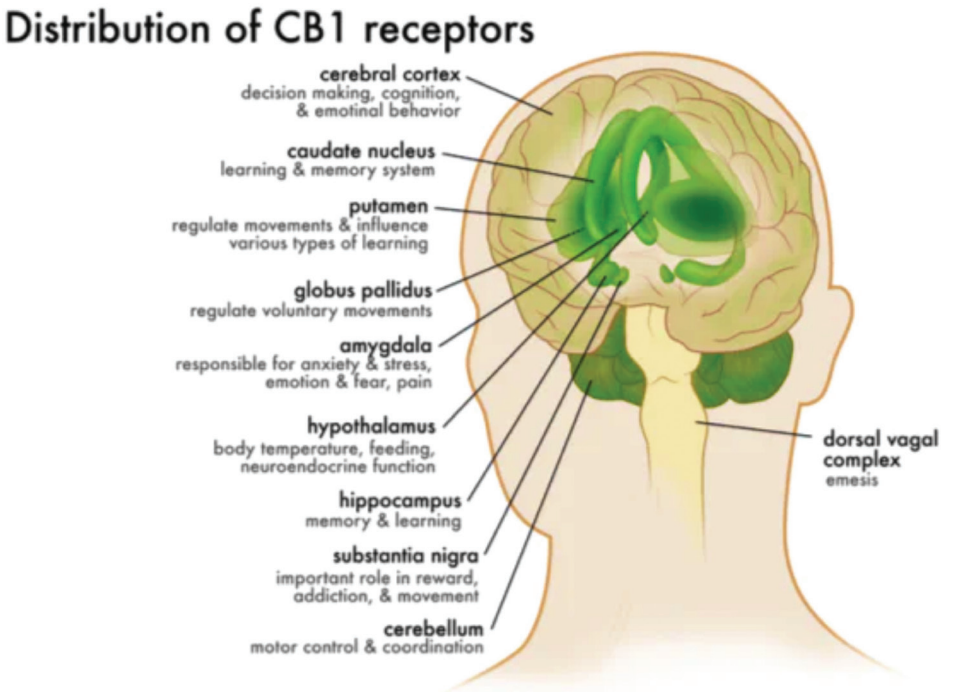

Image 2. Distribution of CB1 in the Brain
(courtesy of Ferguson and Ware, J Sleep Disord Ther 2015, 4:2).

Cannabinoid receptors serve as tools for encoding changes, small scanners perpetually ready to detect biochemical signals circulating around the cells.

Researchers also engineered genetically modified 'knockout' mice devoid of the cannabinoid receptor. When THC was administered to a "knockout" mouse, it produced no effect, as there were no binding sites for THC to interact with, preventing any activity from being triggered. This observation provided additional confirmation that THC functioned by activating cannabinoid receptors present in the central nervous system.[7]

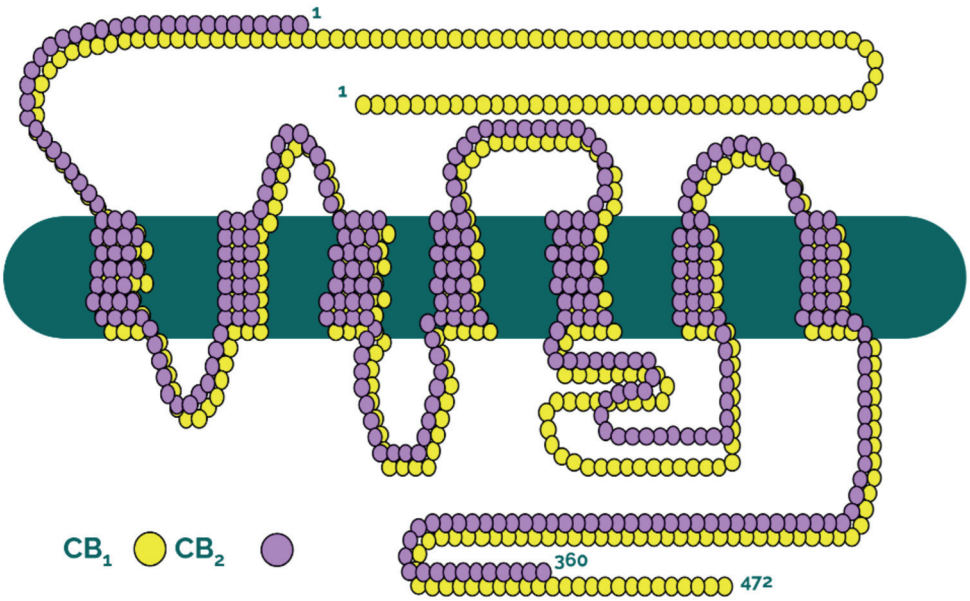

Image 3. CB1 and CB2 receptors.

The CB1 and CB2 Cannabinoid Receptors

Cannabinoid receptors are present throughout the body, embedded in cell membranes.

When cannabinoid receptors are stimulated, they initiate a variety of physiological processes. The two classic cannabinoid receptors are:

- CB1;
- CB2.

Many tissues contain both CB1 and CB2 receptors, each linked to a different action.

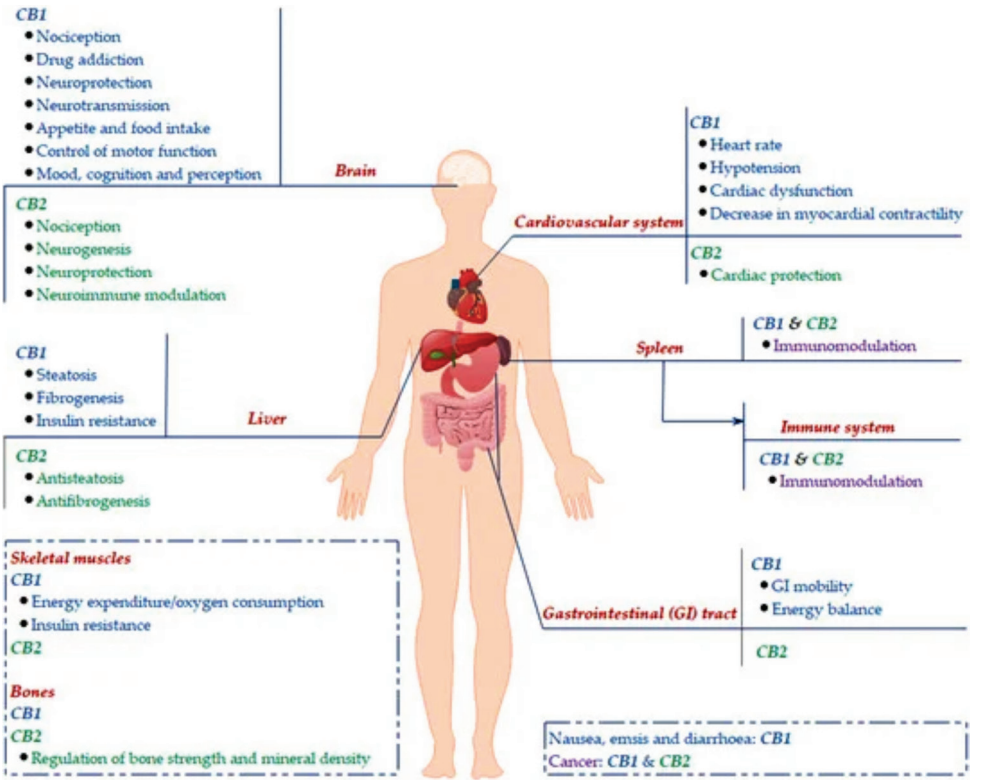

Image 4. Distribution of CB1 and CB2 and their associated functions (courtesy of Dongchen et al., Int. J. Mol. Sci. 2020, 21(14), 5064)

Other Receptors of the Endocannabinoid System

Other receptor classes besides CB1 and CB2 are also now being studied as part of the Endocannabinoid System, such as:[7]

- the class of receptor-channels determining transient changes in potential (TRPs);

- the 'orphan' G protein-coupled receptor (GPR55, GPR18, GPR3, GPR6, etc.);
- the nuclear per1oxisome proliferator-activated receptors (PPARs);
- many others (adenosine, nicotine and glycine receptors, ion channels, etc.).

Distribution of Cannabinoid Receptors

First identified in humans in 1988 through the work of Allyn Howlett and William Devane, classical cannabinoid receptors have been found to be far more abundant in the brain than virtually any other type of receptor.[8] The distribution of cannabinoid receptors is extensive and diverse, spanning the brain and various other body regions, contributing to the broad therapeutic spectrum of cannabinoids.

The CB1 receptor are expressed in the:[6];[9]

- central nervous system (brain);
- peripheral nervous system;
- heart;
- lungs;
- liver;
- gastrointestinal system;
- oral cavity;
- testicles and ovaries;
- bones;
- thymus;
- uterus;
- immune system.

CB2 receptors are mainly expressed in:[6];[9]

- with high density on cells of the immune system, including macrophages, mast cells and spleen;

- the gastrointestinal tract;
- skin;
- bones;
- the central nervous system, present in low density in the spinal cord.

What are the Functions of the Cannabinoid Receptors?

Animal models have enabled the testing of cannabinoid compounds for their efficacy in modifying disease progression or alleviating experimentally induced symptoms.

An illustrative case involves the animal models of osteoporosis, where normal mice and 'knockout' mice were compared. When a synthetic cannabinoid was administered to both groups of mice with osteoporosis, bone damage was mitigated in the normal mice but not in those lacking cannabinoid receptors—highlighting the pivotal role of cannabinoid receptors in regulating bone density.[10]

In fact, a group of researchers later found that activation of CB2 receptors inhibits the formation of bone-absorbing cells (known as *osteoclasts*), down-regulating, the precursors of osteoclasts and tipping the balance in favor of *osteoblasts*, the cells that facilitate bone formation.[11] Further experiments established that cannabinoid receptor-induced signaling modulates:

- pain;
- inflammation;
- appetite;
- glucose metabolism;
- gastrointestinal motility;
- sleep-cycles;
- immune cells;
- the release of hormones and other mood-altering neurotransmitters such as serotonin, dopamine and glutamate.

How does a Classic Cannabinoid Receptor work?

Retrograde signaling functions as an inhibitory feedback system, directing cells to 'cool down' when they are becoming too active.[12]
When stimulated, cannabinoid receptors trigger a cascade of biochemical changes at the cellular level, effectively acting as brakes on excessive physiological activity. This process reduces immune response and inflammation, relaxes muscles, decreases blood pressure, widen bronchial pathways and normalizes overstimulated nerves (as in neuropathic pain or epilepsy).
The endocannabinoids are the only neurotransmitters that take part in 'retrograde' signaling, a form of 'reverse' intracellular communication. In this process, stimulation starts from the postsynaptic neuron, reaching the presynaptic neuron and decreasing its transmission, whether it be excitatory (glutamatergic terminals) or inhibitory (GABAergic terminals).[12]

The Discovery of the Endocannabinoid System

Much like opium studies culminated in the identification of endorphins, (the natural morphine-like substances of our brains), research on cannabis would lead to the discovery of natural substances produced by our bodies, similar to THC: our 'internal cannabis,' to be precise. In 1992, a collaboration between researchers William Devane, Lumir Hanus, Roger Pertwee and Raphael Mechoulam revealed a new neurotransmitter, named 'endogenous cannabinoid' or shortly 'endocannabinoid.' This molecule binds to the same receptors in the brain that are sensitive to THC. The researchers named this substance 'Anandamide,' (abbreviated as AEA), deriving the term from *Ananda*, the Sanskrit word for 'bliss.'[4]
In 1995, Mechoulam's research team discovered, in parallel with a group of Japanese researchers, a second important endocannabinoid, 2-arachidonoylglycerol, abbreviated as '2-AG.' This endocannabinoid binds not only to

the CB1 receptors predominantly present in the brain, but also to a second type of cannabinoid receptors, called CB2.[13];[14]

The Endocannabinoids: Anandamide and 2-Arachidonoylglycerol

What are Endocannabinoids?

Endocannabinoids are molecules produced by our bodies, which activate receptors that are distributed throughout the body. The two best-studied endocannabinoids are Anandamide (AEA) and 2-Arachidonoylglycerol (2-AG).[15] These molecules are synthesized on demand from arachidonic acid derivatives in the cell membrane, they have a localized effect and a limited bioavailability. Endocannabinoids are rapidly degraded by specific enzymes called fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).[15] Chemically, endocannabinoids are eicosanoids—fatty acids with 20 carbon atoms. The concept of the "entourage effect," first proposed by Mechoulam and Ben-Shabat in the late 1990s during their research on 2-AG, describes how inactive or weakly active lipid molecules can synergize with endocannabinoids to enhance their biological activity, suggesting that these compounds work better together than in isolation.[36]

What Functions do Endocannabinoids perform?

Secreted 'on demand' from fatty acids in areas of need, AEA and 2-AG exert their effects in predominantly local and specific ways. According to Mechoulam: "Their actions are ubiquitous. They are involved in most of the physiological systems examined."[1]

Endocannabinoids are key players in the multidimensional biochemical equilibrium of life, known as homeostasis.

Robert Melamede, microbiologist and international Medicinal Cannabis activist, describes the Endocannabinoid System as the *'master mediator'* constantly multitasking, adjusting and readjusting the complex network of molecular thermostats that control our physiological rhythm.[31]

Furthermore, endocannabinoids facilitate communication and coordination between different cell types due to their neuromodulatory activity. For instance, in the event of an injury, cannabinoids are present in the wounded area, where they:

- reduce the release of activators and sensitizers from the injured tissue;
- stabilize firing at excessively high frequencies;
- soothe nearby immune cells to prevent the release of pro- inflammatory mediators.

These are three different mechanisms of action, on three different types of cells to serve one purpose: minimize pain and damages.[16]

Metabolizing Enzymes

The regulation of the Endocannabinoid System (ECS) involves a complex interplay of various metabolizing enzymes, each playing a distinct role in modulating the levels and actions of endocannabinoids.

Biosynthetic Enzymes

The biosynthesis of endocannabinoids is a meticulous process orchestrated by enzymes that contribute to their formation. One of the key endocannabinoids, anandamide, is produced through a series of enzymatic reactions. The enzyme N-acyltransferase (NAT) facilitates the conjugation of arachidonic acid with phosphatidylethanolamine, giving rise to N-arachidonoyl phosphatidylethanolamine (NAPE).[17] Subsequently, NAPE is cleaved by the enzyme NAPE-specific phospholipase D (NAPE-PLD), resulting in the release of anandamide. Another prominent endocannabinoid, 2-arachidonoylglycerol (2-AG), is formed through the hydrolysis of diacylglycerol (DAG), a process catalyzed by diacylglycerol lipase (DAGL).[17]

Degradative Enzymes

In the dynamic regulation of the ECS, degradative enzymes such as Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MAGL) emerge as key players. FAAH is responsible for the degradation of anandamide, breaking it down into arachidonic acid and ethanolamine, thereby ending its signaling activity.[18]

MAGL, on the other hand, is central to the breakdown of 2-AG, cleaving it into arachidonic acid and glycerol.[18]

These enzymatic actions fine-tune the duration and intensity of endocannabinoid signaling, contributing to the maintenance of physiological balance.

Adding to this intricate regulatory network, enzymes like α/β-hydrolase domain-containing 6 (ABHD6) and α/β-hydrolase domain-containing 12 (ABHD12) are involved in the metabolism of 2-AG.[19] ABHD6 hydrolyzes 2-AG, producing arachidonic acid and glycerol, while ABHD12 contributes to its conversion into arachidonic acid and 2-arachidonoyl glycerol ester (2-AGE). These enzymes further diversify the regulatory mechanisms governing 2-AG levels in different cellular contexts.

The orchestrated actions of these metabolizing enzymes impact the overall tone of the ECS. Understanding the roles of these enzymes in endocannabinoid metabolism opens avenues for targeted therapeutic interventions aimed at restoring ECS balance in conditions where dysregulation is implicated. The intricate actions of these enzymes highlight the remarkable complexity and adaptability of the ECS in maintaining homeostasis throughout the body.

Recognition of the Endocannabinoid System by the International Scientific Community

Endocannabinoids and their receptors emerged as a ‘hot topic’ among scientists who shared their findings in highly-specialized journals and during symposia by the International Cannabinoid Research Society (ICRS).

Starting in 1990, specialized scientists studying the Endocannabinoid System began holding annual meetings. In 1992, these meetings were formalized into a scientific research society known as the International Cannabinoid Research Society (ICRS). Founded in the United States by approximately 50 delegates—now grown to over 500 members from around the world—the society initially received support through research funding from the U.S. government.

Interactions within the ICRS began to attract the attention of pharmaceutical companies, which were paying attention to the latest discoveries in cannabinoid science, while few people outside the scientific community were yet aware of them.

Advances in this rapidly growing scientific field would have paved the way for innovative treatment strategies for various diseases, including (but not limited to) cancer, diabetes, pain, arthritis, irritable bowel disease (IBD), Alzheimer's, Multiple Sclerosis, depression and many others.[8]

The Function of the Endocannabinoid System

Which came first, the Cannabis Plant or the Endocannabinoid System?

By tracing the molecular pathways of THC, scientists have discovered a distinctive and previously undiscovered molecular signaling system that is involved in the regulation of a wide range of biological functions. This system is known as the 'Endocannabinoid System' (ECS), named from the plant that led to its identification.

The name might suggest that the plant came first but, as specified by Dr. John McPartland, a medical doctor, phytochemist and cannabis researcher since the early 1980s: "By comparing the genetics of cannabinoid receptors in different species, we estimate that the Endocannabinoid System evolved in primitive animals over 500 million years ago. This ancient internal signaling existed long before cannabis appeared on Earth, when the most complex forms of life were sponges,"[20] Dr. John McPartland.

Why does the Endocannabinoid System exist?

Image 5. Prof. Mauro Maccarrone with the Mechoulam Award 2016, an award given annually by ICRS.

The Endocannabinoid System is present in fish, reptiles, worms, leeches, amphibians, birds and mammals—in all animals except insects.

Considering its long evolutionary history, scientists have deduced that the Endocannabinoid System must fulfill fundamental roles crucial to animal physiology. From sea urochordates to small nematodes, all vertebrate and many invertebrate species share the Endocannabinoid System as an essential component of life, facilitating adaptation to environmental changes.[20]

The discovery of the Endocannabinoid System has extraordinary implications for nearly every area of medical science, including reproductive biology.

Dr. Mauro Maccarrone, professor in biochemistry and one of the leading experts in the field, describes the Endocannabinoid System as the 'guardian angel' of reproduction.[21]

Endocannabinoid signaling plays a crucial role in the entire reproductive process in mammals, encompassing spermatogenesis, fertilization, transport into the oviduct of the zygote, nesting of the embryo in the uterus, fetal development, and even the development of the child after birth.

The receptors of this system proliferate in the placenta and facilitate the 'cross-talk' between the embryo and the mother.[21];[22] This is why the Endocannabinoid System exists in so many different species and has survived millennia of evolution: any disruption in the system could result in serious problems, including ectopic pregnancies and miscarriages.

Israeli neuroscientist Ester Fride demonstrated that 'knockout' mice (mice which have been genetically engineered to lack the components of the ECS), exhibited similarities to children with stunted growth. In the absence of cannabinoid receptors, these mice experienced loss of vitality and premature death. It is now well understood that endocannabinoid levels in breast milk are critically important for the initiation of feeding in infants, and that the interaction between endocannabinoids in mother's milk and receptors on the infant's tongue keeps appetite and food assimilation balanced, ensuring survival of the infant.[23]

Endocannabinoids are the substances our bodies naturally create to stimulate the receptors of the Endocannabinoid System and life itself would not be possible without cannabinoid receptors.[24]

Functions of the Endocannabinoid System

In each tissue, the Endocannabinoid System (ECS) performs different tasks, but the goal is always the same: maintaining homeostasis. This biological balance refers to the maintenance of a stable internal environment, despite fluctuations in the external environment.

Cannabinoids promote homeostasis at all levels of biological life, spanning from sub-cellular processes to the coordination of organs and organism, potentially influencing the interactions between organisms.

One example is autophagy—a process in which a cell isolates a portion of its contents for self-digestion and recycling—mediated by the ECS. This process keeps normal cells alive, orchestrating a balance between the synthesis, breakdown, and subsequent recycling of cellular products. Conversely, this process exerts a deadly effect on malignant cancer cells, inducing programmed cell death (apoptosis).[25];[26] The death of cancer cells through this mechanism promotes homeostasis and survival throughout the body. Professor Vincenzo Di Marzo, one of the world's most influential pharmacologists, has been conducting research on the Endocannabinoid

System since the late 1980s, publishing hundreds of pioneering discoveries; he, together with colleagues Tiziana Bisogno and Luciano DePetrocellis, summarised the functions of the Endocannabinoid System as: "a central regulator capable of modulating and balancing the body's main activities such as eating, sleeping, relaxing, protecting and forgetting."[27]

How the Endocannabinoid System protects the Nervous System

Before the discovery of the Endocannabinoid System, the prevailing understanding in neurobiology held that '*retrograde*' signaling, a form of communication in which signals travel from the postsynaptic neuron to the presynaptic one, was exclusive to the embryonic brain's developmental stages. However, the revelation and exploration of the Endocannabinoid System challenged this notion, revealing that this unique signaling mode is also employed in the adult brain.

We now know that endocannabinoids choreograph a wide variety of processes involved in embryonic brain development, as defined by MacPartland, including the proliferation of stem cells and their differentiation, a process driven by extracellular signals transmitted to cannabinoid receptors.[28]

From the late 1990s, scientists have learned that cannabinoid signalling plays a crucial role in regulating neurogenesis in adults (i.e. the growth of brain cells) and stem cell migration.[29] In addition, it has been established that high levels of endocannabinoids are released in the brain after strokes and other neurological traumas, underscoring the neuroprotective properties of the ECS, which are described by Professor Mechoulam as: *A general protective network, working in conjunction with the immune system and various other physiological systems*.[30]

Clinical Endocannabinoid Deficiency

Endocannabinoid deficiency may result either from a reduction in the number of cannabinoid receptors or from decreased concentrations of Anandamide and/or 2-AG. Individuals exhibit different congenital endocannabinoid levels and sensitivities.[31]

Whether the consequence of poor diet, lack of exercise, toxins from the environment or genetic factors, endocannabinoid deficits are associated with a reduced ability or complete inability to adapt to chronic stress. Prolonged exposure to stress depletes the tone of endocannabinoid signaling and this, in turn, generates unfavorable effects for a plethora of physiological processes.[32]

For example, the immune system is activated during a fever to combat a virus or bacterial invasion. When the job is done, endocannabinoid signaling decreases fever and restores homeostasis. Cannabinoids exhibit anti-inflammatory and effectively 'cooling the body.'

If the feedback (i.e. signaling) circuit becomes dysregulated, or if the immune system overreacts to chronic stress or mistakenly identifies the body's own tissues as foreign, it creates a conducive environment for the development of autoimmune or inflammatory diseases.

Neurologist and researcher Dr. Ethan Russo first hypothesized that '*clinical endocannabinoid deficiency*' underlies migraine, fibromyalgia, chronic inflammation of the gut and a group of other conditions, which respond favorably to cannabinoid-based therapies.[31];[33]

Clinical observations suggest that the ECS is considered to be "understimulated" in pathologies where these symptoms are present, such as pain, sleep disorders, mood disorders, and GI disorders.

Conversely, the ECS has been found to be "over-stimulated" in conditions such as obesity, steatosis, and insulin resistance.

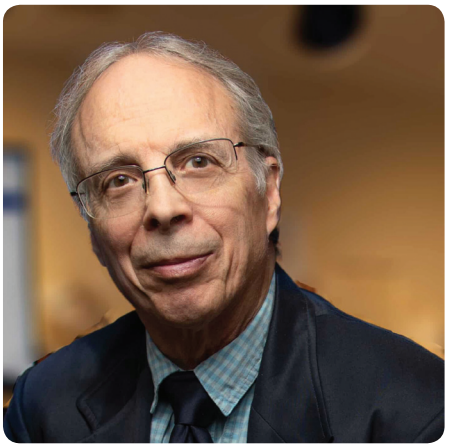

Image 6. Ethan Russo, neurologist, medical researcher and editor.

Exploring DNA's point mutations and other genetic differences within the ECS may be relevant to the clinic beyond the application of cannabinoid-based therapies. Endocannabinoid enzyme deficiencies in fact have been associated with significant impacts on pregnancies. For instance, a deficiency in FAAH, with a consequent increase in Anandamide levels, has been linked to miscarriages, suggesting the potential use of this marker for diagnostic purposes.[34] Moreover, an endocannabinoid deficiency has been implicated in conditions such as infant colic.[35]

Conclusions

The Endocannabinoid System functions as an intricate network of circuits that coordinates many other systems in our body. In this chapter, we have summarized the main knowledge about its role as a regulator of many physiological processes. We have also explored how a decrease in cannabinoid receptors, endocannabinoids or the enzymes responsible for their biosynthesis and degradation, can lead to the development of various pathological conditions that can be treated by restoring the normal cannabinoid tone.

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1.2. The Role of the Endocannabinoid System in Pain Management

Cannabis and Cannabinoids

In recent years, several studies have shown that cannabis derivatives may have a role in treating symptoms related to nervous system disorders.
Cannabis Sativa L. is among the oldest botanical species known to mankind and has a very long history of use for recreational, therapeutic and religious purposes.
More than 500 compounds have been isolated and identified from cannabis, but its medicinal-therapeutic and psychotropic properties have been attributed mainly to delta-9-tetrahydrocannabinol (THC), a psychoactive compound that, along with other lipid compounds such as cannabidiol (CBD) and cannabinol (CBN), are concentrated in the plant's resin.
Due to the numerous properties of this plant, considered to be a genuine medical herb, extensive research has been conducted in order to identify the molecular basis of its pharmacological effects. These investigations, supported by molecular biology and crystallography techniques, have led to the identification and cloning of two receptors (membrane proteins with which THC interacts) that bind to natural cannabinoids and are thus presumably responsible for their effect.
The human body possesses specific binding sites for cannabinoids, distributed on the surface of many cell types. The presence of these receptors in the body has therefore legitimized the hypothesis that the body itself is capable of producing ligands, i.e. substances that physiologically interact with these receptors. Confirmation came from the subsequent isolation of endogenous ligands (substances generated by our bodies) for cannabinoid receptors, called endocannabinoids, as introduced in the previous chapter.

The Endocannabinoid System

The Endocannabinoid System is a complex endogenous communication system among cells. It is composed of cannabinoid receptors (called CB1 and CB2), their endogenous ligands (the endocannabinoids), proteins involved in the metabolism (synthesis and degradation) and transport of endocannabinoids and other enzymatic and receptor systems (TRPs, GPRs, PPARs, etc.).[1]

Based on the location of cannabinoid receptors in the body, it has been hypothesised that the Endocannabinoid System is involved in a large number of physiological processes, including:

- motor control;
- memory and learning;
- pain perception;
- regulation of energy balance;
- food intake;
- sleep/wake rhythms.

CB1 receptors are predominantly expressed in the Central Nervous System (CNS), in particular in the:[2];[3]

- limbic system (involved in memory processes and the control of emotional states such as anger, desire and fear);
- basal ganglia (centres responsible for the control of involuntary motility, comprising the brain structures of the substantia nigra, globo pallidum, caudate nucleus and putamen);
- cerebellum (part of the nervous system that controls balance and coordination of voluntary movements);
- laminae of the dorsal horns of the spinal cord (reception of stimuli);
- ventrolateral portion of the periaqueductal grey area (VL_PAG), the area responsible for pain modulation.

CB2 receptors, on the other hand, are located in the periphery. In particular[4] the B and NK cells of the immune system.

These receptors contribute to the immunosuppressive and anti-inflammatory effects of cannabinoids as they modulate cytokine release. Furthermore, CB2 receptors are expressed by resident immune cells in the Central Nervous System called microglia and, when stimulated, reduce the proinflammatory phenotype of these cells, resulting in a reduction of chronic pain.[5]

CB2 is also present in the skin. Scientists have described how CB2 activation leads to the release of endorphins by keratinocytes (skin cells), which act via the μ-receptor opioid pathway, contributing to the analgesic effect.[6]

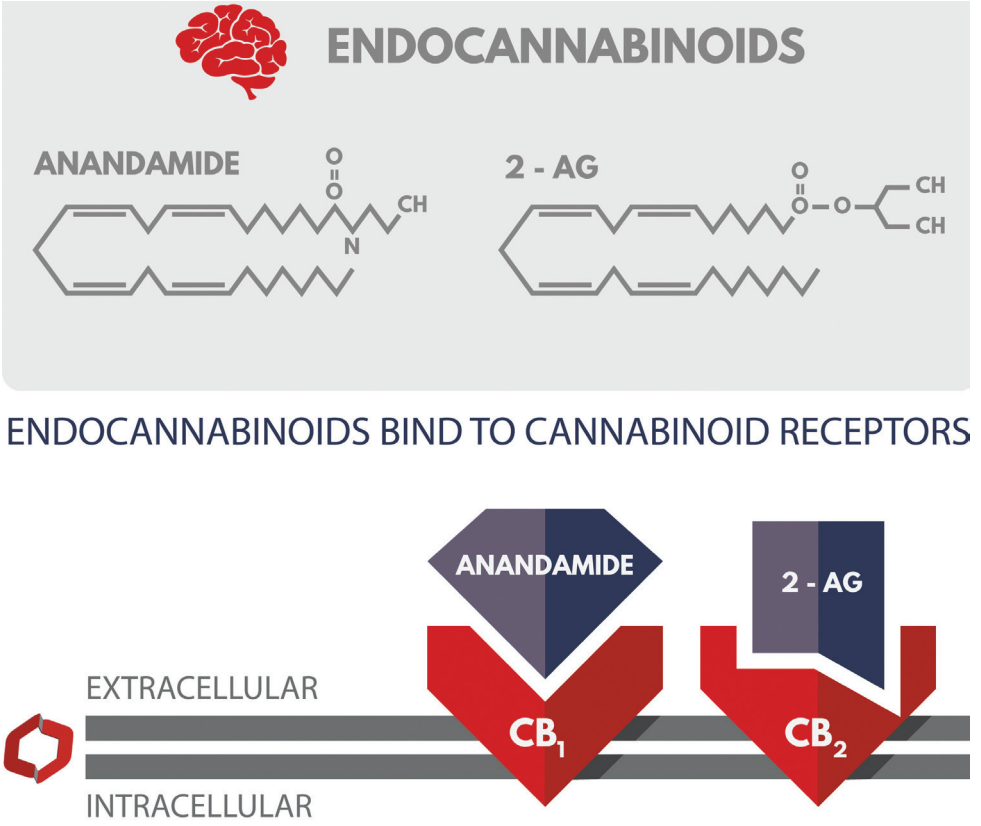

Image 7. Schematic representation of the cell membrane with cannabinoid receptors and the 2 main endocannabinoids (courtesy of Renate Mich, www.officinavisioni.com).

Endocannabinoids

Endocannabinoids are synthesized from phospholipid precursors presumably contained in the cell membrane. They are released outside the cell only when the cell is stimulated, so unlike other neurotransmitters, they are not released from synaptic vesicles.[7]

In 1992, Raphael Mechoulam and his team identified arachidonylethanolamide, which was named anandamide (AEA), and defined this molecule as the first endogenous compound that binds the CB1 receptor with high affinity.[8] In 1995, the second endocannabinoid was identified, 2-arachidonoylglycerol (2-AG), which is more abundant than anandamide in the brain.[9] Both the synthesis and degradation of endocannabinoids occurs by means of certain enzymes.

Endocannabinoids are produced to protect the body from damage caused by various pathological situations by exerting anti-oxidative, immunosuppressive, anti-inflammatory and, in particular, analgesic actions by binding to the CB1 and CB2 receptors;[10] they have been shown to reduce symptoms of persistent pain, allodynia and hyperalgesia.[11]

Pain as a Neurological/Neuropsychiatric Condition

Pain perception is a critical mechanism of the body's self-defense, enabling us to disengage from a potentially damaging stimulus.

When we experience pain chronically, often as a consequence of a nerve or metabolic dysfunction, as in the case of *neuropathic* pain, it is of paramount importance to discover agents capable of targeting the pathways that generate pain.

It is estimated that between 6.9% and 10% of the population experiences a form of neuropathic pain, often as a consequence of other diseases, such as cancer, diabetes, etc.[12]

While the causes of pain may vary, the common consequence can be hyperalgesia (the hyperexcitation of the nervous system) and/or the development of allodynia, where pain is experienced in response to non-noxious stimuli.

- These pain symptoms are referred to in medicine as 'dysesthesias' (think of a real 'tactile hallucination,' resulting from lesions on the spinal cord); or
- 'paresthesias' (characterized by local tingling and hypersensitivity).

These symptoms significantly compromise the quality of life of patients suffering from chronic pain, particularly neuropathic pain.
Hyperalgesia is nothing more than an amplified perception of a painful stimulus. In many cases it is possible to describe:

- a primary hyperalgesia: an enhanced perception of pain stimuli at the specific site of tissue injury;
- a secondary hyperalgesia: an enhanced perception of pain stimuli in the surrounding areas beyond the injury site.

Allodynia is instead characterized by experiencing pain in response to typically non-painful stimuli.
It is a highly limiting symptom, described by patients as an electric shock or as a sudden onset of a needle-like sensation penetrating the body.
In addition to the aforementioned pain symptoms, there are a number of neuropsychiatric changes that are medically termed 'comorbidities,' such as:

- anxiety;
- depression;
- cognitive dysfunction;
- memory loss.

These conditions make neuropathic pain a true neurological/neuropsychiatric disorder for which there is, to date, no satisfactory pharmacological treatment.

Neuropathic Pain

Neuropathic pain is caused by often irreversible damage, affecting the pain perception system. It manifests following an injury to either the central nervous system (brain and spinal cord) or the peripheral nervous system (nerve roots, plexuses, and neurons).
This mechanism also involves the rearrangement of the communication between neurons, known as neuronal plasticity. This leads to a distorted perception wherein innocuous stimuli are interpreted as painful.
The processes that support neuropathic pain can be grouped into two broad categories:

1. *The Ectopic Genesis of Nociceptive Impulses*

The term ectopic comes from the Greek έκ τοπος and literally means 'out of place.' It refers to the occurrence of action potentials that are generated directly in nerve fibers without the activation of the corresponding nerve ending. This phenomenon is also observed in conditions such as epilepsy. In simpler terms, these are irregular electrical impulses generated by axons or ganglia.

2. *The Hypersensitivity of Central Nociceptive Neurons*

At the level of the posterior horn, thalamus and sensory cortex, two types of nociceptive neurons (i.e., brain cells responsible for the perception of pain, from the Latin word 'nocere') have been identified, which exhibit different and well-identified behaviors:[13] The first neuron, the specific nociceptive neuron, is peripherally connected only with painful fibers and responds only to high intensity stimuli (painful stimuli). The second neuron, the broad dynamic spectrum neuron, responds to low intensity stimuli with low discharge frequencies and to high intensity stimuli (painful stimuli) with high discharge frequencies.

Following peripheral damage, whether nerve-related or not, some neurons may undergo functional changes, causing them to fire at high frequencies associated with pain, even in response to typically harmless or only mildly painful stimuli.

The Rationale Behind Cannabinoid-based Therapies

Historically, there was a prevailing belief that the analgesic effectiveness of cannabinoids did not measure up to that produced by opioids. However, contemporary research suggests a shifting perspective, indicating that "Cannabis for medical use may be similarly effective and result in fewer discontinuations than opioids for chronic non-cancer pain."[14] This insight emerged from a recent systematic review and network meta-analysis, signifying a re-evaluation of the therapeutic potential of cannabis in comparison to traditional opioid-based treatments for persistent non-cancer pain.[14] The evolving landscape of scientific inquiry is contributing to an understanding of the efficacy and tolerability of cannabinoids, prompting a reconsideration of their role in managing chronic pain conditions.

Indeed, chronic pain, particularly neuropathic pain, has emerged as a primary focus for the therapeutic application of cannabinoid-based medicines.

There are various forms of pain, including neuropathic pain of a different nature or even pathologies that are still not well defined from an etiopathological point of view such as fibromyalgia, in which the use of drugs such as opioids or NSAID (non-steroidal anti-inflammatory drugs) has little efficacy.

In the case of conditions characterized by neuropathic pain, cannabinoids have proven to possess a good therapeutic efficacy.

This might be attributed to the fact that the spontaneous neuronal firing leading to the pain sensation have been localized mainly in type A afferent myelin fibers, which are rich in cannabinoid receptors, but lack opioid receptors.[15]

It is also conceivable that cannabinoid therapy generates a kind of detachment, distancing the patient from the expectation of pain. Going back to the definition we have given of allodynia as a sudden electrical neuronal firing, we understand that the anticipation of this moment and its expectation is decisive in the onset of those comorbidities, such as anxiety and depression, that turn these types of pain into debilitating diseases.
The drugs currently employed to treat pain primarily consist of opioids and FANS, yet only about 50 per cent of patients experience relief with such treatments. This underscores the potential enormous benefits the clinical field could reap from medications designed to modulate cannabinoid tone.[16]
Furthermore, at the supraspinal level, there appears to be a synergistic interaction between opioid and cannabinoid receptors, suggesting that cannabinoid administration may enhance the analgesic effects of morphine.
Finally, the use of cannabinoids reduces the need for morphine and opioids. THC is able to reduce the minimum effective dose (ED50) of morphine by 55%, methadone by 75% and codeine by 96%.[17]

Endocannabinoids and Pain Relief

Numerous scientific studies provide evidence that the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) induce analgesia. The analgesic effect of cannabinoids is primarily mediated through the activation of CB1 and CB2 receptors.
Other neurotransmission systems may be involved in the analgesic effects of cannabinoids, such as norepinephrine, serotonin, peptide systems (orexin, endorphins) and the purinergic system (adenosine).
Nonetheless, the mediators mostly modulated by cannabinoids are:

- glutamate, the quintessence excitatory amino acid of the central nervous system (CNS);
- gamma amino butyric acid (GABA), the most important inhibitory transmitter of the CNS.

Following an injury, the level of endocannabinoids increases; this occurs both locally, at the site of inflammation, and systematically at other targets along the pain pathway.

This reaction that represents the body's first anti-pain response involves the synthesis of more endocannabinoids for a dual purpose:

1. Inhibit the transmission of pain signals at nerve terminals;
2. Engage anti-inflammatory mediators to reduce damage at the wound site.

The Endocannabinoid System and Pain: Conclusions

In conclusion, the Endocannabinoid System represents an extremely important pharmacological tool for the treatment of chronic degenerative diseases, including neuropathic pain, and other forms of pain with very strong affective and emotional components, such as fibromyalgia or endometriosis. As research progresses, unlocking the full potential of cannabinoid-based medicine holds promise for changing the treatment landscape, offering new hope and avenues for individuals dealing with diverse forms of chronic pain and associated comorbidities.

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1.3. The Endocannabinoid System in Sexual Function and Childbirth

Endocannabinoids are lipid messenger molecules that play a key role in promoting and maintaining homeostasis in the body. Their role is so pivotal that they influence every stage of human development, from conception and embryo implantation to birth and the early days of life.

The Link between Endocannabinoids and Sexual Activity

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the primary endocannabinoids, convey their signals by binding to cannabinoid receptors, predominantly CB1 and CB2. and are subsequently degraded by enzymes such as FAAH and MAGL or recycled by the cell.

Recently, studies have been conducted on mice to understand the role of endocannabinoids in male sexual behavior. These studies have shown that administration of the endocannabinoid AEA stimulates sexual activity in males with copulation difficulties,[1] even reducing ejaculation thresholds in sexually apathetic subjects.[2]

These effects of AEA are mediated by the CB1 receptor and have also been observed in healthy mice. In addition, the action of this endocannabinoid varies significantly with dosage, sometimes causing opposite effects.[3]

Cannabis also influences sexual functioning and satisfaction. The results of a recent survey indicated that men, women and LGBTQIA+ perceived that cannabis use increased their sexual functioning and satisfaction, particularly increased desire and orgasm intensity.[4] Moreover, in men with sexual dysfunction, mild cannabis consumption may be associated with a more favorable anthropometric and lipid profile and with a better penile arterial vascular response to intracavernous prostaglandin injection.[5]

Taken together, recent findings seem to indicate the possible use of cannabis for treating sexual dysfunctions, both in women, men and in LGBTQIA+ individuals.

How the Endocannabinoid System Regulates Fertility in Men

Both CB1 and CB2 receptors are receptors of the *Endocannabinoid System* (ECS) present in spermatozoa.
The level of Anandamide is crucial for controlling the percentage of live and motile sperm, for modulating energy consumption and for controlling the number of testosterone-producing Leydig cells.
These functions are controlled by the CB1 receptor, while CB2 receptor activation is responsible for initiating sperm production and regulating their movement.[4]

How the Endocannabinoid System Regulates the Female Reproductive System

Virtually every event inherent to the female reproductive system is affected by one or more elements of the ECS, which is localized in the cells and tissues of the female reproductive organs.[5]
Both AEA and 2-AG have been identified in the uterus and an appropriate regulation of their levels is essential for successful embryonic passage through the oviduct and implantation in the uterus. This process involves the enzymatic degradation of the two endocannabinoids (AEA and 2-AG) by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) at crucial moments during embryonic development and implantation.[6]
According to research findings, the pivotal role of these enzymes could potentially provide a new diagnostic tool. Specifically, women who suffered miscarriages exhibited low levels of the FAAH enzyme when compared to those who successfully completed pregnancy.[7]
Furthermore, pregnancy also seems to modify cannabis-derived compounds metabolism and pharmacokinetics. Indeed, cytochrome isoforms such as the CYP2C9 and CYP3A4 are known to be induced in pregnant individuals and in vitro by pregnancy hormones.[8] This induction of CYP2C9

and CYP3A4 is predicted to lead to altered THC and 11-OH-THC disposition and potential change in pharmacodynamic effect.[8]

How the Endocannabinoid System Regulates Fetal Development

CB1 receptors also play a crucial role in the formation of the fetal brain. These receptors are in fact responsible for the differentiation of neuronal progenitor cells into neurons or glial cells. Additionally, CB1 receptors act as 'guides' for the connections between neuronal cell extensions (axons), indicating the right path to follow and where to make connections with other cells.[6]

How Cannabinoid Receptors Control Childbirth

Recent data suggest that the Endocannabinoid System plays a crucial role in a variety of birth-related events, and alterations in the CB1 signaling pathway have been associated with premature birth. Indeed, a study by Wang's group demonstrated that a defect in the CB1 receptor signalling pathway can alter normal progesterone and estrogen levels, with consequent effects on the duration of pregnancy.[9]
CB1 receptors are also involved in the process of labor, as they appear to alter and coordinate the endocrine axis of corticotropin-releasing hormone, a substance that is released at high levels near childbirth, as a *trigger* signal to end the pregnancy.[9]

The ECS in the Regulation of Breastfeeding and Infant Appetite

Once outside the protective environment of the womb, endocannabinoids still continue to be very important for the survival of the newborn. Indeed, research has discovered that endocannabinoids, oxylipins and other similar compounds are present in breast milk.[10] Notably, 2-AG, the most abun-

dant endocannabinoid in human milk, is crucial in stimulating appetite in newborns and facilitating lactation.

Moreover, studies on mice have revealed the crucial role of 2-AG for the correct innervation of the tongue muscles in pups and the concurrent stimulation of appetite through its binding to CB1 receptors.[11] When researchers 'blocked' the CB1 receptors with an antagonist, the pups' growth resulted inhibited, leading to their demise within a week. Interestingly, the co-administration of THC to pups, reactivating the CB1 cannabinoid receptors, nearly completely reversed the effects caused by the antagonist drug, restoring the pups to a normal growth trajectory.

Conclusions

Endocannabinoids play a key role in all phases of the reproductive cycle and seem to favour sexual activity. A deficiency in the Endocannabinoid System can result in deleterious effects on fertility and the survival of the newborn. Further studies are needed to clarify whether and how phytocannabinoids may offer potential benefits for couples trying to conceive.

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1.4. The Endocannabinoid System and the Sleep-Wake Cycle: Implications for Insomnia

The Importance of Sleep

Sleep is one of the fundamental activities of every living being. There is no animal that does not sleep. Sleep patterns vary widely across the animal kingdom, from the sleep record of koalas, animals that can sleep up to 22 hours per day, to the opposite record of *Drosophila melanogaster*—the fruit fly, which shares about 80% of its genome with humans and seems to sleep only a few minutes a day. Strange but true, even jellyfish sleep, despite not having a real brain but only a diffuse nervous system. Even bacteria regulate their activity in light-dependent cycles, although the concept of sleep is not applicable to them and to other organisms as plants.
Why do we sleep? What is the role of sleep in human and animal life? Scientists have not yet provided an unequivocal answer to this question, offering only more or less valid hypotheses.

Some theories suggest that sleep functions to 'prune' nerve connections, eliminating unnecessary ones, while others propose that it enhances memory by re-processing waking experiences. Another perspective suggests that sleep acts to cleanse the brain environment of potentially toxic substances, and some believe it serves as a means to restore energy. Finally, there are arguments asserting that sleep's essential purpose is to provide rest for the body. It is likely that sleep fulfills a combination of these purposes, and there may be more functions yet to be discovered.
What is definitive is that the alternation of sleep and wakefulness is governed by the circadian rhythm.

The Circadian Rhythm

The circadian rhythm, found in both prokaryotes and eukaryotes, is the periodic variation of the body's activities over a 24-hour period. The term is derived from the Latin *circa diem*, which stands for about a day. The circadian rhythm functions as an internal clock that cyclically regulates activities essential to the organism on a daily basis,, including:

- hormone secretion;
- cell regeneration;
- body temperature;
- blood pressure;
- sleep-wake cycle.

The main anatomical centers of circadian rhythms, known as internal oscillators or *pacemakers*, are located in the liver and a specific region of the brain called the suprachiasmatic nucleus of the hypothalamus.
The circadian rhythm is influenced by both endogenous and exogenous stimuli, which can be considered metronomes that 'keep the time' within the organism:

- Endogenous stimuli comprise various proteins, including the one encoded by the *PER* gene: this protein is exclusively produced during the night, entering the cell nucleus to inhibit its own production. Consequently during the day, the synthesis is halted; in this way, the cells 'understand' that they are switching from light to dark and vice versa.
- Exogenous stimuli that regulate rhythms and reset the biological clock on a daily basis are referred to as *Zeitgebers* (from the German: 'time-givers'). These stimuli primarily include, but are not limited to:
  - light-dark alternation;
  - temperature of the environment;
  - social needs (e.g. consistent meal times with the family).

In the absence of *Zeitgebers*, especially the influential factor of light, circadian rhythms persist but their duration varies. For instance, individuals who have spontaneously decided to live in dark caves exhibit a 36-hour sleep-wake cycle.

The Sleep-Wake Cycle

The sleep-wake cycle is the pattern of alternating between sleep and wakefulness, consisting of at least three stages:

1. Waking: this stage is characterized by different levels of attention and activity, depending on the tasks the subject is performing. The general electrophysiological activity of the brain in this phase is mainly characterized by β waves (13.5-20 Hz), which become α waves (8-13 Hz) when the eyes are closed. In this phase, the individual is aware of their thoughts, emotions, sensations, and surroundings.. The waking phase is modulated by neurons located mainly in the lateral and posterior hypothalamus, which synthesize various neurotransmitters, such as orexins/hypocretins and histamine, and by brainstem neurons that synthesize

noradrenaline (locus coeruleus), serotonin (dorsal raphe nucleus) and acetylcholine (pontine tegmental nucleus of the pedicle).

2. Non-REM phase: this stage, occupying approximately 75 percent of total sleep, lacks rapid-eye-movements (REM). Also referred to as slow-wave sleep, the primary function of this phase is the consolidation of declarative memory, involving conscious recollection. Non-REM sleep is facilitated by the anterior hypothalamus, where GABA serves as an important inhibitory neurotransmitter, while adenosine and the prostaglandin PGD2 participate in its regulation. This stage comprises four phases:
   - stage 1, or the falling asleep stage, characterized by the presence of α-waves;
   - stage 2, or light sleep, characterized by θ waves (4-7.5 Hz) and other types of waves—biphasic and sleep spindles—that serve to lower the cortical excitation of the brain and inhibit the processing of unnecessary information;
   - stage 3, or deep sleep, characterized by θ waves and δ waves (0.1-3Hz) and the absence of dreams;
   - stage 4, or actual deep sleep, wherein θ waves are completely replaced by δ waves, responsible for deeper relaxation and heightened activity of the unconscious mind.
3. REM phase: also known as the paradoxical sleep phase. During this phase, despite being asleep, brain activity is very intense with an alternation of alpha, beta and theta waves. This is the phase in which individuals dream and there is a gradual increase in blood flow, breathing and brain activity along with a paralysis of the muscles in the arms and legs. REM sleep is mainly promoted by nuclei located in the brainstem along with neurotransmitters, such as acetylcholine and glutamate, as well as neuropeptides, such as the melanin-concentrating hormone (MCH).

Image 8. Conventional circadian rhythm (Image Credit: elenabsl / Shutterstock.com).

The REM and non-REM phases alternate cyclically 4-5 times during the night, with a total duration of about one and a half hours.

The sleep-wake cycle is controlled by circadian rhythms, which regulate the time duration of the REM and non-REM phases and the body's homeostasis, so that the amount of sleep aligns with the amount of wakefulness that precedes it.

The duration of sleep or wakefulness is influenced by the amount of light that hits the retina: here, in addition to photoreceptors that process visual images, there are also ganglion cells that inform the brain about the amount of light present. In simple terms, a decrease in the amount of light stimulates the pineal gland to produce melatonin, which in turn promotes sleep.

As a general guideline, it is recommended to get at least eight hours of sleep per day. However, the optimal amount of sleep varies among individuals, influenced by the different needs of the body and social commitments. In any case, in any individual, disruption of the normal sleep-wake cycle and sleep-related issues can have a very negative impact on quality of life.

Sleep Disorders

The alterations in the normal sleep-wake cycle can be grouped in two main types:

- transient alterations;
- persistent alterations.

Transient alterations depend on changes in one's habits, and include:

- jet-lag syndrome: experienced when crossing more than two time zones; it is characterized by difficulty falling asleep, fragmented sleep, early awakening and daytime sleepiness;
- shift work syndrome: affecting those engaged in night shifts.

Persistent alterations fall into four broad categories:

- dyssomnias: characterized by abnormalities in the quantity, quality or rhythm of sleep, they include insomnia in its various forms, altered perception of sleep state (where the patient complains of insomnia, but objective monitoring reveals normal sleep), hypersomnia (excessive sleep state), narcolepsy (a neurological disorder characterized by hypersomnia and, sometimes, cataplexy), obstructive sleep apnea syndrome, restless legs syndrome (a neurological disorder characterized by nocturnal leg twitching, motor restlessness, uncontrolled leg movements, a compelling need to move the lower limbs);
- parasomnias: when there is abnormal behavior or pathophysiological events during sleep. Examples include REM sleep behavioural disorder, nightmare disorder (continuous occurrence of terrifying dreams

that cause awakening), night terror disorder (or *pavor nocturnus*, which affects pediatric patients), somnambulism with jerk in sleep (sudden, brief tremors of the lower limbs and sometimes of the entire body, often associated with the sensation of falling), somniloquy (or 'talking in one's sleep,' seems to be related to emotional stress, fever or even depression, but can also occur in healthy individuals), bruxism (unconscious teeth grinding), nocturnal enuresis (inability to control one's bladder, typical of children);

- sleep disorders associated with medical or psychiatric illnesses: disorders associated with serious neurological diseases, such as fatal familial insomnia, a very rare condition that often has a fatal outcome;
- proposed sleep disorders: disorders that cannot be classified into the previous categories, such as hypnagogic hallucinations (hallucinations during falling asleep), laryngospasm in sleep (abrupt awakening associated with the sensation of being unable to breathe), myoclonus (involuntary movements of certain muscles during non-REM sleep), sleep choking syndrome (feeling of suffocating in sleep), subvigilance syndrome (inability to maintain an alert state while awake) and neurogenic tachypnoea (increased respiratory rate when asleep).

The Endocannabinoid System in the Sleep-Wake Cycle

The sedative effects of cannabis were well known even in ancient texts, from the legendary Emperor Shen Nong to Pliny the Elder. The initial modern scientific studies, which confirmed what was noted and reported in the oldest texts, date back to the mid-19th century.[1];[2];[3] More recently, various studies have shown that the Endocannabinoid System is involved in the regulation of circadian rhythms and the sleep-wake cycle. A 2001 study revealed that administering tetrahydrocannabinol (THC) increased brain temperature in rats, maintaining circadian fluctuation, while during the abstinence period there is a reversal of the circadian temperature rhythm.[4] This work was the first to show that components of the Endo-

cannabinoid System are regulated by circadian rhythms or that, in some cases, they themselves act as *Zeitgebers*.

CB1 receptor expression is indeed highest during the day and lowest at night.[5] CB2 receptors do not appear to be under circadian influence.

The levels of the two main endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), vary according to the day-night cycle:

- anandamide levels are higher in the dark;
- 2-AG levels increase during the light phase.[6];[7]

The concentrations of the enzymes that degrade endocannabinoids (FAAH, MAGL and DAGL) also fluctuate during the day, as the case of cannabinoid-like compounds such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA).[8]

However, the reciprocal influence of the Endocannabinoid System on circadian rhythms is not unambiguous and depends very much on the experimental model used. Furthermore, the contribution of the individual components of the Endocannabinoid System on the sleep-wake cycle cannot be unequivocally established, due to conflicting data in the literature.

What appears evident is that the sleep-wake cycle modulating action of cannabinoids occurs mainly through their action on CB1 receptors. In contrast, CB2 receptors seem not to be involved, although an action on other components of the endocannabinoid system cannot be ruled out.

Following the activation of central CB1s, primarily located at the presynaptic level,—by endo—or phyto-cannabinoids—there is a reduction in the release of various neurotransmitters that induces a decrease in neuronal activity, either by blocking excitatory actions or by increasing inhibitory tone. This mechanism parallels the effects of many hypno-inducing compounds (alcohol, benzodiazepines, etc.).

In general, considering the available data, it is believed that administering the endocannabinoids anandamide and 2-AG, as well as inhibiting the enzymes responsible for their degradation, induces sleep, particularly non-REM sleep. In contrast, endocannabinoid-like agents such as OEA and PEA

appear to promote wakefulness, potentially reducing cell activity in the lateral hypothalamus.[9]

Cannabis, Insomnia and the Sleep-Wake Cycle: Conclusions

As shown by numerous scientific studies, the Endocannabinoid System is involved in the regulation of:

- circadian rhythms;
- the sleep-wake cycle;
- the neurobiological processes of sleep.

There is a clear overlap between the central endocannabinoid components and the neuronal systems involved in sleep regulation. Although the mechanisms are not well understood, acting on the Endocannabinoid System can alter sleep, both in terms of time spent in specific states of sleep and/or wakefulness, and in terms of sleep architecture and modification of specific sleep-related brain rhythms.
However, scientific studies do not unambiguously clarify how individual endocannabinoid components alter the sleep-wake cycle. This is probably due to the different experimental approaches used. In general, the endocannabinoids anandamide and 2-AG are believed to promote sleep while the cannabinoid-like compounds PEA and OEA seem to promote wakefulness.

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1.5. The Endocannabinoid System in the Gastrointestinal Tract

The Gastrointestinal System

The gastrointestinal (GI) tract consists of a series of hollow organs connected in a continuous tube that begins at the mouth and, through various twists and turns, ends at the anus. The organs that make up the GI tract include the mouth, esophagus, stomach, intestines (with their various subdivisions), and anus.

Together with the liver, pancreas and gallbladder, it forms what is known as the 'Digestive System.'[2]

The activities of the GI system are, for the most part, independent of our will and are coordinated by a series of neurons of:[3]

- the Central Nervous System;
- the Peripheral Nervous System;
- the Enteric Nervous System.

Another fundamental constituent of the GI tract is the microbiota—once known as intestinal microflora—, the 'good' bacteria that, in symbiosis with the human body, aid in food digestion and play a preventive role in

the development of various diseases.[4] Together, these components work in unison to perform the primary function of the gastrointestinal (GI) tract: the digestion of food.

Through a painstaking series of processes, food is transformed in the GI system into the energy needed to perform the various functions of life. In this fundamental aspect of animal biology, the Endocannabinoid System plays a crucial regulatory role.

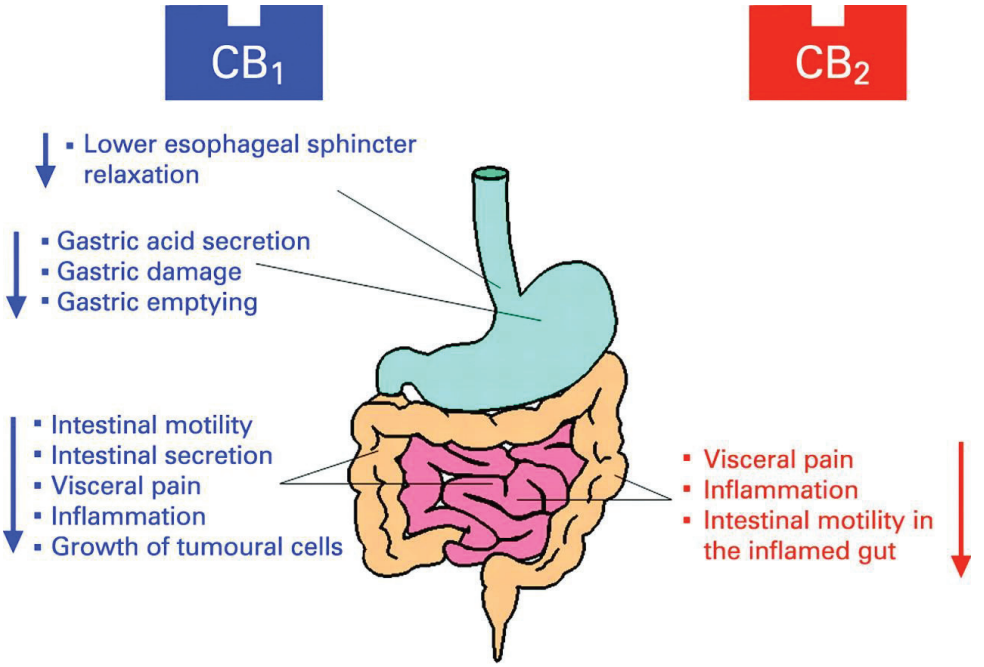

Image 9. Role of CB1 and CB2 receptors in the GI tract (courtesy from Izzo & Camilleri, Gut. 2008 Aug;57(8):1140-55).

The Endocannabinoid System in the Gastrointestinal Tract

The first report of the presence of the Endocannabinoid System in the animal GI tract dates back to 1995, when Raphael Mechulam and colleagues-the same who first identified THC- isolated the endocannabinoid 2-arachidonoylglycerol (2-AG) in the canine intestine.[5] Later, another *endocannabinoid*, Anandamide, and the enzyme responsible for its degradation (FAAH) were

identified in the mouse intestine.[6];[7] Subsequently, components of the ECS were identified in virtually every portion of the human and animal GI system. CB1 receptors are present almost everywhere in the GI tract, especially in the stomach and colon, the terminal portion of the intestine.[8] Here they are mainly found on epithelial cells, the lining cells of the intestinal wall. CB1 receptors are also found on neurons that control the activities of the GI system, especially those of the Enteric Nervous System.[9]

CB2 receptors are present in the Enteric Nervous System, but they are mainly found on immune cells throughout the GI tract.[10] Enzymes responsible for the catabolism of the two main endocannabinoids, i.e. their degradation, have been found throughout the GI tract.[11];[12]

Here we can also find palmitoylethanolamide (PEA), oleoylethanolamide (OEA) and other similar compounds.[13] Although these molecules do not act directly on CB1 or CB2 receptors, they function similarly to endocannabinoids, are called cannabinoid-like compounds and play an important role in the GI system, especially in preventing the onset of inflammatory conditions.[14]

The Endocannabinoid System and Gastrointestinal Homeostasis

To extract nutrition from ingested food, it must be metabolized. By following the path of food through the GI tract, we can understand how the Endocannabinoid System is able to regulate the Gastrointestinal system.

The Role of the ECS in the Esophagus

After being minced in the mouth, the food passes into the esophagus. From there, through an elastic opening, the *esophageal sphincter*, the food enters the stomach. Relaxation of the esophageal sphincter is one of the main causes of gastro-esophageal reflux disorder (GERD), a condition that affects one in three people at least once a month.[15]

In a 2009 clinical study in healthy volunteers, the daily administration of 10 or 20 milligrams of THC was able to decrease relaxation of the esophageal sphincter and consequently all reflux symptoms.[16] Experiments in animal models showed that this effect was mainly due to the activation of CB1 receptors.[17]

The Role of the ECS in the Stomach

Once in the stomach, food is further reduced in size by the action of hydrochloric acid, secreted by the cells of the gastric wall. An abnormal production of hydrochloric acid causes what is known as 'heartburn,' which, in severe cases, can lead to gastritis or ulceration, i.e. a lesion of the gastric wall. Even before the identification of cannabinoid receptors, a team of US scientists noticed that administering THC to rats with gastric ulcers induced by anti-inflammatory drugs, resulted in a reduction of gastric secretion and, more significantly, a decrease in the formation of ulcers—thus highlighting the gastroprotective effect of cannabinoids.[18]

The Endocannabinoid System does not only protect against drug-induced ulcers. In 2003, a group of pharmacologists discovered that, in laboratory mice, activation of the CB1 receptor was able to reduce gastric secretion induced by cholera toxin.[19]

An alternative approach to enhance the gastroprotective effect of endocannabinoids is to block their degradation systems so that their action is prolonged over time.[20]

A further effect of CB1 receptor activation in the stomach is the slowing of gastric emptying.[21]

This action of CB1 can be exploited in cases of gastroparesis, a chronic condition that consists of partial paralysis of the stomach, resulting in delayed emptying. In people suffering from gastroparesis, the stomach empties more slowly, which can lead to loss of appetite, nausea and even vomiting. Currently, there is no specific cure for this condition, but the use

of drugs that counteract the action of cannabinoids, as the antagonists, may prove to be an effective strategy.

The Role of the ECS in the Gut

From the stomach, food must then travel all the way through the intestine so that the nutrients it contains are absorbed and any waste is eliminated. This is done through a movement of the intestinal wall called peristalsis, a series of contractions and relaxations that, like a pump, propel food from the duodenum, the initial part of the intestine, to the colon.

Hypermotility, a condition associated with abnormal intestinal motility, is characterized by increased intestinal inflammation and is often linked to disorders such as irritable bowel syndrome (IBS). The causes of hypermotility are not yet well understood, resulting in poor food absorption and various pathological conditions. The Enteric Nervous System, a self-functioning neuronal network, directly controls intestinal motility, and the Endocannabinoid System plays a regulatory role in this process.

In a study published in the *Canadian Journal of Pharmacology* in 1978, findings revealed that THC had the capability to decrease intestinal motility in guinea pigs.[22]

Thirty years later, another study showed that cannabidiol (CBD), the non-psychotropic cannabinoid found in the cannabis plant, was also able to reduce inflammation-induced intestinal hypermotility in laboratory mice.[23]

The action of these phytocannabinoids, as well as that of endocannabinoids and synthetic cannabinoids, is mainly due to the stimulation of CB1 receptors present in the Enteric Nervous System.[24] Once activated, CB1 receptors reduce the release of acetylcholine (ACh) from enteric nerves and this, together with other mechanisms that are not fully understood, causes a decrease in intestinal contractility and thus motility.[25]

It is no coincidence that, in the *Handbook of Experimental Pharmacology,* one of the world's most authoritative pharmacology journals, CB1 receptors are referred to as the physiological 'brakes' of the GI system.[26]

The Interaction of the ECS with the Microbiota

In the gut, ingested food interacts with the microbiota, billions of microorganisms—predominantly bacteria, but also including yeasts, viruses and other organisms—that reside permanently within the human body and those of other animals. These microorganisms engage in a mutually beneficial relationship, aiding in the degradation and absorption of food while providing protection against infections.[27] The Endocannabinoid System is capable of modulating the composition of the microbiota and, consequently, its impact on gastrointestinal physiology. The mechanism underlying the interaction between the Endocannabinoid System and the microbiota is still poorly understood.

A collaborative study between several European research institutions, in which mice with an obesity-inducing genetic modification were used, showed that activation of the ECS by the microbiota—through an unclear mechanism—leads to an increase in fat mass, as a consequence of an increase in intestinal permeability.[28]

Conversely, blocking the CB1 receptor reduces obesity and changes the composition of the microbiota, favouring the presence of protective bacterial species.[29] Probiotics, microorganisms that when administered in the right quantities have positive effects on intestinal pathophysiology, also interact with the gastrointestinal Endocannabinoid System.[30]

The Endocannabinoid System and the microbiota are thus able to influence each other and, as the mechanisms of this interaction are still unclear, further research could identify new pharmacological targets in diseases such as obesity and metabolic syndrome.

The Endocannabinoid System and the Regulation of Feeding Behaviour

So far, we have described the journey of food in the GI system, from ingestion to absorption. For this process to occur, however, it is necessary to eat. In other words, one must experience hunger, which drives humans and animals to seek food to satisfy the body's metabolic needs, as energy requirements are met through food consumption. This essential aspect of seeking and consuming food is termed *feeding behaviour*.

It has been known since ancient times that the ingestion of cannabis, as well as the habit of smoking it, induces an increase in appetite, colloquially referred to as 'munchies.' In the past, it was believed that the phenomenon of 'munchies' was merely a suggestion resulting from cannabis intoxication. However, scientific research has demonstrated that this effect is genuine and is mediated by various mechanisms, both central and peripheral.

Towards the end of the 1990s, it was clearly demonstrated that endocannabinoids, as well as phytocannabinoids, were able to stimulate appetite through activation of the CB1 receptor, but the mechanism by which this occurs has only been clarified (at least in part) more recently.[32]

The Role of the ECS in Neurons

One of the mechanisms by which the Endocannabinoid System stimulates hunger in our brains has been discovered by a team of French researchers led by the Italian scientist Giovanni Marsicano. In their study, the researchers administered THC to laboratory mice and observed an increase in food intake. Very interestingly the mice also exhibited a greater sensitivity to odors. At this point, the scientists considered using genetically modified mice in which the CB1 receptor present in the neurons of the olfactory bulb was inactive. In these genetically modified animals, THC did not induce the sense of hunger.[33]

The following year, in 2015, the renowned journal *Nature* published another study on this subject that highlighted a 'paradoxical' mechanism through which the Endocannabinoid System regulates hunger.[34] Scientists at Yale University studied the effect of CB1 receptor activation on pro-opiomelanocortinic neurons (POMCs). These neurons are activated during satiety, reducing the sensation of appetite. Therefore, scientists expected that activating CB1, which is known for increasing appetite, would result in a reduction in the activity of POMC neurons. However, this was not the case. Undeterred, researchers conducted a more detailed analysis of their data and discovered that POMC neurons, under normal conditions, release two substances: a hormone called α-*Melanocyte-stimulating hormone*, with an anorectic effect that suppresses appetite, and beta-endorphin, a neurotransmitter that induces a heightened sense of well-being by acting on the same receptors as opioids.

However, when POMC neurons, as in the experiment, are activated by cannabinoids, they release only beta-endorphin. Consequently, the anorectic effect of the hormone, which usually blocks appetite, is no longer present, and only the pleasurable sensation released by beta-endorphin remains, allowing appetite to persist.[35] This research, along with similar studies, highlights the role of endocannabinoids in what scientists have long referred to as 'hedonistic hunger'—the pursuit of food for pleasure rather than necessity.

A significant study published in 2012 in the journal *Neuropharmacology* investigated the effects of THC on feeding behavior in mice. In the experiment, mice were given sugar as food, with or without THC. Although THC did not influence the amount of sugar consumed in either group, the mice that received THC exhibited a 'hedonistic' response to the food, demonstrated by increased licking of their paws and whiskers as a sign of pleasure. Additionally, these mice displayed elevated levels of dopamine, a neurotransmitter involved in reward and gratification mechanisms. Notably, the THC-induced effects were abolished when a CB1 receptor antagonist was administered.[36]

This indicates, as further research points out, that the Endocannabinoid System is involved in the perception of 'liking' or 'not liking' a particular food. In a study published in *Nature Medicine*, *the* administration of probiotics to laboratory mice was shown to increase CB2 receptor activity, which correlated with a decrease in abdominal pain and visceral hypersensitivity.[31]

The Endocannabinoid System in the Regulation of Energy Balance

The Endocannabinoid System also exerts its influence on the 'classic' hunger regulatory system—scientifically referred to as homeostatic hunger. Specifically, it interacts with the ghrelin/leptin signaling system. These substances are hormones produced by the stomach and fat cells, respectively, in response to the body's metabolic needs. Once they reach the hypothalamus, the region of the brain responsible for maintaining energy balance, they regulate appetite by performing opposite actions:

- ghrelin—whose production peaks just before eating or when fasting—stimulates appetite;
- leptin—whose production peaks just after eating—induces satiety.

In the GI system, activation of the CB1 receptor causes an increase in the release of ghrelin in the stomach, thus increasing hunger.[37]
In animal models, both the administration of anandamide and 2-arachidonoylglycerol increased the sense of hunger, an effect that is abolished by blocking CB1 receptors present on the 'capsaicin-sensitive' intestinal neurons (TRPV1 neurons), suggesting that these neurons are involved in the sensation of appetite.[38];[39]
Within the hypothalamus, the presence of ghrelin increases the endocannabinoid levels, thereby contributing to increasing appetite. Conversely, blocking the CB1 receptor in this region of the brain decreases the ghrelin's overexpression. This observation indicates that the Endocannabinoid Sys-

tem is essential for the sensation of hunger, even under physiological conditions, extending beyond the 'hedonistic' mechanism of food seeking.[40]
In addition to their interaction with ghrelin, endocannabinoids also play a crucial role in modulating the effects of leptin.

Interaction with the Orexin System

Another class of molecules involved in the regulation of appetite is the orexins (also known as hypocretins), which are neurotransmitters primarily located in hypothalamic neurons, where, in contrast to endocannabinoids, orexins play an excitatory role.[42]
The role of orexins is mainly to regulate the sleep-wake rhythm and energy balance, but they also regulate the sense of appetite—as the name suggests. In fact, activation of the receptors for orexins (OX1 and OX2) increases food intake.[43]
Anatomical studies have shown that orexin receptors overlap with CB1 receptors in many areas of the brain, suggesting a common role in at least some physiological actions.[44]
In animal models of obesity, in which the ghrelin/leptin system is impaired, there is an increase in the concentration of orexins in the brain, which in turn induces an increase in the concentration of endocannabinoids through stimulation of the OX1 receptor, and this probably contributes to exacerbating obesity.[45];[46] In addition, blocking the CB1 receptor inhibits the OX1-induced increase in appetite.[47]
This increase in hunger correlates with an increase in locomotor activity and insomnia. This seems to suggest that the main function of this system is to induce a state of alertness and readiness to seek for food when it is scarce. Conversely, the Endocannabinoid System appears to prepare the body for nourishment and additionally serves to enhance the pleasure associated with food intake.
In any case, increasing appetite can be a significant and beneficial outcome in immunocompromised patients, individuals undergoing chemotherapy,

or psychiatric patients, including those suffering from anorexia nervosa. Exploiting the Endocannabinoid System in this context may emerge as a valuable therapeutic strategy.

Conclusions

The Endocannabinoid System is extensively involved in the GI tract, influencing crucial functions ranging from hunger perception to nutrient absorption.

Acting on one of these mechanisms with the use of phytocannabinoids, cannabinoid-like drugs, antagonists or drugs that interfere with the biosynthesis or degradation of endocannabinoids may prove to be an effective strategy in the treatment of numerous gastrointestinal disorders, from functional disorders to obesity, from chronic inflammation to motility disorders.

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1.6. Neuro-Gastro-Cannabinology

A Novel Paradigm for Regulating Mood and Digestive Health

Neuro-Gastro-Cannabinonology explores the intriguing interface of neurology, gastroenterology, and cannabinoid science. This emerging field examines how the Endocannabinoid System (ECS) mediates the complex interactions between the brain and the gastrointestinal (GI) tract, influencing both mood and digestive health.

The Role of the Endocannabinoid System in the Gut-Brain Axis

The ECS is a widespread biochemical network involving cannabinoid receptors, endogenous cannabinoids, and metabolic enzymes that manage various physiological processes. In the GI tract, the ECS regulates activities crucial for maintaining intestinal homeostasis such as motility, fluid secretion, and pain sensation. Beyond its peripheral functions, the ECS is instrumental in the Central Nervous System, indirectly impacting gut functions through mechanisms like appetite control and energy balance. Neurotransmission within the Central Nervous System can affect

GI functions, and vice versa, through the gut-brain axis. This bidirectional communication system allows the brain and gut to send signals to each other, potentially affecting a person's emotional state as well as their digestive health. Dysregulation in this system can lead to mood disorders like anxiety and depression, which are often associated with GI disturbances such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).

Interaction Between the Microbiota and the Endocannabinoid System

Recent studies highlight the significant role of gut microbiota in influencing the ECS, which in turn affects the central nervous system and overall health. Microbiota can modify the expression and function of cannabinoid receptors and metabolic enzymes, impacting the production of endocannabinoids and related compounds. These interactions can influence emotional behaviors and stress responses, linking gut health directly to mood and cognitive functions.

For instance, specific probiotic strains can enhance intestinal barrier function and modulate immune responses, potentially reducing the psychological stress response. Conversely, stress and mood disorders can alter gut microbiota composition and function, which may exacerbate GI symptoms and disorders.

Therapeutic Potentials of Modulating the ECS

Given the ECS's central role in integrating signals between the gut and the brain, targeting this system could offer new therapeutic avenues for treating disorders at the intersection of neurology and gastroenterology. For example, pharmacological manipulation of the ECS could help treat conditions characterized by both mood and digestive symptoms, such as depression and IBS.

Prebiotics and probiotics can influence the ECS by altering microbiota

composition and activity, thereby potentially mitigating the effects of stress and mood disorders on the GI tract. Additionally, phytocannabinoids like THC and CBD, as well as endocannabinoid-like molecules such as palmitoylethanolamide (PEA), could be used to modify ECS activity, offering a direct method to enhance gut-brain communication.

Conclusions

Neuro-Gastro-Cannabinonology represents a promising new paradigm that blends neurology, gastroenterology, and cannabinoid science to explore and treat complex interactions between the gut and brain. This interdisciplinary approach could lead to innovative treatments that address the root causes of related disorders, rather than just managing their symptoms. As research progresses, this field may provide a deeper understanding of how modulating the ECS and microbiota can improve both mental and digestive health, ultimately leading to more holistic approaches to health care.

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1.7. **Insight: Palmitoylethanolamide (PEA): An Overview**

In recent years, several studies have amply demonstrated the analgesic and anti-inflammatory properties of palmitoylethanolamide (PEA), suggesting an important role for this lipid molecule in controlling the genesis of pain in the periphery, as well as in inflammatory phenomena.[1]

Introduction

Initially considered to play a predominantly antiphlogistic (anti-inflammatory) role through the reduction of the release of inflammatory mediators by mast cells, monocytes and macrophages, PEA is now identified as a key element in the regulation of far more complex pathways that affect not only inflammation, but also the processes underlying itch and pain, both neurogenic and neuropathic.[2];[3]

Is PEA an endocannabinoid?

Image 10. Professor Rita Levi Montalcini, Nobel prize in Medicine.

PEA possesses cannabinergic effects but, despite its high clinical potential, the mechanisms responsible for its analgesic and anti-inflammatory properties are not fully understood. The structural analogy of PEA with the endocannabinoid Anandamide (AEA) suggested at first that both lipids might share the ability to bind peripheral CB2 cannabinoid receptors.

Indeed, several studies have shown that the analgesic activity of PEA, but not the anti-inflammatory activity, depends on the activation of CB2 cannabinoid receptors. The use of the CB2 receptor antagonist SR144528, which blocks these receptors, can inhibit the analgesic effect of PEA, suggesting that its analgesic mechanism may involve indirect activation of endocannabinoid pathways. To explain this apparent contradiction—namely, that the anti-inflammatory effects were not blocked—it has been suggested that PEA may act as a false substrate and inhibit FAAH, the enzyme responsible for hydrolyzing AEA.

According to this theory, in the presence of PEA, the enzyme FAAH preferentially degrades PEA rather than endocannabinoids. Consequently, the concentration of endocannabinoids increases, indirectly favoring the analgesic effect of the compound. For this reason, PEA is defined as a *cannabimimetic, cannabinoid-like* or *indirect endocannabinoid compound*.[4]

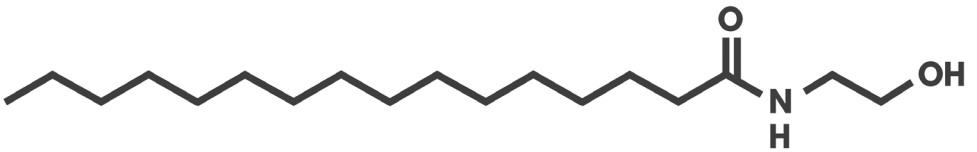

Image 11. N-Palmitoylethanolamide (courtesy of Renate Mich, www.officinavisioni.com).

PEA Biosynthesis and Metabolism

The increase in local PEA levels at inflammatory sites is significant and it is undoubtedly linked to its protective and pro-homeostatic role. In fact, PEA is produced and accumulated locally during inflammatory processes. PEA, like all Fatty Acid Ethanolamides (FAEs), therefore, is not stored, but is synthesized at the moment, in response to intracellular Ca^{2+} level. Specifically, the biosynthesis of PEA occurs in two steps:

1. The first step consists in the conversion of fatty acids derived from membrane phospholipids to phosphatidylethanolamine (PE), catalyzed by an *N-acyltransferase* (NAT) regulated by calcium ions and cyclic AMP; the result is the formation of the FAE precursors, known as N-acyl phosphatidylethanolamine (NAPE). The specific FAE precursors formed depend on which fatty acids are initially converted to PE (e.g. the initial transfer of palmitic acid will produce a PEA precursor, while arachidonic acid will produce an anandamide precursor).
2. The second step involves the detachment of membrane-bound NAPE to release PEA: this process is mediated by the NAPE-specific *phospholipase D* (PLD). This hydrolase shares sequence homology with other members of the phospholipase family and recognizes different NAPE species, producing PEA together with other FAEs.[5] Ultimately,

the inactivation of PEA occurs through hydrolysis by *'N-Acylethanolamine-hydrolyzing Acid Amidase'* (NAAA) to form palmitic acid and ethanolamine.

The Role of PEA

The acronym ALIA, originally coined by a group of Italian researchers in 1993, initially stood for *Autacoid Local Inflammation Antagonism* and described the mechanism of action of PEA. However, its meaning has since evolved to *Autacoid Local Injury Antagonism*, reflecting a broader recognition of its involvement in protective systems beyond inflammation.[6]

PEA and Genes

PEA acts as an agonist of nuclear receptors called *Peroxisome Proliferator-Activated Receptors* (PPARs), i.e. receptors present on the nuclear membrane and directly communicating with genes. In particular, the PPARα are considered the primary biological targets for PEA, providing a potential explanation for the molecule's anti-inflammatory activity.[7]

Indeed, PPARα activation has neuroprotective and, more generally, cytoprotective functions in various animal models. Following ligand binding, the PPARα receptor detaches itself from the *Heat Shock Protein 90* (Hsp90) and heterodimerizes with the *trans-retinoic X receptor* (RXR). The PPAR-RXR complex migrates into the nucleus where it binds to a specific area of DNA called the *PPAR response element* (PPAR-RE), the promoter area of the target gene.[8]

PPARs have the ability to both activate and repress the transcription of the target gene. This dual functionality enables PPARs to regulate lipid and sugar metabolism while simultaneously exerting *transrepression* to inhibit the transcription of pro-inflammatory proteins.

In humans, as well as in rats and mice, the PPARα receptor is predominantly expressed in brown adipose tissue, skeletal muscle, liver, heart, and kidneys.

In the brain and lungs there is low expression of this receptor, although recent works have shown a discrete presence of these receptors centrally, where PEA seems to be involved in synaptic plasticity and neurogenesis.[9] Recently, it was shown that, through genomic mechanisms mediated precisely by stimulation of the PPARα receptor, PEA is able to positively modulate CB2 receptor expression in primary cultures of microglial cells.[10] This new mechanism may explain why, in various pathological conditions, some effects of PEA are antagonized by CB2 receptor blockade.

In addition to its *genomic mechanism,* where PEA directly interacts with genes through the activation of the PPARα receptor—non-genomic mechanisms of PEA action have also been proposed, as several studies demonstrate its rapid reduction of acute inflammation.[7] The rapid onset of anti-inflammatory actions cannot be attributed to gene modifications, which tend to take longer, confirming the hypothesis of an alternative mechanism besides PPAR receptor stimulation.[8]

The Benefits of PEA

PEA is naturally present, albeit in small quantities, in foods such as:

- egg yolks;
- peanut oil;
- soy lecithin;
- tomatoes;
- corn;
- peas.

In chronic pathological conditions, supplementation with exogenous PEA has proven beneficial in addressing imbalances and maintaining homeostasis.

Research evidence indicates that an imbalance in ECS tone may contribute to the development of pathological conditions such as psychological and neurodegenerative disorders. Acting as an endocannabinoid-like lipid mediator, PEA possesses analgesic and anti-inflammatory properties. It supports the ECS by modulating endocannabinoid signaling and indirectly activating cannabinoid receptors, known as the entourage effect.
Human clinical studies have highlighted significant benefits of PEA in the reduction or management of the following:

- inflammation;
- pain;
- neurodegenerative diseases;
- psychological disorders.

The safety of PEA is generally confirmed, but further research is needed to better understand its pharmacokinetics and potential in conditions not related to pain. In a meta-analysis of 10 human clinical studies on pain, PEA has proven effective, generally well-tolerated, and no serious or suspected adverse events associated with PEA were observed (at dosages up to 1,200 mg/day for 365 days).[11] To further confirm the role of PEA in the treatment of chronic pain, a recent systematic review and meta-analysis of double-blind randomized controlled trials concluded that PEA is an effective and well-tolerated treatment for chronic pain.[12]

Conclusions

PEA is an endogenous molecule with anti-inflammatory, lipolytic and neuroprotective properties. Its mechanism of action is complex and multi-target, which makes PEA a substance that can intervene in various physiological and pathological processes. To date, several pharmaceutical formulations containing PEA exist.

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1.8. **Insight:** Homeostasis, Resilience and the Endocannabinoid System

Social isolation refers to the state in which an individual or a group experiences a lack of contact or meaningful interaction with others in their community or society. It can result from various factors, including physi-

cal separation, emotional withdrawal, or a lack of social support. Social isolation can occur voluntarily, such as when someone chooses to spend extended periods alone, or involuntarily, due to factors like geographical distance, illness, or societal circumstances.

Social isolation is characterized by high physical and emotional stress, such as that caused by the Covid-19 pandemic and the restrictive measures taken to prevent its spread. During periods of high stress, the functions of the Endocannabinoid System—responsible for regulating the body's balance—, are altered. These alterations make people more susceptible to negative thoughts, aggressive behavior and an increased risk of general health deterioration.

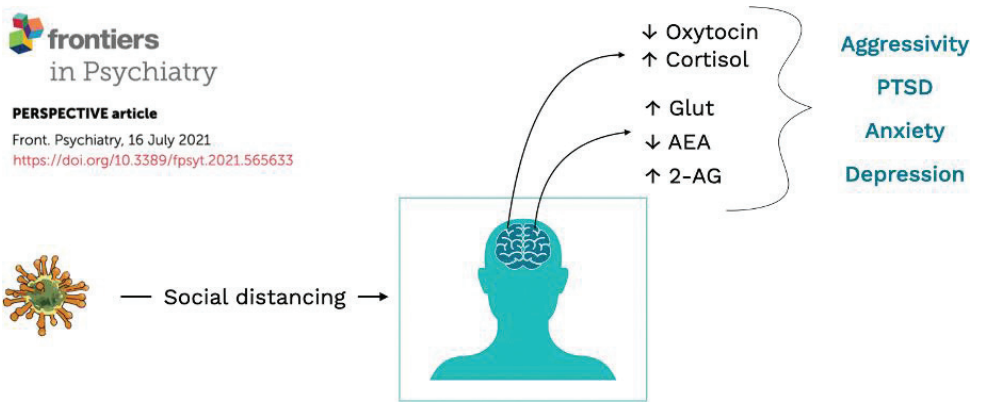

Image 12. Lifestyle Interventions Improving Cannabinoid Tone During COVID-19 Lockdowns May Enhance Compliance With Preventive Regulations and Decrease Psychophysical Health-Complications (courtesy of Brugnatelli V, Facco E, Zanette G. Front Psychiatry. 2021).

Recent literature indicates that certain non-invasive lifestyle changes can enhance the endocannabinoid tone, leading to a subsequent improvement in an individual's psycho-physical well-being and socio-economic health.[1]

Social Isolation and Resilience

Numerous scientific studies have shown that social isolation induces neuro-psychiatric changes that can lead to psychosis, suicide, anxiety and

depression.[2] All these conditions are related to an alteration of the Endocannabinoid System through various mechanisms, including modulation of the functions of the *hypothalamic-pituitary-adrenal axis*, HPA.[3];[4]

The Endocannabinoid System is responsible for maintaining homeostasis, i.e. the correct balance between the body's various functions. A shift in the expression of some of its components—such as receptors, enzymes, endogenous mediators—alters the so-called 'endocannabinoid tone.'[5]

In situations where uncontrolled life events or social restrictions have led to an increase in stress, fear, and negative emotions, re-establishing a proper endocannabinoid tone may prove to be a useful strategy to improve our ability to resist adversity and restore homeostasis. In other words, it may increase our resilience, an increasingly popular term encompassing not only the ability to withstand the shocks of life, but also the ability to emerge strengthened from adversity.

According to one of Brugnatelli's recent paper entitled *Lifestyle Interventions Improving Cannabinoid Tone During COVID-19 Lockdowns May Enhance Compliance With Preventive Regulations and Decrease Psychophysical Health Complications* in the journal *Frontiers in Psychiatry*, it is possible to improve endocannabinoid tone through lifestyle modifications that include the use of probiotics, exercise, hypnosis, meditation, and Medical Cannabis. [1]

Pathophysiology of Endocannabinoid System Modifications Induced by Isolation

CB1 receptors, key components of the Endocannabinoid System, are expressed throughout the brain, but especially in areas that regulate stress and emotions:[6]

- prefrontal cortex (PFC);
- hippocampus;
- amygdala.

A decrease in the concentration of CB1 receptors in the brain induces anxiety. Studies have revealed that social isolation can lead to a loss of neurons in the prefrontal cortex, resulting in an increase in aggressive behavior. Isolation also alters the Endocannabinoid System in the hypothalamus and this is correlated with an increase in stress, through an overactivation of the HPA axis: this induces an increased release of cortisol, also known as the stress hormone.[7];[8]

High-stress conditions also alter the expression of the two main endocannabinoids, anandamide, which is decreased, and 2-arachidonoylglycerol, which is increased during stress.[8];[9] Stress also alters the expression of certain genes of the Endocannabinoid System and these changes are usually related to the development of behavioral disorders such as anxiety, depression and post-traumatic stress disorder (PTSD).[10];[11]

Taken together these data suggest the need for strategies aimed not only at decreasing stress, but also at helping to restore proper endocannabinoid tone, the latter being strongly linked to individual reactions to stressful environments and events.

Strategies for Improving the Endocannabinoid System

It is possible to strengthen the Endocannabinoid System through simple changes in our lifestyle, resulting in an improvement not only in our psycho-physical well-being but also in our immune system, which can thus more effectively fight the pathogens that attack us.

One intervention does not exclude the other; on the contrary, integrating the proposed practices is essential to ensuring greater success.

Nutraceutical Interventions

Our gut houses billions and billions of microorganisms, a population far larger than all the cells in our body, which together form what is known as

"the gut microbiota." Alterations in the microbiota are correlated with an increase in anxious and depression-like behavior and modifications of the endocannabinoid tone.[12] Using probiotics to re-establish a proper microbiota helps restore endocannabinoid tone (through an increase in anandamide) and decrease anxiety and stress.[13]

Palmitoylethanolamide (PEA) may also be helpful in improving depression-like behavior. PEA can help with post-Covid neurological symptoms, such as anxiety and depression, and to counteract excessive Covid-19-induced inflammation and loss of sense of smell.[14]

Foods can also be useful for restoring a proper endocannabinoid tone. For instance, dark chocolate can decrease cortisol release and it also contains N-acylethanolamines, Inhibitors of endocannabinoid-degrading enzymes, which consequently increase endocannabinoid levels.[15]

Beta-caryophyllene, a terpene contained in Medical Cannabis and various foods such as carrots and black pepper, exhibits not only anti-inflammatory effects but also enhances endocannabinoid tone and exerts antidepressant effects.[16]

In black pepper we can also find *guineesine*, an alkaloid that increases anandamide levels.[17]

Black truffles contain substances that can increase endocannabinoid levels, as do all foods that contain kaempferol, a flavonoid normally found in foods such as capers, saffron, rocket, blackberries and many other edible plants.[18]

Finally, there is turmeric, whose main constituent, curcumin, does not appear to significantly increase the expression of endocannabinoids levels but has been shown to induce antidepressant effects.[19]

Phytotherapeutic Interventions

The plant world—a perennial source of molecules with biological activity—can be exploited to enhance endocannabinoid tone. Naturally, the most exemplary plant capable of achieving this is *Cannabis Sativa L.*

Data from various US states and Canada—where legislative frameworks facilitate access to medical or recreational cannabis—indicate that demand for cannabis increased during lockdown periods. As pointed out by the authors of the study, there is a rationale for the use of cannabis in these circumstances.

Research has shown that depressive-like behavior induced by distancing and social isolation is mitigated by activation of cannabinoid receptors. Furthermore, isolation induces a reduction of dopamine D2 receptors in the PFC, which can be balanced by CB1 stimulation.[20]

The increase in cannabis use in the USA and Canada, especially as a self-medication product, is not correlated with an increase of depression, anxiety or sleep problems. However, the use of products that do not induce the psychotropic effects of tetrahydrocannabinol (THC) should be encouraged. Cannabidiol (CBD) can represent a safer alternative for some individuals. CBD—a major constituent of cannabis and endowed with anxiolytic, antidepressant and antipsychotic activity—was tested in animals in isolation, confirming its beneficial effects in attenuating aggressive behavior through a mechanism associated with increased levels of Anandamide and activation of cannabinoid and serotoninergic receptors. CBD has also been proposed as a specific intervention to attenuate Sars-Cov-2 symptoms and infection.[21];[22]

Another interesting plant is *Echinacea*, which can increase endocannabinoid levels and activate CB2 receptors (with anti-inflammatory activity). Besides being a powerful stimulant of the immune system, studies have shown that *Echinacea* is also able to induce anxiolytic effects.[23]

Physical Activity

Mens sana in corpore sano. Without disturbing the Latin poet Juvenal, physical activity has been shown to play an important role in maintaining mental health, decreasing anxiety and alleviating depressive symptoms,

and has been recommended as a regular practice during the pandemic to prevent metabolic and immunological dysfunction.
It should be noted that numerous studies have shown that regular physical activity, even moderate exercise such as simple running, cycling, hiking and other not particularly intense aerobic exercise, is associated with increased expression of endocannabinoids, particularly Anandamide, and reduced activity of the enzymes that degrade them.[24];[25]

Hypnosis and Meditation

One of the most interesting aspects of this study is the attention paid by the authors to practices that only recently, and even with some difficulty, gained the interest of the scientific community, including hypnosis and meditation.
Although very different, these two techniques of 'mental introspection' have many aspects in common, including their relevance to the so-called placebo effect. To note, it is precisely the placebo effect that involves the activation of the endocannabinoid and opioid systems.
Both practices, defined by the authors as two sides of the same coin, highlight the importance of a holistic approach that encompasses the inseparable unity of mind-brain-body-environment.
Numerous data has shown how hypnosis and meditation can improve metacognitive control and generate intentional changes in unconscious brain areas and circuits that lead to exceptional results. One noteworthy example is hypnotic analgesia. Moreover, these practices help to develop awareness, deconstruct and restructure the patient's problems, improve mind and body control and manage functional and psychosomatic disorders.[26];[27]
From a neuropsychological perspective, both hypnosis and meditation strongly influence the *default mode network*, a neuronal circuit involved in self-referential processing, and the anterior cingulate cortex, an area

of the brain that may play a central role in dissociative identity disorders and PTSD.[28]

According to the authors, to effectively address traumatic events such as Covid-19 and the resulting social restrictions, it is necessary to establish a two-way relationship between mind and brain, where changes in the brain affect changes in the mind and vice versa. Consequently, while pharmacological and nutraceutical interventions can indirectly improve certain brain functions and help diminish the symptoms of a disease, behavioral techniques directly modulate the same brain functions through cognition and a reorganization of the mind-brain relationship.

In this way, both hypnosis and meditation can help improve the neuropsychological components of various psychological and psychiatric disorders and foster resilience.[29]

Social isolation and the Endocannabinoid System: Conclusions

Resilience is a neologism that has come into common usage especially since the *lockdown* period. Derived from physics where it indicates the ability of a material to absorb a shock without breaking, in biology and psychology resilience can be defined as the ability to withstand adversity by maintaining homeostasis, recovering the initial equilibrium after a disruption, or the ability to achieve a new equilibrium through allostasis, the maintenance of stability through change.

Being resilient by maintaining homeostasis aids in emerging unscathed (if not better) from stressful situations such as social isolation. From a physiological point of view, maintaining homeostasis is the primary function of the Endocannabinoid System. Elevating the endocannabinoid tone, through simple lifestyle changes, individuals are better able to resist stress and states of anxiety or depression that are increasingly common in today's world.

This is the basis for the proposals of the researchers of the University of Padua, Italy, authors of the study, according to which by integrating nutraceutical interventions, phytotherapy and behavioral techniques it is possible to maintain a correct endocannabinoid tone, achieving 'protection' from stress "in difficult times."[1]

Thus, the use of probiotics, specific foods such as cocoa, black pepper or turmeric, plants such as cannabis and echinacea, and mental techniques such as hypnosis and meditation, by promoting the maintenance of a balanced endocannabinoid tone, improve mental health and the immune system, contributing to an individual's well-being especially in the presence of strongly conditioning environmental stimuli.

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1.9. **Insight:** The Endocannabinoid System and Stress-related Anxiety

Stress seems to be an inseparable condition of everyday life.

It manifests due to factors such as excessive or insufficient workload, traffic, the continual inundation of more or less valuable information, and the fast-paced demands imposed by our society.

We coexist with stress and, while some individuals seem to have adapted to this condition, for others it can cause considerable problems. First of all, it often triggers uncontrollable anxiety, which negatively affects both one's psycho-social well-being and interpersonal relationships.

Cannabis Sativa L. has often been proposed as a remedy to reduce anxiety. However, although its utility seems to be somewhat accepted, the mechanisms by which it operates in the brain are still unclear.

At least until a recent publication in the journal *Neuron*, where a group of US researchers unveiled one of the possible mechanisms by which the Endocannabinoid System is involved in the prevention of stress-related anxiety.[1]

Stress and Anxiety

Stress represents an imbalance in an organism's normal state of equilibrium, known as homeostasis. This imbalance can be induced by both external and internal factors to which the individual responds. The response may involve either adjusting the internal balance to align with the environment or modifying the external environment to meet one's needs.

Stress is therefore not always a negative factor. Rather, it is a component of the General Adaptation Syndrome, through which the individual reacts to environmental stresses. Stress can be regarded as a very ancient phylogenetic defense mechanism.

When humans lived in constant contact with a sometimes-hostile nature, they needed to react promptly to even the slightest stimuli to ensure their survival. This dynamic persisted for thousands of years, until the advent of modernity, when natural dangers gradually diminished.

However, the innate ability to react to stimuli has not diminished. What has changed is that while stress was once triggered by tangible threats, such as the smell of a predator or an unrecognized noise, preparing us for escape and thus survival, now stressors are more intangible. Rather than preparing us for escape, they can induce psycho-physical imbalances that in some cases result in anxiety.

It is well known, in fact, that a prolonged stress factor causes the onset of anxiety. Like stress, anxiety is not necessarily a negative condition; rather, it is our body's way of signaling that something is wrong. However, frequently, the source of this concern lies within our minds, beyond our control. This can lead to a state of anxiety that is no longer temporary and useful to react to, but becomes a chronic disorder that negatively affects daily activities.

The connection between stress and anxiety has been recognized for decades. The longer and more prevalent a stress-inducing phenomenon, the higher the likelihood of developing anxiety disorders.

The brain areas involved are more or less understood. It is known that the amygdala—the area responsible for processing fear—is hyper-activated under stress conditions and that its signaling to the prefrontal cortex—the area responsible for processing complex cognitive behavior—is increased. Stress thus induces a 'coupling' between the amygdala and the prefrontal cortex. The endogenous mechanism behind this coupling—previously unknown—has been, at least in part, revealed.[1]

Cannabis for the Treatment of Anxiety?

US researchers used state-of-the-art techniques, such as optogenetics (a combination of optical techniques and genetic manipulation), to demonstrate that the endocannabinoid 2-arachidonoylglycerol (2-AG) links the amygdala with the prefrontal cortex and that stress induces a decrease in its expression, which correlates with the development of anxiety states.
Through this very well-designed study and using innovative techniques, the authors demonstrated that stress induces a 'collapse' of the endocannabinoid 2-AG activity between the amygdala and the prefrontal cortex, and this induces stress that, if prolonged over time, can result in anxious behavior. According to the authors, "these data suggest that CB1 receptor-mediated enhancement of 2-AG signaling, e.g. by inhibition of the 2-AG-degrading enzyme (MAGL), could be an attractive therapeutic approach for the treatment of stress-induced psychiatric disorders."
Since cannabis can mimic the action of 2-AG, this research seems to confirm what both anecdotal reports and scientific research have long indicated: cannabis appears to be useful in the treatment of anxiety disorders. "The role of endocannabinoids is very important in maintaining complex homeostatic brain processes. In fact, their role in brain areas deputed to the integration of external stimuli, anxiety states and unpleasant emotional-sensory events, as well as in central sequelae associated with chronic pain, is well established," comments Livio Luongo, professor of pharma-

cology, member of the Italian Society of Pharmacology (SIF) and recent author of a research that identified four new phytocannabinoids in *Cannabis Sativa L*. (see chapter **2.7. Exploring Four New Phytocannabinoids in Cannabis**): "The study is interesting, though very technical, and looks at a specific circuit, the one that goes from the amygdala to the cortex. The data show that certain components of Cannabis Sativa could be used, at appropriate concentrations, in certain states of anxiety. An interesting example of this is Cannabidiol (CBD), a phytocannabinoid currently widely used for the treatment of symptoms associated with anxiety states."

Indeed, various studies have shown that CBD, rather than THC, appears to be the anxiolytic component of cannabis, although its effect is dose-dependent.

Thus, stimulating the Endocannabinoid System—even through the use of cannabis—seems to be a good strategy to fight stress anxiety. Some doubts, however, remain unaddressed.

It is yet to be determined why not all individuals develop anxiety when subjected to stress. There may be other circuits that compensate for the decrease in 2-AG signaling, which are more functional in some individuals than in others. Can these be induced by a shift in mindset? Furthermore, these data, although very interesting, must be confirmed in human experiments.

What has been further emphasized by this research—if it is still necessary—is the key role that the Endocannabinoid System plays in regulating important functions of the body, especially behavioral functions.

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CHAPTER **2.**

PHARMACOLOGY OF CANNABIS AND CANNABINOIDS

2.1. Introduction to Medical Cannabis

What is Medical Cannabis

The term “Medical Cannabis” refers to the medicinal use of products derived from the dried female inflorescences of *Cannabis Sativa L.* (the designation L. refers to Linnaeus, the scholar who first scientifically classified cannabis, among other numerous plant varieties, in the 18th century).
Medical Cannabis is sourced from medical grade cannabis varieties cultivated under rigorous protocols. Each step, from the care of the plants to the packaging of the finished product, must adhere to the international standards of Good Agricultural and Collecting Practice (GACP) and European Good Manufacturing Practice (euGMP).
Ensuring maximum product transparency is essential to meet the needs of patients, doctors, pharmacists and regulators. This transparency is guaranteed by the laboratory analyses that are carried out during the various stages of production.

Therapeutic Components of Cannabis

Cannabis is a ‘phytocomplex,’ meaning it contains a diverse array of substances with pharmacological activity. However, only two are presently recognized as active ingredients of the plant:

- Tetrahydrocannabinol (THC);
- Cannabidiol (CBD).

Each Medical Cannabis variety contains these two compounds in unique and distinct proportions.
The substances most extensively studied for their pharmacological properties within the plant are:

- cannabinoids (around 150);
- terpenes (over 200);
- flavonoids (around 20).

Additionally, there is an abundance of other important molecules, such as amino acids, fatty acids, alkaloids, etc.[1];[2]
Given the phytocomplex nature of cannabis, it is well established that it interacts with a multitude of different receptors and cellular systems, defined as "network pharmacology."
This characteristic allows Medical Cannabis to be employed in treating very different symptoms, at different times of the day, and among epidemiologically distinct groups of people. Understanding the properties of the components of the plant enables the customization of cannabis therapy for everyone, minimizing side effects and maximizing therapeutic benefits.

Characteristic of Medical Cannabis varieties

Medical Cannabis varieties are usually categorized based on the:

- proportion of cannabinoids;
- terpene profile.

These plants originate from cannabis varieties that have been selectively bred by humans to exhibit specific characteristics.

Cannabinoids: General Aspects

Phytocannabinoids

The term cannabinoid is derived from the word cannabis. Until recently, it was believed that these compounds were only present in the Cannabis Sativa L plant, but recently they have been identified in other species, such as:[1] Rhododendron, the genus Radula, some legumes, as well as some mushrooms.

The prefix "phyto," derived from the Greek word "phytos" meaning plant, designates these cannabinoids as plant-derived, distinguishing them from the cannabinoids naturally produced within our body, known as endocannabinoids. However, the terms cannabinoids and phytocannabinoids can both be used to define the cannabinoids in the cannabis plant.

From a biochemical perspective, phytocannabinoids are lipidic compounds belonging to the class of terpenophenols.

Phytocannabinoids are bioactive compounds that interact with the human organism, particularly the Endocannabinoid System, giving rise to psychotropic and/or therapeutic effects. Among the approximately 550 compounds identified in cannabis, around 150 are classified as phytocannabinoids. The production of phytocannabinoids by the plant is essential for its survival.

Similar to how our body synthesizes endocannabinoids for the regulation of homeostasis, cannabis produces phytocannabinoids to defend itself against exogenous substances, ensuring survival in the face of adversity. Phytocannabinoids act as a defense mechanism, protecting the plant from environmental hazards such as insects, free radicals, pathogens, UV radiation, and adverse weather conditions.

The Biosynthesis of Cannabinoids

In the cannabis plant, the biosynthesis of phytocannabinoids—or, simply, cannabinoids-involves a highly intricate network of enzymatic processes

and occurs within specialized structures known as "glandular trichomes."[3] Cannabinoids are synthesized and accumulated in the plant as carboxylic acids, or, 'pre-cannabinoids.' These cannabinoids can undergo decarboxylation, a process through which they lose their acidic portion and become neutral. For instance, cannabigerolic acid (CBGA), produced by the plant, can be decarboxylated to form cannabigerol (CBG), as explained later in this chapter.[4]

CBGA is the direct precursor of tetrahydrocannabinolic acid (THCA), as well as the precursor of cannabidiolic acid (CBDA) and cannabichromenic acid (CBCA).[4] In general, nearly all cannabinoid biosynthetic reactions involve enzymatic catalysis. Catalysis is a chemical phenomenon by which the speed of a reaction is increased by the intervention of a substance called a catalyst, which is not consumed by the reaction itself.

In biology, the catalysts are enzymes. Therefore, the various conversions of CBGA to form other cannabinoids are enzymatically catalyzed. For each reaction, a specific enzyme, known as a synthase, has been identified:[4]

- THCA synthase;
- CBDA synthase;
- CBCA synthase.

The distinct expression of CBDA and THCA synthases in a cannabis variety determines the plant's different chemical production, known as its chemotype.

CBDA and THCA synthases share high similarity in terms of their affinity (binding capacity) for CBGA and their catalytic capacity. CBCA synthase, on the other hand, exhibits a higher affinity for its substrate (CBGA), but its catalytic capacity is lower, resulting in a reduced production of CBCA. This is the reason why CBCA is present in low levels and thus considered a minor cannabinoid and cannabis varieties are mainly distinguished on the basis of their THC:CBD ratio.[4]

The CBD and THC chemotypes are regulated by a gene called B, which has

two forms or alleles, B_D and B_T. These alleles determine the formation of CBD and THC chemotypes, respectively (the characteristic of THC and CBD will be analysed in detail in the subsequent sub-chapters).[5]

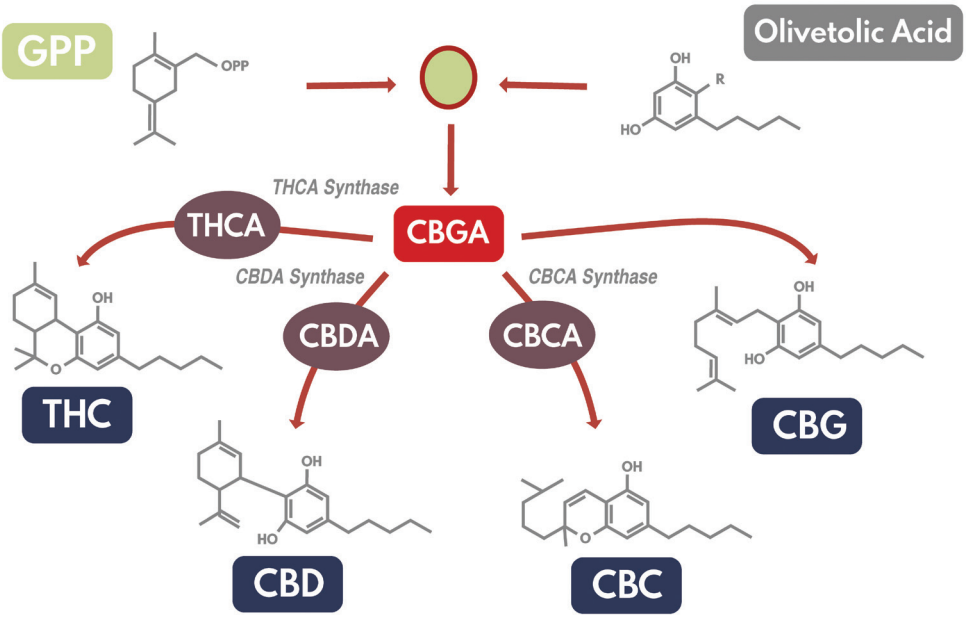

Image 13. Biosynthesis pathways of phytocannabinoids: CBGA, the precursor of phytocannabinoids, is synthesized from the geranyl diphosphate (GPP) prenylation of olivetolic acid, a reaction catalyzed by olivetolate geranyltransferase (GOT) (courtesy of Renate Mich, www.officinavisioni.com).

Varieties with high % of THC

Plants with a THC-dominant profile, which are the most prevalent, possess a gene characterized as B_T/B_T, indicating that both alleles or forms of the gene are B_T.[5]

These varieties contain high concentrations of the acidic cannabinoid THCA, which can be decarboxylated to produce THC, usually ranging between 5 and 26%.

Varieties with high % of CBD

Plants with a high CBD content have a gene characterized as B_D/B_D (this means that both alleles, or forms of the gene, are BD).[5] These cannabis

varieties boast high levels of the cannabinoid CBDA (or cannabidiolic acid). The percentage of CBD that can be obtained from these varieties by decarboxylation is usually between 5 and 20% as a final product, with THC levels falling often below 1%.

Varieties with Balanced % of THC: CBD

Finally, there are varieties that contain medium to high concentrations of both THCA and CBDA, often in a 1:1 ratio. Through decarboxylation of these varieties, THC percentages between 5-10% and CBD percentages between 6-15% can be obtained.

Decarboxylation: How Heat transforms Cannabis

Cannabis varieties are categorized based on the proportion (usually percentage) of the 'neutral' cannabinoids THC and CBD. These molecules are present in very low concentrations in the cannabis inflorescences during harvest, as they are only obtained through a transformative process.

This transformation, known as decarboxylation, involves the application of heat at approximately 100/120 °C to facilitate the removal of a CO_2 molecule, leading to the conversion of acidic cannabinoids into neutral cannabinoids.[6]

Variables like adjusting the duration, temperature, and solutions employed during the decarboxylation of inflorescences contribute to variations in the final yield of cannabinoids.[7]

Effects of Cannabis with a high THC %

Cannabis plants with a high THCA content can be used, after decarboxylation, to obtain Medical Cannabis with a high THC concentration.

THC and some of its isomers are cannabinoids known to potentially induce psychotropic effects, such as variations in alertness and/or mood, depending on the dosage.

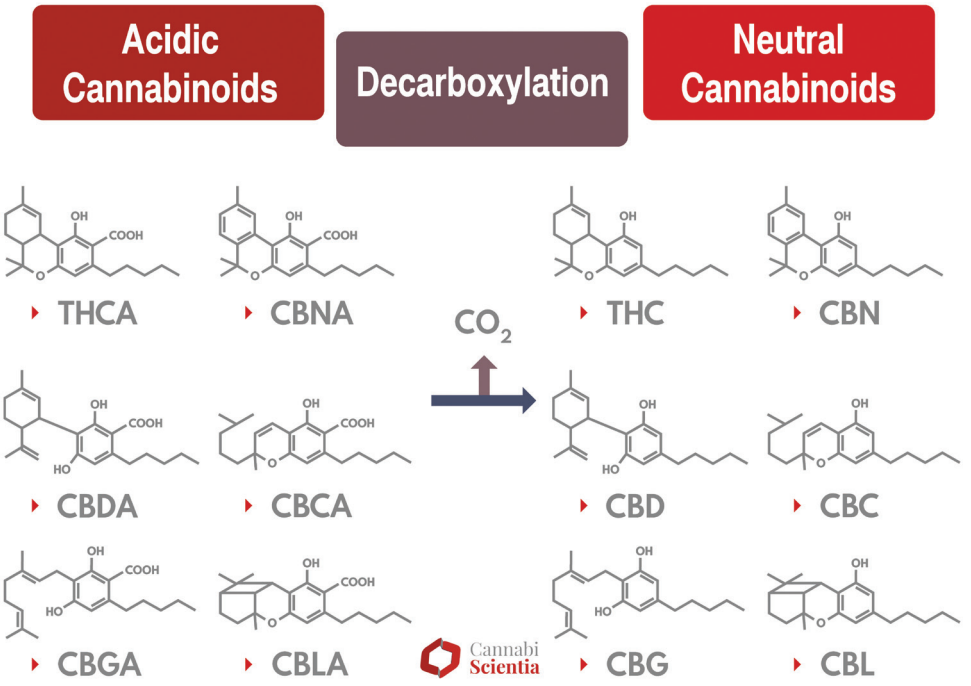

Image 14. Decarboxylation of main cannabinoids (courtesy of Renate Mich, www.officinavisioni.com).

The effects of THC include:[8]

- euphoria;
- relaxation (including muscle relaxation);
- drowsiness;
- asthenia;
- analgesia;
- appetite stimulation;
- antiemesis.

Medical Cannabis with a high THC content is indicated mainly, but not exclusively, for controlling muscle spasms, chronic pain and increasing appetite.

There is considerable personal variability in the effects of cannabis with a high THC concentration, and the main side effects consist of:[9]

- narcosis;
- dizziness;
- nausea;
- tachycardia;
- reduced cognitive abilities;
- impaired coordination and work performance;
- psychotic episodes or panic attacks.

While these effects are acute and, therefore, do not extend beyond the time THC is present in the plasma, it should be considered to avoid administering cannabis with a high THC concentration to patients with heart disease or mental health disorders, as it may increase the risk of exacerbating symptoms.[10]

Effects of Cannabis with a high CBD %

CBD and derivatives are cannabinoids that do not induce psychotomimetic effects.[11] Cannabis plants with a high CBDA content can be used, after decarboxylation, to obtain Medicinal Cannabis with a high CBD concentration.[12] The most investigated effects of CBD are:[13]

- anti-inflammatory;
- anxiolytic and antipsychotic;
- neuroprotective;
- analgesic;
- anti-epileptic;
- antiemetic;
- inhibiting the proliferation of cancer cells.

Medical Cannabis with a high concentration of CBD is particularly used for:[13]

- regulating mood;
- controlling inflammatory disorders;

- decreasing convulsions (epilepsy);
- alleviating nausea;
- decreasing pain.

Depending on the condition, varying concentrations of THC may be required to optimize therapeutic effects.

Indica or Sativa?

The terms *Indica* and *Sativa* are botanical classifications that delineate the physical characteristics of a plant rather than the effects it induces.
The diverse effects elicited by different cannabis varieties are contingent upon their cannabinoid and other component concentrations, such as terpenes, collectively referred to as their *chemovar* composition, rather than their plant phenotype.
The outdated terms Sativa and Indica persist in the nomenclature of many countries, including the Czech Republic's legislation and numerous medical cannabis brands.
For informational purposes, we provide below the primary effects traditionally associated with 'indica' and 'sativa,' although it's important to note that sativa- or indica-dominant varieties encompass plants with varying proportions of THC:CBD that influence their overall effects. It is crucial to recognize that this classification lacks a robust scientific foundation.

Indica-dominant Cannabis

In general, varieties classified as 'Indica' are associated with a predominance of analgesic and sedative effects, exerting a more pronounced influence on the body. This aligns with a higher percentage of components, such as the acyclic terpene myrcene, which is theorized to enhance THC-induced effects through various mechanisms.[19]

Sativa-dominant cannabis

Sativa varieties are commonly associated with predominantly cerebral effects. Sativa-dominant strains are often favored by consumers for daytime activities due to their typically energizing effects.[19]

Minor Cannabinoids

Minor cannabinoids refer to the lesser-known cannabinoids found in the cannabis plant, distinct from the major cannabinoids like THC and CBD. While THC and CBD are more extensively studied and present in higher concentrations, minor cannabinoids are present in smaller amounts. Although research on minor cannabinoids is ongoing, they are believed to contribute to the overall therapeutic effects of cannabis through interactions with the Endocannabinoid System.

Acidic Cannabinoids

As outlined above, via enzymatic reactions, cannabis plants naturally synthesize all cannabinoids in their acidic chemical form. Acidic cannabinoids are the predominant phytocannabinoids in raw cannabis plants. Acid cannabinoids have no psychotropic effects because they do not penetrate the blood-brain barrier (the network of capillaries that protects our brains), and interact mainly with the receptor system in the body's periphery.

Despite being less extensively researched, acidic cannabinoids such as CBDA (cannabidiolic acid) and THCA (tetrahydrocannabinolic acid) have shown distinct medicinal effects, including but not limited to addressing issues like nausea, pain, obesity, and neuroprotection. Importantly, these acid cannabinoids operate through mechanisms different from those associated with CBD and THC.[14]

As illustrated in a 2020 study, THCA demonstrated notable effects in a laboratory animal model of diet-induced obesity. It significantly decreased fat mass and body weight gain, improved glucose tolerance and insulin

resistance, and effectively prevented hepatic steatosis, adipogenesis, and macrophage infiltration in adipose tissue.[15]

The researchers also demonstrated the mechanism of action of this phytocannabinoid. THCA was identified as a partial and selective modulator of PPARγ receptors, exhibiting a reduced adipogenic (fat-stimulating) activity compared to the full PPARγ agonist rosiglitazone, commonly used in antidiabetic treatment. Additionally, THCA demonstrated potent neuroprotective activity by stimulating PPARγ, suggesting its potential consideration in the treatment of conditions like Huntington's disease and potentially other neurodegenerative and neuroinflammatory diseases.[16]

Given that THCA is inherently present in the cannabis plant and is converted into THC only through decarboxylation, there is a hypothesis that raw cannabis might have potential effectiveness in treating diabetes. (For further details on the role of THCA in metabolic diseases, refer to the subsequent chapters.)

Cannabigerol (CBG)

In addition to THC or CBD chemotypes, there are also CBG-dominant plants, which have a defined B0 allele that causes a defect in the synthesis of the other cannabinoids.[4]

CBG—present in the cannabis plant at low concentrations—has several properties:

- produces no psychotropic effects;
- can be easily and inexpensively synthesised in the laboratory from olivetol and geraniol, readily available compounds.

It has strong antibacterial activity and does not induce antimicrobial resistance (an in-depth discussion of the pharmacology of CBG will be presented in the next chapters).

Varinic Derivatives

The cannabinoids we have discussed so far are the most common and have a pentyl side chain (with 5 carbon atoms). These compounds are all derived from a common 21-carbon-atom (C) precursor, namely the cannabigerolic acid (CBGA).[4]

Within the cannabis plant, there are also propyl (3-carbon atom) homologues of CBD, THC, CBC and CBG, referred to as cannabidivarin (CBDV), delta 9-tetrahydrocannabivarin (THCV), cannabichromevarin (CBCV) and cannabigerovarin (CBGV).

All these compounds originate from a shared precursor with 19 carbon atoms, known as cannabigerovarinic acid (CBGVA), similar to how CBGA is the common precursor for pentyls.[4]

These cannabinoids, along with numerous others continually being identified through scientific research, present future prospects and, in some cases, have potential applications in the present.[17]

CBDV is currently an orphan drug for Rett and Fragile X syndrome.

In addition, clinical trials are ongoing in which the effects of CBDV are being tested for:

- autism spectrum disorder (ASD);
- neuropathic pain;
- partial epilepsies;
- pervasive childhood developmental disorders;
- Prader-Willi syndrome.

Even for THCV, which exhibits an opposite action to THC, several clinical studies have been carried out, revealing its potential effectiveness in controlling glycaemia in subjects with type 2 diabetes and counteracting the side effects of THC.[18] (The pharmacology of THCV and CBDV will be discussed in more detail in subsequent chapters.)

Terpenes and Flavonoids

Medical Cannabis varieties are also distinguished based on their terpeno-phenolic profile, indicating the proportion of molecules that give different fragrances (*terpenes*) and pigmentations (*flavonoids*) to the plants. Terpenes, along with flavonoids, define the plant's unique terpeno-phenolic profile.

These substances could play an important role in mediating or modulating the therapeutic effects of cannabinoids.[19]

Overview of Terpenes in Cannabis

Terpenes not only contribute to the plant's fragrance and pigmentation but also significantly influence its therapeutic properties. Terpenes can enhance the effectiveness of cannabinoids by facilitating their brain uptake and modifying their pharmacological effects.

Key Functions and Interactions

Terpenes and cannabinoids, produced from the common precursor geranyl pyrophosphate (GPP), are synthesized in the cannabis plant's trichomes. They are known for creating the 'entourage effect,' where their combined action produces more potent effects than any single compound alone. This synergistic interaction is crucial for the therapeutic potential of cannabis, enhancing its analgesic, anti-inflammatory, and anti-anxiety properties.

Notable Terpenes and Their Effects

- *β-Caryophyllene*: A sesquiterpene that activates CB2 receptors and exhibits strong anti-inflammatory properties, β-caryophyllene holds promise for treating inflammatory conditions.
- *β-Myrcene*: Known for its analgesic and anti-inflammatory effects, β-myrcene enhances the permeability of the blood-brain barrier, which helps cannabinoids like THC to exert stronger effects. It also

affects THC's affinity for CB1 receptors, potentially increasing the analgesic efficacy of cannabis.

Role of Flavonoids

Flavonoids, another key group of compounds in cannabis, are antioxidants and anti-inflammatories that protect the plant from environmental stressors. Unique flavonoids in cannabis, such as Cannflavins, complement the anti-inflammatory actions of terpenes and cannabinoids.

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2.2. Delivery Methods and Pharmacokinetics of Medical Cannabis

Medical cannabis offers various routes of administration, each influencing the therapeutic effects differently depending on the chosen method and product type.

Pharmacokinetics of Medicinal Cannabis

Pharmacokinetics involve 4 processes that regulate the achievement and maintenance of an optimal drug concentration within the body:

- absorption;
- distribution;
- metabolism;
- elimination.

Absorption

Absorption refers to the process through which the drug enters the body—i.e., into the bloodstream—from the site of administration. Absorption of Medical Cannabis varies depending on the chosen route of administration, as discussed in the following paragraphs.

The main methods of administering Medical Cannabis are:

- inhalation (via the respiratory tract);
- oral ingestion (by mouth);
- topical application (through the skin).

Distribution

Distribution of a drug refers to the process by which the drug spreads throughout the body after it enters the bloodstream. This involves the movement of the drug from the bloodstream into various tissues and organs where it exerts its pharmacological effects. The distribution of a drug depends on factors such as its chemical properties, the blood flow to different tissues, the presence of binding proteins, and the permeability of cell membranes.

Cannabinoids are lipophilic molecules that are rapidly distributed to highly perfused tissues such as the lungs, heart, brain and liver. In a second phase, called the 'β-elimination phase,' cannabinoids are distributed to lipophilic tissues, such as the adipose tissue, where they are stored for an extended duration.[2]

Metabolism

Metabolism refers to the biochemical processes through which a drug is chemically altered within the body, to facilitate its elimination through processes such as oxidation, reduction, or hydrolysis. This process is essential for the body to eliminate potentially harmful substances and to regulate the concentration of drugs in the bloodstream.

When cannabinoids are ingested orally, they are absorbed through the gastrointestinal tract and transported to the liver via the hepatic portal vein. In the liver, they undergo extensive first-pass metabolism, where enzymes break down the cannabinoids into various metabolites.

The primary enzyme responsible for metabolizing cannabinoids in the liver is cytochrome P450 (CYP450), particularly the CYP3A and CYP2C isoforms. These enzymes catalyze chemical reactions that convert cannabinoids into metabolites that are more water-soluble and easier for the body to excrete through urine or bile.

Additionally, cannabinoids can undergo metabolism in other tissues besides the liver, such as the brain, intestine, and lungs, albeit to a lesser extent compared to the liver. This decentralized metabolism contributes to the overall clearance of cannabinoids from the body.

For instance, the psychoactive cannabinoid tetrahydrocannabinol (THC) is metabolized first into 11-hydroxy-THC (11-OH-THC), an active metabolite with similar or greater potency, and, during a second step, into non-psychotropic molecules such as 11-Nor-9-Carboxy-THC (THCCOOH), a metabolite that is more soluble in water and thus eliminable.[3] Metabolic differences exist, and they can vary significantly both between individuals (inter-subject variability) and within the same individual over time (intra-subject variability). These differences can be influenced by various factors, including genetic makeup, age, sex, diet, liver function, and the presence of any underlying medical conditions.

Genetic variations in enzymes involved in drug metabolism, such as the cytochrome P450 enzymes mentioned earlier, can significantly impact how cannabinoids are metabolized in the body. For example, individuals with certain genetic polymorphisms may have altered enzyme activity, affecting the rate at which cannabinoids are broken down and cleared from the body. Age-related changes in metabolic function, such as decreased liver enzyme activity in older adults, can also affect cannabinoid metabolism.

Similarly, differences in metabolism between males and females have been observed, potentially due to hormonal influences.

Dietary factors, such as the consumption of fatty foods alongside cannabinoid administration, can influence the absorption and metabolism of cannabinoids. Liver function plays a critical role in cannabinoid metabolism, so any impairment in liver function, such as liver disease, can alter the metabolic pathways and clearance of cannabinoids from the body.

Furthermore, individual health conditions or medications may interact with cannabinoid metabolism, leading to variability in how cannabinoids are processed and eliminated.

Elimination

Elimination encompasses the processes involved in completely removing a drug from the body. In the case of cannabinoids, elimination occurs primarily through feces and urine. The plasma elimination half-life of cannabinoids typically ranges from 1 to 4 days. Within 5 days following a dose, approximately 80-90% of THC is excreted from the body, while a single dose of cannabinoids may take around 5 weeks for complete elimination.

It's important to note that these elimination estimates can significantly extend for chronic cannabis users. In such cases, THC metabolites, particularly THC-COOH-glucuronide, can still be detected in urine for up to 80 days or more following the last use. This prolonged detection period reflects the accumulation of cannabinoids and their metabolites in the body over time, especially in chronic users, due to repeated exposure and slower clearance rates.

The slow elimination period of cannabinoids is due to their prolonged release from adipose and other tissues, facilitated by their high lipophilicity, and the subsequent re-entry into the circulatory system.

Unlike THC, a significant proportion of cannabidiol (CBD) is excreted unchanged.

Choosing the most appropriate route of administration

The administration route employed with Medicinal Cannabis are:

- systemic;
- local.

Table 1.

SYSTEMIC	LOCAL
Inhalation	Topical
Oral	Rectal/vaginal
Oromucosal / sublingual	Ocular
Rectal*	Transdermal*

Routes of administration—centrally vs peripherally acting.
** Literature debates over systemic vs local application. The outcome heavily depends on the dosage.*

The selection of the administration method should primarily consider the symptoms to be treated, to determine whether a systemic or local effect of Medical Cannabis is required.
In certain instances, the same patient may require both uses, depending on symptomatology, time of day or individual preference.
The main difference between systemic and local administration lies in the fact that a systemic intake of cannabis may cause psychotropic effects, whereas a local intake does not, as it does not penetrate the central nervous system (CNS).

Systemic Administration of Medical Cannabis

Administration with a systemic effect involves the introduction of Medical Cannabis derivatives into the bloodstream, allowing it to circulate throughout the body and reach its target site of action, which may be located at a considerable distance from the initial site of application. This method ensures that the therapeutic compounds of the plant are dis-

tributed widely and can exert their effects on various tissues and organs throughout the body.

The risk of experiencing side effects or psychotropic effects is higher with systemic administration due to the potential for cannabinoids—like THC and its isomers—to exert effects in the Central Nervous System. In contrast, local administration confines the therapeutic effects to the immediate area of application, reducing the likelihood of systemic side effects. The routes of administration for systemic action of Medical Cannabis include:

- Inhalation (smoking or vaporization);
- Oral ingestion (extracts, edibles, capsules, tinctures and oils, etc);
- Sublingual (under the tongue- technically transdermal or mucosal);
- Transdermal (patches or certain creams);
- Rectal/vaginal suppositories.

Systemic Medical Cannabis preparations exhibit considerable variability, particularly in three key pharmacokinetic properties: absorption, distribution, and metabolism.

Administration by Inhalation

Intake via inhalation ensures a quicker onset of effects compared to oral administration, although the duration of effects is typically shorter. Inhalation is commonly accomplished using a vaporizer, which is a CE-marked medical device that utilizes hot, filtered air. Ordinary aerosol devices are not suitable for this purpose. Cannabis inflorescences are placed into the vaporizer; The filter is at the air intake, before the air passes through the plant material, which is then consumed in vapor form.

Pharmacokinetics of Inhalation

Following inhalation, Medical Cannabis enters the bloodstream directly, resulting in a high concentration of absorbed cannabinoids. It's estimated that around 10-35% of the initial THC reaches the circulatory system following this route of administration.

The bioavailability of THC is therefore around 25%, with great variability among individuals. Pharmacological effect begins typically within a few minutes of inhalation, and the maximum plasma concentration of THC, known as *Cmax,* is achieved between 6 and 10 minutes after the first inhalation. These effects typically decline within 3-4 hours, with THC levels reduced to around 20% of Cmax within 30 minutes.[4]

Inhalation: Appropriate Candidates

Inhalation administration is ideal for individuals experiencing acute issues such as pain, muscle spasms, and nausea, as it offers rapid and intense relief, although the effects do not last as long as with oral administration.

Guidelines for Dosing

The physician prescribes the quantity of inflorescences to be used, the intervals between successive inhalations, and the frequency of inhalations throughout the day.

Factors such as the temperature of the device, the number, duration, intensity, and interval between inhalations influence the maximum plasma concentrations of cannabinoids and terpenes-phenols, as well as the peak time (the time at which the maximum plasma concentration is reached). These factors facilitate self-titration of the dosage based on symptoms.

Oral Administration

Medical Cannabis can be administered by mouth (*oral administration*), or by placing it under the tongue (*sublingual*), from where it is then absorbed.

Pharmacokinetics of Oral Administration

Oral administration of cannabis involves consuming cannabis products by mouth, typically in the form of capsules, edibles, or tinctures. The product is usually swallowed with water or another beverage. After ingestion, the cannabis product enters the stomach, where it begins to break down. Stomach acid and digestive enzymes start the process of breaking down the com-

ponents of the cannabis product. The partially digested cannabis product moves into the small intestine, where most of the absorption takes place. The cannabinoids and other active compounds in the cannabis product are absorbed through the lining of the small intestine and enter the bloodstream. Once absorbed, the cannabinoids are carried to the liver through the portal vein. In the liver, they undergo metabolic processing, known as the first-pass effect. During this process, enzymes in the liver break down some of the cannabinoids before they enter systemic circulation. After passing through the liver, the remaining cannabinoids enter systemic circulation and are distributed throughout the body via the bloodstream. From there, they can exert their effects on various tissues and organs.

Following oral intake of cannabis, a relatively small percentage of THC, typically between 10-20%, enters the circulatory system. This limited bioavailability is primarily attributed to extensive hepatic metabolism in the liver and the poor solubility of THC in water. Similarly, CBD exhibits comparable bioavailability and oral absorption characteristics to THC.

The preparations used for oral administration of Medical Cannabis can vary significantly. Factors such as temperature, processing duration, the use of carriers (e.g., olive oil), and solvents (e.g. alcohol) for extraction can influence the absorption and bioavailability of cannabis compounds, thereby affecting the resulting effects.

The preparations mainly used for oral administration are:

- Oils (extracts): Cannabis oils are concentrated extracts of cannabinoids that can be swallowed directly or mixed with food or beverages. Cannabis oils are typically extracted using methods such as CO2 extraction, ethanol extraction, or solventless methods like cold pressing and are subsequently dissolved in a medium-chain triglyceride (MCT) or olive oil, coconut oil, or occasionally in hemp or sunflower seed oil; the patient uses a dropper to dose. They can also be used topically for localized relief.
- Tinctures: Cannabis tinctures are made by steeping cannabis flower or concentrates in alcohol or glycerin. The cannabinoids and ter-

penes are extracted into the liquid solution. Cannabis tinctures can be administered orally by placing drops under the tongue (sublingually), and can also be added to food or beverages for consumption.

- Oromucosal spray (Sativex®): Cannabis-infused sprays are designed for oral use and are sprayed directly into the mouth.
- Capsules: presumably the most compliant method of oral administration (no taste), but advisable only with patients with whom an optimal dosage has been established, as it cannot be portioned. Cannabis capsules are filled with cannabis oil or powdered cannabis extract and are swallowed like any other pill.
- Herbal tea (Decoction) or opening capsules to brew as tea (herbal tea capsules): cannabis-infused tea which requires the patient or caretaker to actively prepare their own product (difficult standardization of final dosing).

These products are primarily distinguished by their method of intake, preparation, and subsequent decarboxylation of the acidic cannabinoids present in the plant.

Cannabis Oil-Extracts

Cannabis plant extracts—or oils—are rich in cannabinoids and terpenes, providing a concentrated dose of these compounds. Oils are typically decarboxylated products and differ in the method used to extract cannabinoids. The cannabinoid composition of each plant extract varies depending on the variety. These extracts are termed oils due to their viscous consistency or because they are dissolved in carrier oils (such as olive, MCT, sunflower, peanut, coconut, or hemp oil) to facilitate administration. The color of cannabis extracts can range from shades of yellow to green and is usually clear, with potential traces of plant material at the bottom. The consistency and final color may vary based on the THC content and the presence of waxes and lipids, which contribute to the adhesive properties of the extract.[7]

Image 15. Example of cannabis extracts.

Tinctures

Tinctures of Medical Cannabis are available in both alcoholic and glycolic forms. These tinctures utilize decarboxylated cannabis and are typically administered sublingually using a dropper. The main distinction between the two types of tinctures lies in the extraction process of cannabinoids from the cannabis material. Alcoholic tinctures extract cannabinoids at ambient temperatures, while glycolic tinctures require heat for extraction. The choice between the two is often based on personal preference regarding the use of alcohol. Alcoholic tinctures should be stored away from light and heat to prevent alcohol evaporation, and it's recommended to keep the container tightly closed and refrigerated. Alcoholic tinctures can also be easily administered using catheters, nasogastric tubes, or PEG tubes. Glycol tinctures can also be utilized for electronic cigarettes (e-cigs).[9]

Oromucosal Spray

Oromucosal sprays are another method of administering cannabis, where oils are formulated into a spray and often mixed with 1% salt and stored with a piece of pure silver to prevent microbial contamination. These sprays are applied under the tongue, similar to oils. A well-known example of a standardized spray formulation is *Nabiximols* or Sativex®, derived from two cannabis varieties with one high in THC and the other high in CBD. The

cannabinoids are balanced in exact proportions and dissolved in an alcohol-based solution, dispensed from a spray bottle with measured doses for sublingual application. However, prolonged use of oromucosal sprays may in certain cases lead to oral mucosal lesions, especially in patients undergoing chemotherapy or other treatments with symptoms like dry mouth and difficulty swallowing. Hence, caution is advised in such cases.[8]

Capsules

Due to the ease of use, capsules are a very important and used route of administration. The capsules may be either encapsulated cannabis oil, i.e. capsules containing cannabinoids dissolved in oil: tiny gastro-resistant capsules to be swallowed with a little water; or they may be cannabis inflorescences (any variety) at the exact dose required by the doctor, chopped and decarboxylated and combined with maltodextrins—sweet substances (also for diabetics)—and coconut oil (certified pharmaceutical grade), added separately, directly by the pharmacist at a later date.
These products are ready-to-use. Once swallowed, the capsule opens, and the drug is released and absorbed into the stomach and intestines.
Unlike oils taken sublingually, the onset of effects with capsules is slower. The dosage is fixed and precise, but the disadvantage is that they cannot be fractionated.

Herbal Tea (decoction) or herbal tea capsules

Herbal tea (decoction) or herbal tea capsules are often recommended as the initial therapy for patients new to Medical Cannabis, particularly for older individuals seeking neuroprotective effects or relief from chronic pain. They can also help alleviate symptoms of gastrointestinal issues such as cramps, nausea, and diarrhea. Additionally, these preparations are beneficial for regulating sleep cycles and managing symptoms of premenstrual syndrome like cramps, bloating, and mood swings. However, it's important to note that relying solely on decoctions for patients with severe conditions is not advisable. They are better suited as complementary forms of

administration alongside other methods. This is because decoctions have limitations in efficiently decarboxylating and extracting cannabinoids due to the high temperature (approximately 100 °C) and the water-based extraction matrix, which is not optimal for lipophilic compounds like cannabinoids. As a result, cannabis decoctions typically contain a lower percentage of decarboxylated cannabinoids. Moreover, the absorption of cannabinoids from herbal teas varies depending on factors such as how the tea is strained and whether it's consumed with or without food. This variability makes dosing unreliable and unpredictable, with differences even among different types of teas and depending on the container used (plastic containers are not recommended).[6]

Oral Administration: Appropriate Candidates

Oral administration of Medical Cannabis is recommended for patients experiencing chronic conditions such as chronic pain, inflammation, and neurodegeneration. Oral administration is generally preferred for both pediatric and adult patients, as it often ensures better therapeutic compliance compared to inhalation. Additionally, certain tinctures can be administered through PEG (percutaneous endoscopic gastrostomy) and NG-tube (nasogastric tube) for patients who are unable to swallow or have difficulty with oral intake.

Timing of Oral Administration

The peak plasma concentrations of THC achieved through oral administration are approximately one-tenth of those obtained through inhalation. The maximum effect is typically reached within 2 to 4 hours after ingestion and can last up to 12 hours. It is important to note that the ratio of THC to 11-hydroxy-THC is different when consuming cannabis by ingestion vs inhalation, since inhaled cannabis bypasses the initial first-pass metabolism and thus results in lower levels of the more potent 11-hydroxy-THC.
After oral administration, it takes 30 to 90 minutes for the pharmacological effect to begin, with cases of up to 3 hours, depending on the preparation, food intake and individual metabolism. To avoid or diminish experienc-

ing side effects, it is crucial for the treating physician to be aware of the cannabinoid content of the prescribed preparation. Additionally, patients should wait at least 3 hours before considering a new dosage. Patients should also be aware of the long duration of action, of up to 12 hours.

Sublingual Administration of Medical Cannabis

Sublingual intake of medical cannabis involves placing cannabis extracts, tinctures or spray under the tongue and allowing them to absorb directly into the bloodstream through the mucous membranes. When absorbed sublingually, the product skips first-pass metabolism and enters the bloodstream directly, so the plasma concentration of cannabinoids is slightly higher.[5] Sublingual administration allows for precise dosage control, as the number of drops or sprays can be easily measured using a dropper or spray bottle.

Local Administration of Medical Cannabis

Local administration of Medical Cannabis involves applying cannabis-based products directly to a specific area of the body for localized symptom relief. This method allows for targeted treatment of pain, inflammation, or other conditions affecting a particular area without affecting the rest of the body to the same extent as systemic administration methods. In the existing literature, there are no documented cases of psychoactive effects resulting from topical preparations. This is because the concentration of cannabinoids in these formulations is typically not sufficient to penetrate the skin barrier and enter the circulatory system. As a result, topical applications primarily provide localized relief without inducing psychoactive effects.
Typical topical formulations include:

- Topical gels and creams;
- Transdermal patches, a method that is not yet widely used in Europe, (but present in North America);[10]
- Eyedrops;
- Suppositories.

Topical Preparations: Transdermal Patches, Gels and Creams

Cannabis oil can be applied directly to the skin in the case of skin cancers, burns, ulcers or warts.

For topical gels and creams, the selection of the "constituent" or the "basic ointment" is a critical aspect in formulating topical preparations. This constituent determines the diffusion properties of the ointment and can be adjusted according to the specific requirements of the formulation. Substances containing ceramides, such as beeswax and lanolin or jojoba oil, are useful for medium diffusion combined with reconstitution of the upper-dermal layer with fatty acids. Vegetable oils provide moderate and slow diffusion, resulting in limited penetration into deeper layers of the skin.

These preparations are indicated for patients with arthritis, skin problems (psoriasis, dermatitis) or with topical lesions (hemorrhoids, cancers, ulcers) or for localized muscle and/or joint pain.

Transdermal patches are adhesive patches infused with cannabis extracts that deliver cannabinoids through the skin and into the bloodstream. These patches are designed to provide sustained release of cannabinoids over an extended period, offering long-lasting relief from symptoms. Transdermal patches are commonly used for pain management and may contain a combination of THC and CBD or other cannabinoids.

Other Methods of Administration

Ocular administration

Cannabis eye drops allow ocular administration of cannabinoids. Unlike inhalation or oral administration, this method primarily affects the eyes locally rather than producing systemic effects and does not induce psychotropic effects. Cannabis eye drops are used by patients suffering from conditions such as glaucoma or corneal neuropathic pain, as well as for the prevention of cataracts.[11]

Utilizing natural or synthetic cannabinoid directly in the eyes presents a challenge due to their highly lipophilic (and therefore hydrophobic) nature,

making it difficult for cannabis oil formulations to dissolve in water. This poses a significant obstacle, as cannabinoid-based must penetrate the watery tear layer above the cornea to reach the eye.

It has been shown that various microemulsions and cyclodextrins can improve the corneal penetration of cannabinoids. These formulations have been tested for their ability to lower intraocular pressure and pain– with good results.[13];[14]

These products must be manufactured in sterile environments and may cause eye inflammation, depending on the specific preparation. It is currently not a regulated method in most European countries.

Suppositories

Suppositories are designed to be inserted into bodily orifices such as the rectum or vagina, where they dissolve, soften, or melt, thus releasing cannabinoids locally, exerting both a localized and systemic effect. This method, by skipping first-pass metabolism usually encountered with oral administration, allows a greater proportion of THC to reach the circulatory stream than from ingested cannabis, and less psychotropic effects (less 11-OH-THC it's produced, which is more psychoactive than THC). Nevertheless, suppositories are deemed more effective for addressing localized issues and have demonstrated good clinical outcomes when employed for conditions such as hemorrhoids and vulvodynia.

On the contrary, relying on suppositories as an efficient method for systemic intake, raises doubts. In oncological patients, where medium to high concentrations of cannabinoids are often required, cannabis suppositories are recommended in conjunction with other methods of intake, such as sublingual drops.

Vaginal suppositories are effective in relieving pain, such as menstrual cramps and endometriosis, and provide antibacterial effects. Women with hormonal imbalance problems, such as a lack of menstrual regularity, have also experienced excellent results in restoring normal vaginal microbial balance, thanks to suppositories.[12]

Table 2.

	Oil	Extract/resins	Capsules	Tea	Tinctures	Inhalation	Topical
Belgium	X		X				X
Czech Republic	X	X	X	X		X	X
Denmark	X		X	X			X
Germany	X	X	X		X	X	X
Ireland	X	X	X			X	
Italy	X	X	X	X	X	X	X
Malta	X					X	
Poland	X					X	
Portugal	X		X			X	
Sweden	X					X	
Switzerland	X	X	X	X		X	X
UK	X	X	X			X	

Routes of administration permitted by law in some European countries.

Precautions and Possible Side Effects

Cannabis and its derivatives are generally well tolerated. Even in experiments on primates where the highest dosages (over 9000 mg/kg) were administered, no deaths were reported. With Medical Cannabis, the concept of 'personalized medicine' should be always applied. Personalized medicine with Medical Cannabis involves tailoring cannabis-based treatments to individual patients based on factors such as genetics, medical history, symptom profile, and response to treatment. This approach recognizes that different patients may respond differently to cannabis-based therapies and aims to optimize treatment outcomes by matching specific products and dosages to each patient's unique needs.

It's important to note that cannabinoids typically exhibit a biphasic dose-response relationship, rather than a linear one. For this reason, side effects of cannabinoids are dose-dependent, meaning that they vary depending on the dosage administered.

For patients who have little to no experience with cannabis (cannabis-naïve), it's recommended to initiate therapy with low doses and gradually increase

them until the optimal dosage is determined for each individual, thereby minimizing any potential adverse effects. Conversely, for individuals who are already chronic users of cannabinoids, it may be necessary to implement protocols aimed at resetting receptor sensitivity to normal levels.

The most commonly observed acute effects are largely dependent on the psychotropic action of THC, whereby sedation, dizziness, euphoria, dysphoria, feelings of loss of control, short-term memory impairment, altered perception of time, and reduced psychomotor performance.

Physical effects include dry mouth, impaired movement, muscle relaxation, difficulty in articulating speech, increased heart rate, decreased blood pressure and dizziness. Patients may categorize these effects as either pleasant or unpleasant (e.g. muscle relaxation may be a desired effect.) As mentioned, acute effects depend on the dose and generally disappear within a few hours or 24 to 72 hours without specific treatment.

During long-term therapy, patients may experience tolerance, characterized by a diminished response to the drug due to repeated intake over time. This problem can usually be avoided simply by changing the variety of cannabis or the method of administration. Side effects may also exhibit tolerance and tend to diminish over time with continued use.

Cannabis has the potential to induce psychological dependence and subsequent withdrawal symptoms, although these phenomena are mainly observed in recreational users and are rarely associated with therapeutic dosages.

The use of cannabis with a high THC concentration should be carefully evaluated by the physician—in patients with a predisposition to psychosis, whether mild or severe. In particularly vulnerable individuals, the use of cannabis may lead to earlier onset of symptoms than in the absence of cannabis. However, cannabis products with less psychoactive effects may aid in symptom management.

The use of Medical Cannabis should be carefully evaluated in immunocompromised or cardiovascular patients, paediatric patients, or during pregnancy or breast-feeding.

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2.3. Pharmacology of Tetrahydrocannabinol (THC)

Pharmacodynamics of THC

Tetrahydrocannabinol (THC) is the main phytocannabinoid found in *Cannabis Sativa L.* plants. Typically, it is found in amounts ranging from 0.5-5% to 25-30%, depending on the variety. Chemically, THC is a substance with a structure resembling that of Anandamide—the amide of bliss—, the first endocannabinoid to be discovered in the 1990s. More specifically, it can be considered a benzopyran derivative with substitutions, including a hydroxide and several methyls. Its structure makes this compound very lipophilic, so it easily passes the blood-brain barrier and distributes well in the brain, where it exerts most of its effects by interacting with cannabinoid receptors.

THC primarily acts as a partial agonist at cannabinoid receptors, particularly CB1 and CB2 receptors, which are distributed throughout the central nervous system (CNS) and peripheral tissues. By binding to these receptors, THC exerts various effects on neurotransmission, neuroplasticity, and immune function.

CB1 receptors are predominantly found in the brain and spinal cord and are responsible for the psychoactive effects of THC.

Activation of CB1 receptors modulates neurotransmitter release, affecting processes such as pain perception, memory, appetite, and motor control.

The interaction with CB1 makes THC effective in the treatment of various pathological conditions, including:

- chronic pain;
- nausea and vomiting;
- anorexia from chemotherapy or AIDS;
- spasticity (such as that induced by multiple sclerosis or other pathological conditions);
- Gilles de la Tourette syndrome;

- glaucoma;
- potentially neurodegenerative diseases (such as Alzheimer's or Parkinson's);
- anxiety or depressive syndromes.

The interaction with CB1 receptors in the brain is also responsible for the main side effects of THC:

- nausea;
- dizziness;
- xerostomia (dry mouth);
- red eyes;
- increased anxiety and stress;
- euphoria;
- impairment of short-term memory;
- impaired motor coordination;
- catalepsy (abolition of voluntary muscle movements).

CB2 receptors are primarily located in immune cells and peripheral tissues, where they play a role in modulating immune responses and inflammation. THC's interaction with CB2 receptors contributes to its immunomodulatory and anti-inflammatory effects.

THC also interacts with other receptors:[2]

- Transient receptor potential vanilloid channels 2 (TRPV2): THC acts as an agonist at TRPV2 receptors. TRPV2 channels are involved in various physiological functions, including pain sensation, regulation of body temperature, and cell growth. Activation of TRPV2 receptors by THC may contribute to its analgesic effects and modulation of cellular processes.
- Transient receptor potential ankyrin type 1 (TRPA1): agonist; TRPA1 channels are known as "chemosensors" and are activated by vari-

ous chemical irritants and environmental stimuli. Activation of TRPA1 receptors by THC may mediate some of its sensory effects, such as the perception of taste, pain, and irritation.

- TRP subfamily M (TRPM8) receptor: antagonist. TRPM8 channels are primarily involved in sensing cold temperatures and are activated by menthol and other cooling agents. By antagonizing TRPM8 receptors, THC may modulate sensory processing related to temperature sensation.
- GPR55 Receptor (G protein-coupled receptor): it is a partial agonist of GPR55 receptors, which are involved in various physiological processes, including the modulation of pain, inflammation, and bone density.
- PPARs Receptors (Peroxisome Proliferator-Activated Receptors): it is a partial agonist of PPAR receptors, particularly the PPARγ receptor. The PPARγ receptor plays a role in the regulation of gene expression, inflammation, and metabolic processes.
- 5-HT Receptors: it can interact with different subtypes of serotonin receptors, particularly the 5-HT1A and 5-HT2A receptors. These receptors are involved in the regulation of mood, cognition, and perception. They also play a role in the emetic response, including nausea and vomiting. Its interaction with 5-HT receptors may be considered partial agonism.
- D2 Receptors (Dopamine): it may modulate dopamine release by interacting with D2 receptors as a partial agonist. Dopamine is a neurotransmitter associated with the reward system, motivation, and pleasure. D2 receptors also play a key role in motor control and movement regulation.
- Adenosine Receptors: it is also a partial agonist of adenosine receptors, particularly the A2A receptors. Activation of these receptors can modulate neurotransmitter release and influence various physiological processes, including sleep-wake cycles and inflammation.

The THC molecule interacts with various molecular targets present in our body, beyond receptors, such as enzymes; an example is:

- FAAH Enzyme (Fatty Acid Amide Hydrolase): it inhibits the activity of FAAH, an enzyme responsible for the degradation of endocannabinoids in the body. Inhibition of FAAH leads to increased levels of endocannabinoids such as anandamide, which may further contribute to the effects of THC.

Pharmacokinetics of THC

Data on the pharmacokinetics of THC are derived from studies on its synthetic counterpart, dronabinol.[3]

Absorption

Due to its high solubility, dronabinol exhibits nearly complete absorption, ranging from 90 to 95%, following a single oral dose. However, due to the interplay of hepatic first-pass metabolism and its considerable lipid solubility, only a fraction, typically 10 to 20%, of the administered dose reaches systemic circulation. After oral administration, dronabinol typically manifests its therapeutic effects within 0.5-1 hour, with a peak effect of 2-4 hours. Pharmacokinetic parameters reveal a maximum plasma concentration (Cmax) of approximately 1.32ng/mL with a median time to reach this peak concentration (Tmax) of 1.00 hours.

Distribution

Dronabinol exhibits a significant apparent volume of distribution, estimated to be around 10 L/kg.

Metabolism and elimination

THC is metabolized mainly in the liver, by cytochrome P450. 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) is the main active metabolite,

capable of inducing psychological and behavioral effects similar to THC. 11-OH-THC is then metabolized into 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH), the main inactive metabolite of THC. THC and 11-OH-THC are present in plasma in approximately equal concentrations, varying at time-point. Concentrations of THC and its metabolite peak approximately 0.5 to 4 hours after oral administration and decrease for several days.

THC is eliminated through urine and feces. The elimination half-life is around 4 hours, but THC remains in the body for a long time. A single dose can still be detected even after 36 hours.

Pharmacogenetic Properties of THC

The pharmacogenetic properties of THC refer to individual variations in drug response due to genetic differences. Certain genes involved in the metabolism and activity of THC can influence its effectiveness, susceptibility to side effects, clearance from the body, and interaction with other drugs. Some of the main pharmacogenetic properties of THC include:

- CYP2C9 Genotype (Cytochrome P450 2C9): CYP2C9 is an enzyme involved in the metabolism of THC. Genetic variants of this gene can affect its metabolic rate, which in turn may influence individual responses to the drug and interactions with other drugs metabolized by the same enzyme.
- CYP3A4 Genotype (Cytochrome P450 3A4): CYP3A4 is another enzyme involved in THC metabolism. Genetic variants of this gene can influence the rate at which THC is metabolized, and thus its clearance from the body and its interaction with other medications.
- PPAR-γ Genotype: THC can bind to and activate PPAR-γ receptors. Genetic variants of PPAR-γ may influence the response to THC's effects and the susceptibility to certain medical conditions associated with cannabinoid use.

- CB1 and CB2 Cannabinoid Receptor Genotypes: Genetic variants of the cannabinoid receptors CB1 and CB2 can influence individual responses to THC's effects and susceptibility to side effects.
- FAAH Gene Genotype: Genetic variants of FAAH can affect the degradation of THC and may potentially influence its effectiveness and the duration of its effects.

The pharmacogenetic properties of THC are still under investigation, and the interaction between genetics and THC response can be complex and influenced by many other environmental and individual factors.[4]

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2.3.1. Separating THC's Therapeutic Effects from the Side Effects

Tetrahydrocannabinol (THC) via CB1 is responsible for many of the therapeutic effects of cannabis, but also for the main side effects.
The interaction with CB1 receptors in the brain is also responsible for the main side effects of THC:

- euphoria;
- nausea;
- dizziness;
- dry mouth;

- eye redness;
- increased anxiety and stress;
- short-term memory impairment;
- impaired motor coordination;
- catalepsy (loss of voluntary muscle movement).

Several studies have shown that motor impairment and catalepsy are due to the action of THC on a specific area of the brain: the basal ganglia system.
Is it possible to separate the desired effects of THC from the undesired ones, so as to have a drug that is more manageable?

The Basal Ganglia

Various research has shown that motor impairment and catalepsy are due to the action of THC on a specific area of the brain: the basal ganglia system, rich in CB1 receptors.[1]
The basal ganglia are a group of brain neurons that mediate interactions between the cerebral cortex and the thalamus, essential for the control and coordination of motor activity. The central nucleus of the basal ganglia is the striatum.
Neurons of the striatum have the highest levels of CB1 cannabinoid receptor expression in the brain.
These neurons can be divided into 2 populations, which form:

- the indirect striatal pathways, which terminate in the region of the external Globus Pallidus;
- the direct striatal pathways, which terminate in the region of the Substantia Nigra reticulata.

This latter circuit, called the striatonigral circuit, is a potential target for explaining both the beneficial and deleterious effects of THC, due to its crucial role in regulating motor function and pain transmission.

At the neuronal level, CB1 receptors are mainly associated with the plasma membranes of axon terminals, where they regulate synaptic transmission. However, various studies show that CB1 receptors are also present in intracellular compartments, in particular associated with the mitochondria, organelles present in all animal cells that are responsible for energy production. CB1 receptors are thought to influence memory and sociability at the mitochondria level by modulating bioenergetic processes.
The existence of different subpopulations of CB1 receptors, located in different cellular compartments, suggests that their activation by cannabinoids could lead to distinct effects within the same circuit.

Separating the Therapeutic Effects of THC from the Side Effects[1]

In some cases, at least potentially, it is possible to separate the therapeutic effect of cannabis and THC from their adverse effects.
This is the conclusion reached by a recent study published in the journal *Neuron*.[1]
Researchers have shown that the activation of CB1 receptors at different subcellular locations, in the same neuronal circuit, can result in distinct behavior. CB1 receptors in the direct striatal pathway are in fact responsible for the multimodal action of THC which, acting on this neuronal circuit, induces both catalepsy and an anti-nociceptive effect (useful in cases of pain).
Catalepsy—a side effect—depends on THC's interaction with mitochondrial CB1 receptors, while the anti-nociceptive effect is induced by stimulation of neuronal membrane CB1 receptors.
Thus, by acting on different subcellular signaling pathways within the neurons, researchers were able to dissociate the analgesic effect from the catalepsy induced by an acute injection of THC or other synthetic cannabinoids.

THC: Separating Therapeutic and Side Effects

Every pharmacologically active substance, whether natural or synthetic, can induce side effects. It is often challenging to separate the therapeutic effects from the undesirable ones, as both result from the interaction of that compound with a specific receptor, or are inherent in its mechanism of action.

This was also thought to be the case with cannabis, although recent research seems to cast doubt on this paradigm. Indeed, it appears that the therapeutic and undesired action of the main component of cannabis, THC, depends on the interaction with different subcellular pools of CB1 receptors. Further supporting the possibility of separating therapeutic effects from side effects, another paper recently published in the *Journal of Medical Chemistry,* shows that peptide compounds similar to THC are able to induce analgesic effects without causing cognitive impairment.[2]

These results are crucial for a better understanding of the mechanisms of action of cannabis and for the development of new therapeutic strategies, based on its beneficial effects, such as analgesia, while avoiding its undesirable effects, such as catalepsy.

It remains valid what Paracelsus famously stated: "All things are poison, and nothing is without poison; the dose makes the poison." In the context of cannabis-based therapy, the true distinction between remedy and harm lies in the expert capacity to tailor the dose to the patient's individual needs—maximizing therapeutic outcomes while minimizing adverse effects.

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2.4. Pharmacology of Cannabidiol (CBD)

Cannabidiol (CBD) was the first phytocannabinoid identified in cannabis by Dr. Roger Adams in 1940.[1] Additionally, it has also been found in hops leaves and can be produced through chemical synthesis.

In the cannabis plant, it is produced in the form of cannabidiolic acid (CBDA), which is converted into CBD by decarboxylation.

Structurally, CBD is an isomer of THC. The two compounds have the same molecular formula (same number and type of atoms) but a different atomic spatial arrangement.[2] The CBD typically found in the cannabis plant has the double bond at position 2 of the non-benzoic ring.

Unlike THC, CBD does not induce intoxicating effects.

CBD is present in cannabis plants at concentrations ranging from less than 1% to approximately 15%. It can be extracted from these plants or produced synthetically in the form of crystals. CBD is the key component in drugs like Nabiximols/Sativex® (containing 2.7 mg THC and 2.5 mg CBD per 100 µL) and Epidiolex® (containing 100 mg of pure CBD per mL of product).

Pharmacodynamics

The pharmacological activity of CBD depends on its interaction with various receptors and enzymes, although its complete mechanism of action remains not fully understood. CBD interacts with a diverse array of molecular targets, with over 65 identified thus far. The primary targets of CBD include:[3];[4];[5];[6]

- CB1 receptor: acts indirectly or as a negative allosteric modulator;
- CB2 receptor: low-affinity agonist;
- adenosine receptors: A1 and A2 agonist;
- glycine receptors: GlyR agonist;
- G protein-coupled receptors (GPRs): GPR55 antagonist; GPR3, GPR6, GPR12 agonist;

- peroxisome proliferator-activated receptors (PPARs): PPARγ agonist;
- nicotinic acetylcholine receptor (nAchRs): α-7-nAChR antagonist;
- μ-δ opioid receptors: negative allosteric modulator;
- transient receptor potential vanilloid (TRPV) channels: low-potency full agonist of TRPV1, causes rapid desensitisation of TRPV1; agonist of TRPV2, TRPV3, TRPV4;
- transient receptor potential ankyrin type 1 (TRPA1): agonist;
- TRP subfamily M 8 (TRPM8) receptor: agonist;
- serotonergic receptors: 5-HT1A agonist;
- voltage-gated sodium channels (VGSCs): CBD can block VGSCs, without inducing anticonvulsant effects;
- voltage-gated Calcium Channels (VGCCs): inhibitory effect;
- fatty acid amide hydrolase (FAAH), an enzyme that metabolises endocannabinoids: inhibitory effect, especially at high concentrations;
- cyclooxygenases and lipoxygenases: inhibitory effect on COX1 and COX2 and on lipoxygenases (5-LOX, 15-LOX);
- neurotransmitter transporters: CBD inhibits the reuptake of serotonin, noradrenaline and, to a lesser extent, GABA;
- equilibrative nucleoside transporter 1 (ENT1), adenosine transporter: inhibitory effect;
- anandamide transporters: inhibitory effect.

Main effects of CBD

As a result of binding to its molecular targets, the main effects attributed to CBD are:[7]

- anti-convulsant;
- antipsychotic;
- anxiolytic;
- anti-inflammatory;
- immunomodulatory;
- antioxidant and neuroprotective;
- antiemetic;

- anti-hyperalgesic (chronic neuropathic pain);
- muscle relaxant;
- bradycardic/hypotensive;
- slowing intestinal motility;
- anti-carcinogenic (lung cancer, glioma).

Possible molecular targets of CBD in the various conditions in which it is effective

- epilepsy (drug resistant, Dravet and Lennox-Gastaut syndrome): VDAC1, 5-HT1A, GlyR, GPR55, adenosine modulation (ENT1);
- movement disorders (dystonia, dyskinesia and catalepsy): 5-HT1A, VDAC1;
- neurodegenerative diseases (Parkinson's, Alzheimer's, dementia): VDAC1, GPR55, ENT1, CB2;
- pain (inflammatory and neuropathic): TRPV1, TRPA1, TRPM8, FAAH, CB1, CB2;
- anxiety and psychosis: 5-HT1A, adenosine modulation (ENT1), FAAH, CB1.

Side Effects

The World Health Organization (WHO) report on CBD concluded that it has a good safety profile with limited side effects.[8] Studies with Epidiolex® have reported the following as the most common side effects:[9]

- diarrhea;
- headache;
- decreased appetite;
- drowsiness.

Conversely, a recent meta-analysis reported that, in children with epilepsy, CBD was associated with higher rates of pneumonia than placebo and that high doses of CBD (≥20 mg/kg) were associated with abnormal liver function tests.[10]

Pharmacokinetics

Absorption

Due to low solubility in water, absorption from the gastrointestinal system is irregular and leads to variable pharmacokinetics.

Bioavailability by the oral route is around 6%, due to significant first-pass metabolism in the liver.

Oral (mucosal/sublingual) administration via sprays has a bioavailability similar to that of the oral route, but with less variability.

Distribution

Being very lipophilic, CBD has a high volume of distribution, especially in the brain, adipose tissue and other organs.

Metabolism and elimination

CBD is extensively metabolized by the liver, where it is hydroxylated to 7-OH-CBD by cytochrome P450 enzymes, mainly by the CYP3A (2/4) and CYP2C (8/9/19) isoenzyme families. It is excreted mainly in the faeces and to a lesser extent in urine. The half-life in humans is estimated to be around 18-32 hours.

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2.5. Pharmacology of Minor Phytocannabinoids

2.5.1. Cannabigerol (CBG)

Cannabigerol (CBG) is a non-psychoactive component of cannabis. Its chemical structure and synthesis were described in 1964.

In the plant it is synthesized from the cannabigerolic acid (CBGA). CBGA is subsequently decarboxylated to CBG.

Since CBGA also acts as a precursor to THC and CBD, it is normally found in trace amounts in cannabis. However, varieties with reduced activity of the three main synthetic enzymes can accumulate higher levels of CBGA. [1] Some strains have been bred to contain elevated levels of CBG(A), up to around 15%. As with other minor phytocannabinoids, scientific research on CBG is relatively limited.

Pharmacology[2];[3];[4]

Pharmacodynamics

The pharmacological profile of CBG appears to exhibit characteristics that fall between those of THC and CBD.

CBG interacts with the following molecular targets:

- CB1: reverse agonist/antagonist;
- CB2: reverse agonist;
- G protein-coupled receptors 55 (GPR55): antagonist;
- α-2 adrenoceptor: agonist;
- serotonergic receptors: 5-HT1A antagonist;
- peroxisome proliferator-activated receptors (PPARs): PPARγ agonist;
- transient receptor potential vanilloid (TRPV) channels: TRPV1, TRPV2, TRPV3, and TRPV4 agonist;
- transient receptor potential ankyrin type 1 (TRPA1): agonist;
- TRP subfamily M 8 (TRPM8) receptor: antagonist;
- fatty acid amide hydrolase (FAAH), Monoacylglycerol lipase (MAGL);
- diacylglycerol lipase α (DAGL) (enzymes metabolising endocannabinoids): inhibitory effect;
- cyclooxygenases and phospholipases: inhibits COX1, COX2, and PLA2.

Similarly, CBGA interacts with the same receptors, with the exception of the effects on α-2 adrenoceptor and 5-HT1A, with which CBGA does not appear to interact.

Potential Applications of CBG

The main effects attributed to CBG are:[4]

- antioxidant;
- anti-inflammatory;
- antibacterial;

- neuromodulatory;
- neuroprotective.

Although there are no conclusive human studies, animal data suggest that CBG could be useful in the treatment of various conditions. The main conditions in which CBG could be useful are:[2]

- neuroprotection and neuromodulation in neurological diseases, such as Huntington's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease and Multiple Sclerosis (effects that seem to be largely mediated by PPARγ);
- gastrointestinal diseases, such as colorectal cancer and colitis;
- metabolic syndrome (a combination of insulin resistance, obesity, hypertension, elevated low-density lipoprotein levels and reduced high-density lipoprotein levels);
- bacterial infections.

Side Effects

Limited human studies have been conducted on the side effects of CBG, primarily due to the scarcity of research on this cannabinoid. However, based on its known pharmacological interactions, potential adverse effects may primarily concern cardiovascular issues, particularly arising from its interaction with α-2 adrenoceptors.[2]
These include:

- hypotension/hypertension;
- bradycardia;
- xerostomia.

Pharmacokinetics

There are few studies on the pharmacokinetics of CBG in humans, with most data obtained from animal studies.[3]

Absorption

CBG is rapidly absorbed after oral intake, although there is a high variability in plasma concentrations achieved. The time required to reach the maximum CBG concentration is shortest in the case of inhalation. Peak concentration (T_{max}) is reached around 30/60 min in plasma and 120 min in the brain. C_{max} is around 1-5 µg/ml.

Distribution

CBG is well distributed in the brain and other peripheral organs.

Elimination

The predominant route of elimination for CBG is via urine, primarily as a glucuronic acid conjugate.

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2.5.2. Tetrahydrocannabivarin (THCV)

Tetrahydrocannabivarin (THCV) is the propyl analogue of THC. It is produced in the cannabis plant from Cannabigerovarinic acid (CBGVA), a propyl analogue of CBG. THCV differs from THC in having a side chain with 3 carbon atoms instead of 5.

It is normally present in cannabis in very low amounts (<1%), but in some selected varieties it can be as high as 16%.[1]

In the plant it is produced as tetrahydrocannabivarinic acid (THCVA), which is subsequently decarboxylated to THCV.

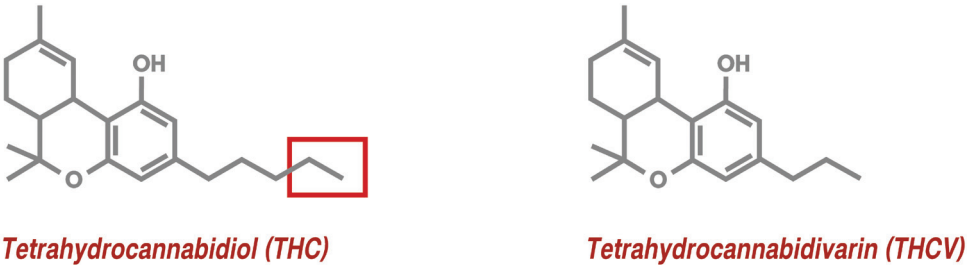

Image 16. Chemical structures of THC and THCV—red square denotes the 2-carbon difference in side-chain (courtesy of Renate Mich, www.officinavisioni.com).

Pharmacology

Pharmacodynamics

Although THCV has a similar structure to THC, it has different molecular targets and a different pharmacological profile.[2]

The main molecular targets of THCV are:

- CB1 receptor: antagonist/reverse agonist;
- CB2 receptor: partial agonist;
- G protein-coupled receptor 55 (GPR55): partial agonist;
- serotonergic receptors: 5-HT1A agonist;
- transient receptor potential vanilloid (TRPV) channels: TRPV1 and TRPV2 agonist;
- TRP subfamily M 8 (TRPM8) receptor: antagonist;
- transient receptor potential ankyrin type 1 (TRPA1) receptor: agonist.

Effects of THCV

The main effects ascribed to THCV are:[4]

- reduced plasma glucose levels;

- decreased appetite;
- increased sense of satiety;
- increased energy metabolism;
- anti-inflammatory properties;
- antipsychotic effects;
- antiepileptic/anticonvulsant properties;
- stimulating bone formation;
- potential reduction of THC side effects.

Research on THCV

THCV has been analyzed in three phase 2 clinical trials:[5]

- Treatment of dyslipidemia/type 2 diabetes, alone or in combination with CBD. Conclusions: THCV could represent a novel therapeutic agent for glycaemic control in subjects with type 2 diabetes.
- Treatment of type 2 diabetes in combination with metformin. Results not available. Conclusions not available at the moment.
- Treatment of weight gain and iatrogenic dyslipidemia associated with olanzapine in schizophrenic patients in combination with CBD. Conclusions not available at the moment.

The potential uses of THCV encompass:[4];[6];[7];[8];[9];[10];[11]

- blood glucose control in subjects with type 2 diabetes;
- control of dyslipidemia;
- treatment of bone injuries;
- control of inflammatory pain;
- control of the negative and positive cognitive symptoms of schizophrenia;
- control of dyskinesia in Parkinson's disease;
- anti-epileptic;
- treatment of nicotine addiction.

Side effects

In the few human clinical studies (with dosages of up to 10mg per day), THCV has not shown any particular side effects. As a consequence of its mechanism of action, THCV can induce a decrease in appetite and body weight.

Pharmacokinetics

To date, there are no pharmacokinetic studies on humans. In animal experiments, THCV shows a rapid oral absorption, a good distribution's volume in the brain, and a rapid elimination phase (elimination half-life exceeds 8 hours).[3]

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2.5.3. Cannabidivarin (CBDV)

Cannabidivarin (CBDV) is a non-psychoactive phytocannabinoid found in cannabis. Compared to CBD, it has a side chain with 3 carbon atoms instead of 5. CBDV is present in low concentrations in cannabis varieties, although there are varieties rich in CBDV (around 4-6%). Currently, GW Pharmaceuticals (now Jazz Pharmaceuticals) is actively developing CBDV as an experimental compound named GWP42006.

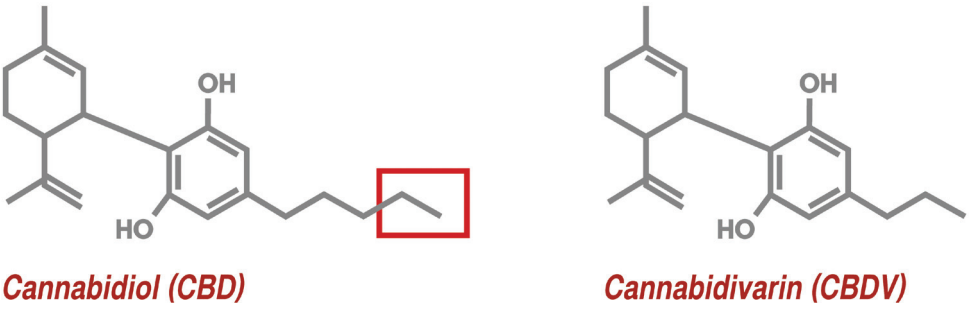

Image 17. Structural comparison between Cannabidiol (CBD) and Cannabidivarin (CBDV): note the shorter propyl side chain in CBDV (right), compared to the pentyl chain in CBD (left), which contributes to their distinct pharmacological profiles (courtesy of Renate Mich, www.officinavisioni.com).

Pharmacology

Pharmacodynamics

While many phytocannabinoids have been shown to act through binding to CB1 and CB2 receptors, CBDV mostly utilizes mechanisms that do not involve these two cannabinoid receptors.

The currently recognized molecular targets for CBDV are:[1];[2]

- transient receptor potential vanilloid (TRPV) channels: TRPV1 and TRPV2 agonist;

- transient receptor potential ankyrin type 1 (TRPA1) receptor: agonist;
- sn1-specific diacylglycerol (DAG) lipase alpha (the main enzyme responsible for the synthesis of the endocannabinoid 2-AG): inhibitory effect.

Effects of CBDV

The effects of CBDV are mainly:

- anticonvulsant;
- neuroprotective.

Use of CBDV

CBDV is currently an orphan drug for Rett and Fragile X syndrome.
In addition, there are several ongoing clinical trials (sponsored by GW/Jazz Pharmaceuticals), in which the effects of CBDV are being tested for:[4]

- autism spectrum disorder (ASD);
- pervasive childhood developmental disorders;
- partial epilepsies;
- neuropathic pain;
- Prader-Willi syndrome.

Pharmacokinetics[3]

Absorption. CBDV has low water solubility and poor oral bioavailability, around 6% in humans. CBDV has a relatively rapid absorption, with peak concentrations observed about 2 hours after oral administration in animal pharmacokinetic studies. Orally administered CBDV in mice was found to reach a plasma C_{max} of 0.47ug/mL and a Tmax of 30 minutes, and a cerebral C_{max} of 0.94 ug/mL and a T_{max} of 60 minutes.

Distribution. Due to its lipophilicity, CBDV easily crosses the blood-brain barrier, and distributes well in the brain and other organs.

Metabolism and elimination. Significant first-pass metabolism by the liver results in irregular absorption from the gastrointestinal tract, low bioavail-

ability and variable pharmacokinetics. No data are available on the elimination's route.

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2.6. Terpenes and Flavonoids

Cannabis plants constitute a phytocomplex, representing a mixture of various natural compounds. Therefore, the effects of this medicinal plant are not only influenced by the concentration of cannabinoids but also by the presence of other molecules and their ratio relative to cannabinoids. Medical Cannabis varieties are indeed also characterized based on their terpeno- phenolic profile (in addition to cannabinoid profile), indicating the proportion of molecules that give different fragrances (terpenes, ketones, aldehydes and a variety of volatile organic compounds, VOC) and pigmentations (flavonoids) to the plants.

These substances could play an important role in mediating or modulating the therapeutic effects of cannabinoids.[1]

Terpenes

Terpenes—like cannabinoids—can modulate the effects of Medical Cannabis. For example, the cannabinoid CBD and the terpene limonene seem to attenuate the asthenic and anxiogenic effects of cannabis in many individuals, whereas the cannabinoid CBC and the terpenes myrcene and linalool might amplify its analgesic and sedative effects.[1]

This is due to the fact that terpenes readily permeate the blood-brain barrier, facilitating the penetration of cannabinoids. Moreover, they may have pharmacokinetics and pharmacodynamic interaction with cannabinoids.[1];[2]

Some terpenes alter the liver's speed in metabolizing cannabinoids, increasing their bioavailability. Others, such as b-caryophyllene, exert their effects by directly activating cannabinoid receptors (CB2 in this case), functioning as authentic 'dietary cannabinoids.'[3]

Additionally, some terpenes present in the cannabis plant possess inherent pharmacological activity, such as notable antibiotic, anti-inflammatory and analgesic activity. These effects complement those of the classical phytocannabinoids and, in many cases, synergistic interactions can occur, giving rise to what is known as the 'entourage effect.'[1]

Terpenes such as limonene exhibit antioxidant and anti-inflammatory activities, and may be useful in protecting smokers from cancer risk.[4] In this context, it is important to note that although cannabis combustion is discouraged for medical purposes, it may be tolerated in terminally ill patients.

In the cannabis plant, terpenes—as well as phytocannabinoids—are produced by small surface outgrowths called trichomes. Both terpenes and cannabinoids are lipophilic compounds, produced from the common precursor geranyl pyrophosphate (GPP) via the mevalonic acid metabolic pathway.[5]

Structurally, terpenes are biomolecules consisting of various isoprene units. In cannabis, the most common terpenes are those consisting of 2 units, termed monoterpenes, and those with 3 units, termed sesquiterpenes.[5]

Effects of terpenes

Plants produce terpenes, also called essential oils, mainly for a defensive role against fungi, bacteria, herbivores or environmental stressors, as well as for communication with other plants or insects and birds.

Essential oils are recognizable by their fragrances, peculiar to the composition of their constituent terpenes.

Cannabis plants produce different types of terpenes. Some categories of terpenes (monoterpenes) are more volatile than others (sesquiterpenes) and may be lost in the final medicinal product.

Monoterpenes such as limonene or menthol, for example, when heated are more susceptible to denaturation and dispersion compared to the more temperature-resistant sesquiterpenes.[1] Therefore, it is crucial to have a comprehensive understanding of the various pharmaceutical preparation methods for cannabis, not only for compounding pharmacists but also for prescribing physicians and patients or caregivers. This knowledge is essential for preserving the volatile components that are needed in specific cases. Each terpene brings distinct medical properties through interaction with its own receptor and/or enzymatic pathways.[1]

This fortunate combination has facilitated ethnopharmacological studies over the years, leading to the acquisition of scientific data on these molecules and the identification of the mechanisms of function and medicinal properties of many terpenes found in cannabis. These studies, combined with the anecdotal experience of patients worldwide, allow us to begin to study the terpene profiles of Medical Cannabis with the aim of tailoring treatments according to specific therapeutic needs. The most prevalent terpenes found in all cannabis varieties are β-caryophyllene and β-myrcene.

β-Caryophyllene

(E)-β-Caryophyllene (BCP) is a molecule consisting of three isoprene units and thus belongs to the sesquiterpene family. It is widespread in nature and is usually found in combination with its isomers Z-BCP and α-Humulene

or Caryophyllene Oxide. BCP exhibits a notable anti-inflammatory activity that has been known in traditional medicine for centuries.

In 2008, it was discovered that β-caryophyllene (BCP) exerts much of its anti-inflammatory action by directly activating Cannabinoid Receptor 2 (CB2)[6] Since BCP is commonly found in black pepper, it is considered a dietary cannabinoid.

The effects of BCP have been extensively studied in vivo. For example, in animals with carrageenan-induced edema, treatment with 5 mg/kg BCP induces a 70% reduction in swelling.[3] Moreover, in animals with pleurisy, BCP demonstrates the ability to reduce edema volume and inhibit intracellular signaling pathways involved in modulating the inflammatory response.

In addition to its anti-inflammatory activity, BCP has been shown to have anxiolytic and antidepressant properties.[7] In *in-vitro* experiments, BCP also showed the ability to inhibit the proliferation of cancer cells.[8]

β-Myrcene

Myrcene or β-myrcene is an acyclic monoterpene that is commonly found in nature, along with other terpenes, in the essential oil of various plants, including citronella (*Cymbopogon citratus*), hops (*Humulus lupulus*, where it contributes to the balsamic aroma of beer), verbena (*Verbena Officinalis*), mango (*Mangifera Indica*), thyme (*Thymus Vulgaris*), laurel (*Laurus Nobilis*) and *Cannabis Sativa L.*

In the cannabis plant, β-myrcene can account for up to 80% of the total terpenes and, among other things, contribute to its characteristic smell.

Myrcene is highly volatile, which can pose challenges in its direct application. However, its notable low toxicity makes it a favorable candidate for various uses. Numerous trials have underscored its beneficial properties, particularly its anti-inflammatory and analgesic effects.

One of the first studies with myrcene showed that intraperitoneal injections of 10 and 20 mg/kg and subcutaneous injections of 20 and

40 mg/kg were sufficient to significantly inhibit pain perception in laboratory mice.[9] Although it has not been fully elucidated, the analgesic effect of myrcene could be mediated by the release of endogenous opioids, endocannabinoids and anti-inflammatory cytokines that act on receptors expressed on primary afferent neurons (in the periphery), thus blocking pain transmission.

In another study, myrcene was able to reduce LPS-induced inflammation, including immune cell migration, which is a key feature of pleurisy and generally of the inflammatory response. In addition, β-myrcene demonstrated immunoregulatory activity capable of inhibiting the production of nitric oxide, as well as interferon gamma (IFNγ) and interleukin-4 (IL-4), which are produced in abnormal amounts during lung inflammation.[10]

Hence, the analgesic and anti-inflammatory effects of myrcene may stem from its ability to diminish peripheral nociception by inhibiting the release of prostaglandins.

The presence of myrcene in the cannabis plant may also enhance the analgesic properties of phytocannabinoids. Indeed, myrcene has been observed to increase the permeability of the blood-brain barrier, thereby allowing external substances to reach the brain more readily. In this way, β-myrcene itself and other substances, including THC, can penetrate the central nervous system more effectively.[11] In addition, β-myrcene has also been effectively used as a permeation enhancer in a transdermal patch designed to transport cannabinoids into the bloodstream.[11]

Furthermore, terpenes, especially myrcene, seem to modulate the affinity of THC for the CB1 receptor, potentially explaining the enhanced analgesic effects observed with the whole cannabis plant, compared to its individual constituents.[2]

To summarize, β-myrcene is a natural compound with a high safety profile, which could be used to induce analgesia in patients suffering from pain, especially inflammatory and chronic pain. These effects complement the well-established anti-inflammatory and analgesic properties of cannabis

and phytocannabinoids. It is also important to remember that some cannabis varieties contain high levels of myrcene, usually those with more "sedative" effects, which, as already pointed out, are referred to as "indica varieties."

α-Humulene

α-Humulene, also known as α-caryophyllene, is a naturally occurring sesquiterpene found in the essential oils of various plants, including hops (*Humulus lupulus*), cannabis (*Cannabis sativa L.*), and balsam fir (*Abies balsamea*). It is particularly noted for its presence in significant quantities in the hops used in brewing beer, where it contributes to the distinctive "hoppy" aroma.

In cannabis, α-humulene can constitute a substantial portion of the terpene profile, enhancing the plant's unique smell and potentially contributing to its therapeutic effects. Unlike many other terpenes, α-humulene is less volatile but shares a similar safety profile, marked by low toxicity, making it suitable for various applications, including medicinal.

Research has indicated that α-humulene possesses several beneficial properties. It has shown potential anti-inflammatory and analgesic effects, which might be mediated through its action on primary afferent neurons, similar to how certain pain perceptions are modulated. Studies involving intraperitoneal administration in rodents have demonstrated significant reductions in inflammation markers, suggesting its effectiveness in treating conditions like paw edema and airway inflammation in asthma models.

α-Humulene has also been observed to exhibit anticancer properties in preclinical studies. It has demonstrated cytotoxic activity against a range of cancer cell lines, including colorectal, breast, and prostate cancers. This effect is thought to be linked to its ability to induce oxidative stress and disrupt mitochondrial function in cancer cells, promoting apoptosis.

Moreover, the sesquiterpene has shown promise in reducing the migration of immune cells, a key feature of the inflammatory response in diseases like

pleurisy. Its capacity to modulate the immune system, reducing the production of key inflammatory cytokines such as nitric oxide, interferon gamma, and interleukin-4, further underscores its potential therapeutic benefits.
Recent studies have also highlighted α-humulene's potential as a permeation enhancer in transdermal patches, aimed at improving drug delivery across skin barriers. This suggests its possible utility in enhancing the bioavailability of phytocannabinoids and other therapeutic agents in topical applications.
Given its broad spectrum of beneficial effects, α-humulene is considered a valuable natural compound with potential applications in treating various diseases, especially inflammatory and chronic pain conditions. Its role in the cannabis plant also suggests a synergistic effect with cannabinoids, enhancing the overall therapeutic potential of cannabis-derived products.

Flavonoids

Flavonoids are secondary metabolites commonly produced by many plants. Plants secrete flavonoids to protect themselves from oxidative stress, pathogens and ultraviolet (UV) radiation. Cannabis, like many other plants, produces flavonoids: over twenty have been identified so far.
Unlike cannabinoids and terpenes, which are mainly found in the inflorescences, flavonoids have been found in the flowers as well as in the leaves and stem of the cannabis plant.
Some flavonoids found in cannabis, such as apigenin, vitexin, kaempferol, quercetin, and luteolin are also present in other plants.
Other flavonoids (cannflavins A, B, C) and lignans (cannabisin A, B, C, D, E, F) are unique to this plant.[13] In some cannabis varieties, cannflavins are produced by the plant already during germination.Flavonoids exert well-known antioxidant and anti-inflammatory effects that may be useful to treat or prevent certain conditions. In addition, flavonoids can act at the cytochrome level by modulating the absorption, distribution, metabolism and elimination of cannabinoids from the body.

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2.7. Exploring Four New Phytocannabinoids in Cannabis

In 2019, a team of researchers isolated and characterized four new phytocannabinoids from the FM2 variety of cannabis produced by the Florence military plant in Italy: THCB, THCP, CBDB, CBDP.
The identification of these new phytocannabinoids represents a step towards a better understanding of the therapeutic efficacy of cannabis.
Of particular interest, for example, is Tetrahydrocannabiphorol (THCP), which has been shown to be some 30 times more potent than its analogue Tetrahydrocannabinol (THC).

New Phytocannabinoids in Cannabis

Cannabis Sativa L. can be considered a small molecular workshop, due to the large number of compounds of potential medical interest that it produces.
To date, a myriad of phytocannabinoids, terpenes, flavonoids, plus nitrogen compounds, hydrocarbons, fatty acids, carbohydrates and a plethora of other substances have been identified in the plant.
Nevertheless, the cannabis plant never ceases to reveal new surprises. Indeed, thanks in part to advances in analytic techniques, the discovery of these four compounds may shed new light on its phytochemical composition and therapeutic potential.
Among the newly identified compounds, two are THC analogues, Tetrahydrocannabutol (THCB) and THCP, and two are Cannabidiol (CBD) analogues, namely Cannabidibutol (CBDB) and Cannabidiphorol (CBDP).

Tetrahydrocannabutol and Cannabidibutol: Derivatives with 4 Carbon Atoms

The first compounds identified were THCB and CBDB. Both have a side chain with 4 carbon atoms (referred to as butyl) instead of 5, which is typi-

cal for their THC and CBD counterparts. The study on butyl derivatives was presented in the *Journal of Natural Product*.
Cannabinoids with the 4-terminal alkyl chain had been previously hypothesized but had never been isolated and characterized until now.

Chemistry of Novel Phytocannabinoids

The binding affinity of THCB to the CB1 and CB2 receptors was determined using the *radioligand binding assay* and molecular *docking*, a computational technique for predicting the binding of a compound to a receptor.
This showed the same receptor affinity but a different binding conformation between THC (5-atom chain), and THCB (4-atom chain), suggesting similar but not identical cannabimimetic activity between the two cannabinoids. The same analyses could not be applied to CBDB, as the exact receptor targets of its CBD counterpart are not known either.
The latest chemical analysis determined that these new phytocannabinoids were present in the cannabis plant in quantities approximately 100 times lower than THC and CBD (0.5 mg/g for THCB and 0.4 mg/g for CBDB).

Pharmacology of new phytocannabinoids

THCB demonstrated efficacy in an initial test of acute inflammatory pain model (formalin test). Subsequent experiments with antagonist drugs showed that this effect is mainly due to interaction with cannabinoid receptors, although an involvement of other receptors, such as TRPs, cannot be excluded.
In order to confirm the cannabimimetic activity of THCB, researchers employed the *tetrad,* a set of 4 behavioral tests: spontaneous activity, immobility/cataplexy, analgesia and temperature changes). Tetrad is widely used to determine whether a drug induces cannabinoid receptor-mediated effects. THCB proved effective in 2 of these tests, immobility and analgesia, at doses comparable with those of THC. The results suggest that THCB may act as a partial cannabinoid receptor agonist.

Tetrahydrocannabiphorol and Cannabidiphorol: 7-Carbon-Atom Derivatives

The same research group also identified two new phytocannabinoids with a 7-carbon atom side chain—THCP and CBDP—in addition to butyl derivatives.

The *radioligand binding assay* showed that THCP has a 33-fold higher affinity for CB1 than THC and 5-10 times higher affinity for CB2. Molecular *docking* confirmed the high affinity for CB1, as the 7-carbon-atom chain is able to maximize hydrophobic interactions at the receptor site.

The results of the *tetrad* were also surprising: THCP demonstrated its cannabimimetic activity, proving effective in all four tests at doses 4-5 times lower than THC, previously considered the most potent phytocannabinoid found in cannabis—until the discovery of THCP.

Future Directions

The isolation and characterization of these four new phytocannabinoids, particularly THCP, hold significant potential for the development of novel therapeutic drugs, especially for pain therapy and the treatment of anxiety, depression, post-traumatic stress disorders, epilepsy and other diseases for which the effects of THC are currently being investigated.

The presence of THCP may account for the pharmacological propertie—and, in some cases, the side effects—of certain cannabis varieties, that cannot be attributed solely to the presence of THC.

The discovery of these new phytocannabinoids suggests the possibility that additional, yet unidentified, compounds may exist.

In fact, the same authors identified two new phytocannabinoids in 2020: cannabidihexol (CBDH), and tetrahydrocannabihexol (THCH), which are n-hexyl homologues of CBD and THC, respectively.[3] Notably, CBDH, characterized from the FM2 Medical Cannabis variety, demonstrated significant antinociceptive activity in mice.[3]

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2.8. Understanding Delta-8-THC and Delta-10-THC

The most well-known phytocannabinoid is undoubtedly delta-9-tetrahydrocannabinol (Δ-9-THC), commonly referred to as THC. In addition to THC, there are additional isomers such as delta-8-THC and delta-10-THC. While these compounds are structural analogues of delta-9-THC, they exhibit distinct pharmacological properties.

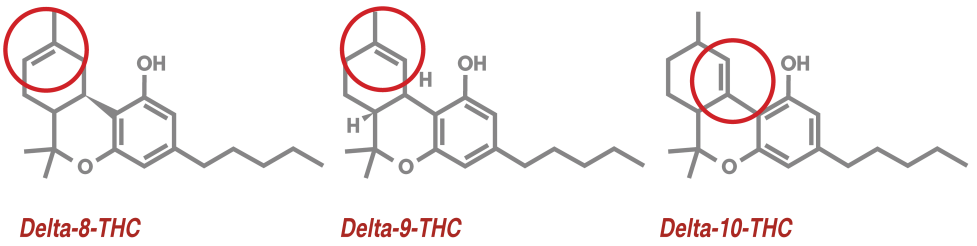

Image 18. The red circle indicates the different location of the double bond in the chemical structure of the isomers of THC (courtesy of Renate Mich, www.officinavisioni.com).

Differences between Delta-8-THC, Delta-9-THC and Delta-10-THC Isomers

Delta-9-tetrahydrocannabinol (Δ-9-THC), or simply THC, is the best recognized and extensively researched phytocannabinoid. It is naturally present

in cannabis in concentrations ranging from 0.5-5% to over 30%. Delta-9-THC is primarily responsible for the analgesic and psychotropic effects of cannabis.

Cannabis additionally produces other variants of THC, albeit in significantly lower amounts (less than 1%), including delta-8-THC and delta-10-THC. Delta-8-THC and delta-10-THC are structural isomers of delta-9-THC, meaning they have the same molecular formula, with the same number and type of atoms but a different three-dimensional arrangement of the atoms.

Specifically, what sets these three compounds apart is the position of a carbon-carbon double bond. In delta-9-THC this double bond is located at the carbon in position 9 of the carbon chain forming the molecule, whereas in delta-8-THC and delta-10-THC it is situated in position 8 and 10, respectively.

While it may seem like a minor difference, the position of this double bond changes the way these compounds interact with receptors in our bodies, affecting their affinity and ultimately their physiological effect.

Delta-8-THC: Properties and Effects

Delta-8-THC was initially synthesized from Cannabidiol (CBD)—the second most abundant cannabinoid in cannabis—around 1940, through a process known as 'cyclization.' Early human studies revealed that, similar to delta-9-THC, delta-8-THC was also capable of inducing psychotropic effects.[2]

In the 1960s, delta-9-THC was identified as the compound responsible for the psychotropic and therapeutic properties of cannabis, including alterations in mood, perception and cognition, as well as the pain-relieving effect. In 1966, delta-8-THC was also identified in cannabis and cannabis products such as hashish, but in negligible quantities.[3] As a result, subsequent research has primarily focused on delta-9-THC.

However, in the following decades, delta-8-THC attracted research interest, mainly due to its greater thermodynamic stability compared to delta-9, making it more manageable for study.[4]

Despite nearly 80 years of research, delta-8-THC is often perceived as a newly identified compound, likely due to the limited attention and publicity these studies have received compared to the more widely recognized research on delta-9-THC.

The human endocannabinoid system comprises two subtypes of cannabinoid receptors, CB1 and CB2. Studies indicate that delta-8-THC exhibits lower potency at the human CB1 receptor than delta-9-THC while exhibiting similar efficacy at the CB2 receptor.

Human Studies on Delta-8-THC

The first study on the effects of delta-8-THC in humans dates back to 1942.[5] Adams investigated the effects of delta-8-THC—derived from CBD—by administering it orally to a group of 77 volunteers from a prison population. The initial dose was 30 mg, which was increased by 30 mg every other day.

When participants reached a dose that was not tolerated, the dose was reduced to the previous tolerable level after which the increment continued at 15 mg daily.

Although a modern psychometric scale was not available, the reported effects were remarkably similar to those of delta-9-THC.

The observed effects were:

- apprehension;
- euphoria;
- loquacity;
- anxiety;
- reduction of inhibitions;
- hunger and thirst;
- feeling of ‘high’;

- inability to manage one's own body;
- uncontrollable bursts of laughter or giggles;
- drowsiness;
- languor;
- exhaustion;
- a pleasant feeling of tiredness.

Subsequently, delta-8-THC was tested using various administration routes, including intravenous injection, inhalation, and oral consumption.

Intravenous Route

In the 1970s, a comparative study of delta-8-THC and delta-9-THC, administered intravenously, demonstrated that both cannabinoids produce qualitatively similar effects.[6]

Both phytocannabinoids induced a significant increase in heart rate and pronounced psychotropic effects, as measured by a visual analogue scale (VAS), in the tested patients. These effects were mediated by CB1 receptors. However, due to the limited number of participants, a quantitative comparison between the two cannabinoids is not feasible. Notably, subjects reported a VAS score of 8/10 following intravenous administration of 6 and 9 mg of delta-8-THC, indicating that it produces a subjective effect comparable to the maximal effect of delta-9-THC. This observation is consistent with findings from in vitro functional assays of the human CB1 receptor, which generally demonstrate a similar maximal efficacy for both cannabinoids.

Inhalation Route

An initial study compared placebo to delta-8-THC (10 mg and 20 mg) and delta-9-THC (5 mg, 10 mg, and 20 mg).[7] Both the 10 mg and 20 mg doses of delta-9-THC resulted in "stronger subjective evaluations of psychotropic effects" compared to the equivalent dose of delta-8-THC. Notably, the 10 mg dose of delta-8-THC resulted in similar evaluations compared to the

5 mg dose of delta-9-THC, suggesting that inhaled delta-9-THC is approximately twice as potent as delta-8. A second study evaluated an 8.3 mg dose of Δ8-THC versus placebo and reported a 'highly significant increase' in heart rate following the administration of delta-8-THC.[8]

Oral Route

In a 1973 study (the same one that investigated the intravenous route), an oral dose of 20 mg delta-9-THC resulted in stronger subjective effects than an equivalent dose of delta-8-THC (3.5 versus 2.2 on a global 0 to 10 rating).[9] However, a higher dose of 40 mg delta-8-THC produced a stronger subjective effect than the 20 mg dose of both molecules. These results would indicate that delta-9-THC is two times less potent than delta-8-THC. However, a later study in 1984, reported opposite results. Both a dose of 50 mg and a 75 mg dose of delta-8-THC exhibited weaker effects than a 20 mg dose of delta-9-THC.[10] The reason for this discrepancy is unclear. The 1973 study employed a crossover design, meaning that participants were not separated into groups, whereas the 1984 study tested delta-8 and delta-9-THC in distinct groups of patients. Both studies had a limited number of participants, potentially leading to spurious results, given the considerable variability of THC effects between individuals and even across test days. Other experimental details, such as whether subjects were administered doses on an empty or full stomach, were not reported, which could affect interpretation. Additionally, a separate study tested oral delta-8-THC in eight children undergoing chemotherapy to assess its anti-emetic properties.[11] Administering a dosage of 18 mg/m2 (equivalent to approximately 31 mg in a typical adult) almost completely prevented vomiting. Side effects were observed in 2 of the 8 subjects and included mild irritability and euphoria.

The semi-legal status of delta-8-THC

In 2018, the United States enacted the 'Farm Bill,' which effectively removed hemp—a variety of the Cannabis Sativa plant species that is cul-

tivated specifically for industrial and commercial purposes, with very low levels of THC—from the federal list of controlled substances, thereby legalizing the sale and commercial use of hemp-derived products. However, this legislation imposes strict regulations, stipulating that hemp products must contain no more than 0.3% delta-9 THC. Notably, the 2018 Farm Bill does not explicitly address the possession, use, or sale of products derived from hemp that may contain other biologically active phytocannabinoids, such as delta-8 THC.

The legalization of hemp production worldwide has created a similar situation to that seen in the United States. While the law does not explicitly prohibit the possession and consumption of delta-8-THC, its sale has seen a dramatic increase in the US, prompting some states to introduce legislation on the matter.

In states where it is permitted, there has been a significant rise in the availability of delta-8-THC-infused candies, sweets, biscuits, e-cigarette liquids, and other similar products. Often packaged in colorful containers adorned with cartoon characters and featuring sweet or fruity flavors, these products may appeal to children and adolescents. Additionally, due to the absence of clear legislative guidelines, the accuracy of their labeling is often questionable, raising concerns within the medical community. Despite these concerns, the semi-legal status of delta-8-THC has led many consumers to embrace it. Anecdotal reports suggest that while delta-8-THC may produce milder psychotropic effects compared to delta-9-THC, it is believed to induce a more favorable state of mental relaxation.

Delta-10-THC: Properties and Effects

While decades of research have thoroughly characterized the biochemical and pharmacological properties of delta-8-THC, there is a notable scarcity of scientific literature on delta-10-THC.

In 1984, the research team led by Professor Raphael Mechoulam, credited with the isolation and characterization of delta-9-THC in cannabis, published a paper detailing the synthesis of new cannabinoids, including delta-10-THC, using a chemical process called "double bond isomerization with basic catalysis."[12] Four years later, the same group published a paper in which the effects of the delta-10-THC were compared with delta-9-THC. [13] These effects were tested on pigeons and it was found that delta-10-THC was less potent than delta-9-THC in inducing psychotropic effects. Since then, scientific interest in this molecule waned until a few years ago when a US company propelled delta-10-THC back into the spotlight.

Effects of Delta-10-THC

In the absence of dedicated clinical studies, information regarding the effects of delta-10-THC currently relies on anecdotal reports found in various publications, blogs, and websites. These accounts typically stem from the experiences and feedback of consumers who have experimented with this substance.

Unlike delta-8-THC, which is naturally produced by the cannabis plant albeit in minimal amounts, delta-10-THC seems to be generated only under specific conditions and as a byproduct rather than a direct product of the plant's metabolic processes. Due to its structural similarity to delta-8 and delta-9-THC, it is probable that delta-10-THC also interacts with cannabinoid receptors, particularly CB1. Many reported experiences suggest psychotropic effects similar to delta-8-THC and delta-9-THC, albeit notably less potent. The prevailing consensus is that delta-10-THC induces a more relaxing effect rather than a pronounced intoxicating one.

The Semi-legal Status of Delta-10-THC

The situation observed with delta-8-THC also extends to delta-10-THC. Following the passage of the Farm Bill in the USA, there has been increased commercial interest in cannabinoids that are not explicitly prohibited by

law, including delta-10-THC. Numerous companies have begun synthesizing and marketing products containing delta-10-THC, particularly e-liquid for electronic cigarettes. Once again, the absence of specific regulations raises questions about the accuracy of product labeling and contents. Health authorities, particularly in the United States, are concerned about the potential use of these products by young individuals who may perceive them as safer alternatives to traditional cannabis derivatives.

Conclusions and Future Perspectives on Delta-8-THC and Delta-10-THC

New compounds with psychotropic activity, such as the delta-8-THC and delta-10-THC analogues, are emerging alongside delta-9-THC.
According to a potency scale, concerning psychotropic effects, the strongest is delta-9-THC, followed by delta-8 and delta-10.
In addition to its psychotropic properties, delta-9-THC is also known for its effects on pain, particularly chronic pain of neuropathic origin.
Delta-8-THC is very similar to delta-9, but somewhat less potent. The psychotropic effect is maintained, although, being less intense, many users report a 'high' without the anxiety or panic attacks sometimes associated with delta-9. The pain-relieving effect is maintained, albeit to a lesser degree, which would also make delta-8-THC interesting for therapeutic use.
In contrast, delta-10-THC has no pain-relieving activity and the 'mental' effect is very mild, relaxing, but not intoxicating. The molecule is however relatively new and scientific studies confirming its properties are lacking.

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2.9. **Insight:** The Link between Tryptophan and Cannabis

In 2022, research unveiled two non-cannabinoid compounds—kynurenic acid and L-kynurenine—previously unrecognized in cannabis plants. These compounds, derived from tryptophan metabolism, exhibit noteworthy neuromodulatory properties and therapeutic potential. The discovery expands our understanding of cannabis beyond its known cannabinoids, offering new insights into its medicinal applications.

Tryptophan Metabolism in Animals

Plants and animals share numerous biochemical pathways, although synthesis and catabolism processes can differ between the two kingdoms. A notable example lies in the L-tryptophan metabolic pathway.
Unlike plants, animals, particularly mammals, including humans, cannot biosynthesize this essential amino acid and typically acquire it through dietary sources.
Foods particularly rich in tryptophan are:

- eggs;
- meat (especially chicken and turkey);
- fish (especially anchovy, sea bream, sea bass, sole, cod, tuna);
- vegetables (endive, cabbage, asparagus, green beans, lettuce, chard, spinach, zucchini);
- dark chocolate;
- nuts (peanuts, almonds, hazelnuts, pistachios, pine nuts, walnuts, chestnuts, cashews);
- sesame seeds;
- raisins;
- milk and dairy products.

Tryptophan serves as a crucial constituent of all proteins within an organism and functions as a metabolic intermediate involved in various biologically significant processes. In the human and mammalian brain, tryptophan acts as the biological precursor to several important molecules, including the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), which, in turn, serves as the precursor to the neurohormone melatonin.

L-kynurenine (KYN) and Kynurenic Acid (KYNA)

Consumption of tryptophan-rich foods correlates with increased production of serotonin and melatonin. While a small fraction of dietary trypto-

phan converts to serotonin in animals, a larger proportion (approximately 95%) metabolizes into L-kynurenine (KYN), subsequently degrading into kynurenic acid (KYNA) or into 3-hydroxyquinurenine.[1]

The formation of KYNA and 3-hydroxyquinurenine marks the initial steps in the biosynthesis process of:

- nicotinic acid;
- nicotinamide;
- B-complex vitamins.

KYN, a molecule with neuromodulatory actions, targets the aryl hydrocarbon receptor (AhR) and plays a crucial role in immune response regulation. Both KYN and KYNA have various effects on the body, primarily due to their involvement in the kynurenine pathway, the metabolic pathway for tryptophan. Here are some of the known effects of KYN and KYNA:[2]

- Neuroprotective: KYNA acts as an antagonist at NMDA receptors in the brain, which are involved in excitatory neurotransmission. By blocking these receptors, KYNA can exert neuroprotective effects, potentially reducing neuronal damage and inflammation in conditions such as neurodegenerative diseases and stroke.
- Antioxidant: Both KYN and KYNA possess antioxidant properties. This antioxidant activity is beneficial for overall cellular health and may play a role in mitigating oxidative stress-related diseases.
- Anti-inflammatory: KYNA has been shown to have anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and chemokines. This anti-inflammatory action can help modulate the immune response and reduce inflammation in conditions such as autoimmune diseases and chronic inflammatory disorders.
- Modulation of neurotransmission: KYNA can modulate neurotransmission by influencing the activity of various neurotransmitter systems, including glutamate, dopamine, and serotonin. By regulating neurotransmitter levels and activity, KYNA may affect mood, cognition, and behavior.

- Cardiovascular protection: Emerging research suggests that KYNA may have cardiovascular protective effects, including vasodilation and regulation of blood pressure. These effects could be beneficial for preventing cardiovascular diseases such as hypertension and atherosclerosis.

Tryptophan Metabolism in Plants

In plants, tryptophan metabolism follows a different biochemical trajectory compared to animals. While plants can self-synthesize tryptophan, its content remains relatively low. Primarily, tryptophan is incorporated into amino acid chains during protein biosynthesis, with a smaller portion converting into biologically significant secondary metabolites, such as *indolacetic acid* (IAA), involved in regulating plant growth.
Although the kynurenine pathway is not prevalent in plants, low levels of KYN and KYNA have been reported in select plants and plant-based foodstuffs. These metabolites have been identified in:

- pumpkin;
- sesame;
- potatoes;
- broccoli;
- various spices;
- medicinal herbs like *Taraxacum* (dandelion), *Urtica dioica* (stinging nettle), and *Chelidonium majus* (greater celandine).

However, it remains unclear whether all plants biosynthesize these metabolites or if they are produced by soil microorganisms and absorbed through the roots. Despite their presence, the specific functions of KYN and its metabolites in plants have yet to be fully elucidated.

KYN and KYNA: Two Human Neuromodulators Identified in the Cannabis Sativa L. plant

In a recent study, researchers analyzed the presence of small secondary metabolites, particularly those associated with the tryptophan pathway, within Cannabis Sativa L.[3]

Employing advanced analytical techniques such as ultra-high-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS), typically used for metabolomic analyses, the researchers meticulously examined the presence of tryptophan and its metabolites, including kynurenine (KYN) and kynurenic acid (KYNA), in various parts of the cannabis plant.

Their findings revealed a progressive increase in the levels of tryptophan, KYN, and KYNA from the base (roots) to the apex (leaves) of the cannabis plant in both soil and hydroponic cultivation settings, at both vegetative and flowering growth stages. Interestingly, leaves consistently exhibited the highest concentrations of KYN and KYNA across both cultivation methods.

This study sheds new light on the presence and distribution of tryptophan pathway metabolites within Cannabis Sativa L, providing valuable insights into the plant's chemical composition and potential pharmacological properties. Further exploration of these compounds could uncover novel therapeutic avenues and enhance our understanding of the medicinal potential of cannabis.

Conclusions

With this work, researchers have uncovered the presence of the significant tryptophan metabolic pathway and its metabolites within *Cannabis Sativa L*. Particularly noteworthy is the identification of kynurenic acid (KYNA) and L-kynurein (KYN) in cannabis leaves.

KYNA, in particular, has gained considerable attention for its important antioxidant, anti-inflammatory, and neuroprotective properties.
Furthermore, a hypolipidemic effect and cardiovascular protective functions have recently been attributed to KYNA, suggesting a potential role as a functional food ingredient for the treatment of obesity and hyperlipidaemia and for modulating the gut microbiota.
The results suggest that Cannabis Sativa L. may be a valuable source of tryptophan, KYN and KYNA. These findings, however, remain to be confirmed by additional research, especially to determine if the levels of KYNA present in cannabis leaf extracts—when used in cosmetics or nutraceuticals—are high enough to produce the various pharmacological effects associated with this compound.

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CHAPTER **3.**

MEDICAL CANNABIS IN CLINICAL PRACTICE

3.1. Pain and Other Pathologies for which Cannabis Has Shown Therapeutic Efficacy

This chapter provides an overview of the fundamental aspects of the primary conditions treatable with cannabis therapy. In the following chapters, these pathologies will be discussed in detail.

Effects of Cannabis in Pain and Spasticity Associated with Multiple Sclerosis and Spinal Injuries

As demonstrated by numerous clinical studies, cannabinoids can help manage the main symptoms of Multiple Sclerosis.[1]
In particular, Medical Cannabis is effective in improving bladder incontinence, muscle rigidity, spasticity, chronic and neuropathic pain and sleep quality.[2];[3];[4]
Cannabis therapy may also be useful in treating spasticity associated with spinal injuries.

Table 3.

Year	Number of studies	Nº of patients	Product and dosage	Results	Side effects
1981, 1983, 1987, 1995, 2004	5	55	Oral THC 2.5-5-10-15 mg / 1d	Decreased spasticity. Improvement in tremors and motor coordination. Subjective well-being improvement. Central pain improvement and nocturia frequency.	Minimum. Euphoria.
2013	1	493	Oral THC 28 mg / 1d	No efficacy in the progression of the disease.	-/-

Multiple Sclerosis (with THC). Summary of the primary clinical studies conducted on Multiple Sclerosis and spinal cord injury with THC.

Studies consulted:

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Table 4.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1994, 2012	2	40	1-3 cigarettes 1.54% -4% THC.	MS	Subjective improvement for some. Reduction of static and pain.	Euphoria
2003, 2004	3	808	Oral THC 2.5 mg Vs. Oral CBD 2.5 mg Vs. THC + CBD (1:1).	MS	THC: reduction in muscle spasms, pain, improved sleep quality. CBD: pain relief. THC + CBD: improvements in sleep, muscle spasms, spasticity, bladder dysfunction.	-/-
2004	1	50	Capsules 2.5 mg THC+0.9 mg CBD.	MS	Improvement in mobility and sleep quality.	-/-
2004	1	14	THC 2.5 mg oral.	MS	No effect on tremors.	-/-
2007, 2006, 2009, 2010 2011, 2012	10	1308	THC + CBD (1:1).	MS	Pain relief. No cognitive impairment. Spasticity reduction. Improvement of urinary functions.	Drowsiness
2005	1	100	THC + oral CBD (1: 1).	MS	No evidence of changes in cytokine levels.	-/-
2006	1	630	oral THC + CBD (2:1), THC 2.5 mg	MS	Reduced incontinence with both products.	-/-
2012	1	279	Oral THC 25mg / 1d	MS	Significant reduction in muscle stiffness.	-/-

Multiple Sclerosis (with full spectrum Medical Cannabis). Summary of the primary clinical studies conducted on Multiple Sclerosis with Full Spectrum cannabis.

Studies consulted:

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- Freeman, R. M., et al. (2006). The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). International Urogynecology Journal, 17(6), 636-641.
- Zajicek, J. P., et al. (2012). Multiple sclerosis and extract of cannabis: results of the MUSEC trial. Journal of Neurology, Neurosurgery & Psychiatry, 83(11), 1125-1132.

Table 5.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1986	1	5	Oral THC 35 mg/d.	Spinal injuries.	Significant decrease in spasticity.	1 patient psychological problems.

Spinal Injuries (with THC). Summary of the primary clinical studies conducted on spinal injuries with THC.

Studies consulted:

- Hanigan, W. C., et al. (1986, February). The effect of delta-9- THC on human spasticity. Clinical Pharmacology & Therapeutics (vol. 39, no. 2, pp. 198-198).

Table 6.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2003	1	4	THC+CBD (1:1) Vs. THC 2.5mg Vs. CBD 2.5mg.	Spinal injuries.	THC: decrease in spasticity, muscle spasms, pains. CBD: significant pain reduction. THC + CBD: reduction of muscle spasms and improvement of sleep.	-/-

Spinal Injuries (with full spectrum Medical Cannabis). Summary of the primary clinical studies conducted on spinal injuries with full spectrum Medical Cannabis.

Studies consulted:

- Wade, D. T., et al. (2003). A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clinical rehabilitation, 17(1), 21-29.

Effects of Cannabis in Chronic and Neuropathic Pain

For millennia, cannabis has been employed in the management of chronic pain.[5] Preclinical evidence with well-characterized animal models of refractory pathological pain indicates that one of the most promising therapeutic uses of phytocannabinoids is in addressing chronic pain.[6]

The therapeutic benefit of Medical Cannabis has been mainly observed in studies on neuropathic pain. This type of pain is common, difficult to treat and has limited treatment options. Consequently, even modest effects may hold significant importance for patients.

In this context, Tetrahydrocannabinol (THC) has demonstrated efficacy in alleviating diabetic neuropathy,[7] while cannabidiol (CBD) has been shown to prevent the onset of peripheral neuropathy in diabetic patients.[8]

Patient preference studies suggest that the side effects of cannabinoids are better tolerated than opioid drugs. Regarding THC, extensive research indicates that even low doses can amplify the analgesic effects of morphine and codeine. Combining opioid and cannabinoid therapy has demonstrated pain-relieving effects in both acute and chronic pain scenarios, allowing for the maintenance of lower dosages to mitigate side effects and prevent drug tolerance.[9];[10];[11];[12]

In contrast, studies evaluating the effects of isolated CBD in acute pain show no beneficial effects.[13];[14] CBD is in fact more indicated for neuropathic and inflammatory pain,[15] especially when used together with THC.[16]

Cannabigerol (CBG) is a minor cannabinoid with analgesic properties against inflammatory pain; it acts by increasing the endocannabinoid tone, primarily by decreasing the reuptake of Anandamide, thereby extending its duration of action. Additionally, CBG synergistically enhances the pain-relieving effects of THC, providing a comprehensive approach to pain management.[17];[18]

The aforementioned effects are also found with cannabichromene (CBC), which similarly enhances the pain-relieving effects of THC and robustly inhibits the reuptake of Anandamide.[19];[20]

Here are the main clinical studies carried out in chronic and acute pain:

Table 7.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1975	2	46	5 mg, 10 mg, 15 mg, 20 mg oral THC Vs. Codeine 60 mg, 120 mg.	Cancer pain.	Pain Relief: 10 mg THC = 60 mg codeine, 20 mg THC = 120 mg codeine Well tolerated: 5 mg, 10 mg THC.	15 mg and 20 mg = frequent ataxia, confusion, dizziness.
1978	3	80	Benzopyrano-peridine 2.4 mg Vs. Codeine 50 mg, 60 mg, 120 mg Vs. Secobarbital 50 mg.	Cancer pain.	Pain relief equivalent to codeine and superior to secobarbital.	Vertigo in 1/3 of the subjects (codeine = 2/3). Sedation equivalent to codeine.
2003	1	21	11-OH-THC 40mg.	Neuro-pathic pain.	Analgesia after 3h.	-/-
2006, 2008	4	196	0.5-1 mg oral THC; 2 mg oral THC Vs. Dihydrocodeine 240 mg; 2.5 mg oral THC.	Fibro-myalgia, chronic pain.	It improves symptoms and is well tolerated. No differences observed between the different dosages. Dihydrocodeine > 2 mg oral THC.	-/-
2010	1	7	Oral THC 20mg.	Neuro-pathic pain (spinal injury).	No more effective than first generation antihistamine.	-/-

Chronic pain (with THC). Summary of the primary clinical studies conducted on chronic pain with THC.

Studies consulted:

- Noyes Jr, R., et al. (1975). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clinical Pharmacology & Therapeutics, 18(1), 84-89.
- Noyes Jr, R., et al. (1975). Analgesic effect of delta- 9-tetrahydrocannabinol. The Journal of Clinical Pharmacology, 15(2-3), 139-143.
- Staquet, M., et al. (1978). Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. Clinical Pharmacology & Therapeutics, 23(4), 397-401.
- Jochimsen, P. R., et al. (1978). Effect of benzopyranoperidine, a Δ-9-THC congener, on pain. Clinical Pharmacology & Therapeutics, 24(2), 223-227.
- Karst, M., et al. (2003). Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomised controlled trial. Jama, 290(13), 1757-1762.
- Rintala, D. H., et al. (2010). Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. American journal of physical medicine & rehabilitation, 89(10), 840-848.

Table 8.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2004, 2007, 2010, 2012, 2013, 2014	952	952	2.5 mg THC spray Vs. 2.5 mg CBD spray Vs. THC+CBD spray (1:1).	Neuropathic pain, allodynia, chemotherapy.	Significant pain relief with THC only, THC + CBD. Improved sleep quality. Long-term efficacy. CBD alone is not effective.	Dry mouth, confusion, euphoria, dysphoria (mild to moderate).
2006, 2007, 2008, 2009, 2010; 2013	184	184	Smoked cannabis (3.5% and 7% THC - 4 inhalations); vaporised cannabis, 1 inhalation, 1.29% and 3.53% THC; smoked cannabis 75 mg.	Peripheral neuropathy; spinal injury; central neuropathy.	Significant improvements after 4h. No difference between the different doses. Improved sleep and anxiety.	-/-
2006	58	58	THC+CBD spray (1:1).	Arthritis	Improvements in pain and sleep.	-/-
2010	30	30	THC+CBD spray (1:1).	Neuropathy diabetes.	No significant improvement (variable misleading depression).	-/-

Year	Number of studies	Nº of patients	Product and dosage	Pathology	Results	Side effects
2014	30	30	Smoked cannabis (1.99% and 3.51%) Vs. 10 and 20 mg THC oral.	Lower back pain.	Improvements in pain. Smoked after 30 min, oral after 2h.	Similar psychoactive effects between the products.
2013	339	339	THC+CBD spray (1:1)- max. 12 sprays/d.	MS neuropathic pain.	Moderate analgesic effect.	-/-

Chronic pain (with full spectrum Medical Cannabis). Summary of the primary clinical studies conducted on chronic pain with full spectrum Medical Cannabis.

Studies consulted:

- Blake, D. R., et al (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology, 45(1), 50-52.
- Nurmikko, T. J., et al (2007). Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain®, 133(1-3), 210-220.
- Wilsey, B., Marcotte, et al. (2008). A randomised, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. The Journal of Pain, 9(6), 506-521.
- Johnson, J. R., et al (2010). Multicenter, double-blind, randomised, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. Journal of pain and symptom management, 39(2), 167-179.
- Johnson, J. R., et al (2013). An open-label extension study to investigate the long-term safety and tolerability of THC/ CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. Journal of pain and symptom management, 46(2), 207-218.
- Langford, R. M., et al. (2013). A double-blind, randomised, placebo-controlled, parallel- group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of neurology, 260(4), 984-997.
- Lynch, M. E., et al (2014). A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of pain and symptom management, 47(1), 166-173.
- Portenoy, R. K., et al (2012). Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomised, placebo-controlled, graded- dose trial. The Journal of Pain, 13(5), 438-449.
- Serpell, M., et al (2014). A double-blind, randomised, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. European journal of pain, 18(7), 999-1012.

- Blake, D. R., et al (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology, 45(1), 50-52.
- Selvarajah, D., et al. (2010). Randomized placebo- controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes care, 33(1), 128-130.
- Issa, M. A., et al. (2014). The subjective psychoactive effects of oral dronabinol studied in a randomised, controlled crossover clinical trial for pain. The Clinical journal of pain, 30(6), 472.
- Langford, R. M., et al (2013). A double-blind, randomised, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of neurology, 260(4), 984-997.

Table 9.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1987	1	10	Oral CBD 450 mg.	Neuro-pathic pain.	No analgesic effects.	
2004, 2007, 2010, 2012, 2013, 2014	8	952	2.5 mg THC spray Vs. 2.5 mg CBD spray Vs. THC + CBD spray (1: 1).	Neuro-pathic pain, allo-dynia, chemo-therapy.	Significant pain relief with THC only, THC + CBD. Improvement of sleep quality. Long-term efficacy. CBD alone is not effective.	Dry mouth, confusion, euphoria, dysphoria (mild to moderate).

Chronic Pain (with CBD): Summary of the primary clinical studies conducted on chronic pain with CBD.

Studies consulted:

- Lindstrom P, et al. (1987). Lack of effect of cannabidiol in sustained neuropathia. Proceedings of the Marijuana 1987 International Conference on Cannabis, Melbourne, September 2-4.
- Notcutt, W., et al (2004). Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia, 59(5), 440-452.

Table 10.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1977	1	10	0.22, 0.44 mg / kg THC IV Vs. Diazepam IV 0.157mg / kg.	Post-operative pain (dental extractions).	No analgesic effect.	0.22mg / kg THC: euphoria, dysphoria 0.44mg / kg THC: anxiety.
1981	1	56	Levonantradol IM 1.5; 2; 2.5; 3 mg.	Post-operative pain (trauma).	Pain relief in every dosage. > 2.5mg = analgesia > 6h.	1/3 dizziness.
2003, 2006	3	181	Oral THC 5mg.	Post-operative pain (hysterectomy), gynecological, prostatectomy, orthopedic.	No effectiveness.	-/-
2003, 2006, 2008	3	42	Oral THC 0.5 mg; 1 mg; 5 mg; 20 mg Vs. Morphine 0.02 IV; Vs. 30 mg THC + morphine 0.02 IV.	Experimental pain.	Oral THC = no effect; THC + morphine analgesic effect only on electrical pain and affective component but not mechanical and sensory component.	Sedation, dry mouth, dizziness, altered perception, euphoria, confusion.

Acute Pain (with THC). Summary of the primary clinical studies conducted on acute pain with THC.

Studies consulted:

- Raft, D., et al. (1977). Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. Clinical Pharmacology & Therapeutics, 21(1), 26-33.
- Jain, A. K., et al. (1981). Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. The Journal of Clinical Pharmacology, 21(S1), 320S-326S.
- Buggy, D. J., et al (2003). Lack of analgesic efficacy of oral Δ-9-tetrahydrocannabinol in postoperative pain. Pain, 106(1-2), 169-172.
- Beaulieu, P. (2006). Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Canadian Journal of Anesthesia, 53(8), 769-775.

- Seeling, W., et al (2006). Delta (9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain. Der Anaesthesist, 55(4), 391-400.
- Naef, M., et al (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain, 105(1-2), 79-88.
- Roberts, J. D., et al (2006). Synergistic affective analgesic interaction between delta-9-tetrahydrocannabinol and morphine. European journal of pharmacology, 530(1-2), 54-58.
- John Redmond, W., et al(2008). Analgesic and antihyperalgesic effects of nabilone on experimental heat pain. Current medical research and opinion, 24(4), 1017-1024.

Table 11.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2006	1	65	THC + CBD (2:1)	Post-operative pain.	10 mg significant reduction in pain.	-/-
2007, 2008	2	33	Smoked cannabis (2, 4, 8% THC); THC + CBD (2: 1).	Inflammatory pain and hyperalgesia (experimental pain).	THC + CBD not effective. Cannabis smoked at 4% THC effective dosages.	-/-

Acute pain (with full spectrum Medical Cannabis). Summary of the primary clinical studies conducted on acute pain with full spectrum Medical Cannabis.

Studies consulted:

- Holdcroft, A., et al (2006). A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology, 104(5), 1040-1046.
- Wallace, M., et al (2007). Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology: The Journal of the American Society of Anesthesiologists, 107(5), 785-796.
- Kraft, B., et al (2008). Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology: The Journal of the American Society of Anesthesiologists, 109(1), 101-110.

Use of Medical Cannabis in Fibromyalgia

The term fibromyalgia indicates a chronic condition characterized by pain in muscles and fibrous connective tissue structures, such as ligaments and tendons. It is characterized by a poly-symptomatology that includes:

- Chronic widespread musculoskeletal pain;
- Generalized hyperalgesia;
- Psychological stress;
- Insomnia and memory issues.

The Endocannabinoid System is involved in modulating the response to chronic pain and stress and may also play a role in fibromyalgia.
Preclinical data in animal models show that CB1 receptor activation has therapeutic potential for the treatment of fibromyalgia symptoms.[21] Analyzing the data in the literature, cannabinoid-induced analgesia seems to depend on the activation of CB1 receptors in peripheral nerve endings. In fact, a decrease in CB1 concentration at peripheral nerve endings results in a reduction of analgesia produced by cannabinoids.[22] Therefore, stimulation of peripheral CB1 receptors may be of particular relevance to fibromyalgia symptoms, as increased peripheral nociceptive input is an important mechanism in the genesis of pain in this syndrome.[22]
In humans, several studies have reported a change in endocannabinoid tone in patients with fibromyalgia. However, few clinical studies have evaluated the effects of cannabis, cannabis extracts, synthetic cannabinoids and endocannabinoid-modulating drugs for the treatment of this symptomatology. Data from clinical trials show that the use of THC (extract or synthetic) or cannabis varieties with a high THC content may be helpful in reducing the symptoms of fibromyalgia, especially those associated with pain.[21]
For instance, a double-blind, randomized, placebo-controlled clinical trial analyzing the effects of nabilone (synthetic THC) on pain and quality of life of fibromyalgia patients, showed that after 4 weeks of treatment (0.5 mg

once daily in the first week, 0.5 mg twice daily in the second week, 0.5 mg in the morning and 1 mg in the evening in the third week, and 1 mg twice daily in the fourth week), patients who received nabilone recorded significant improvements in the clinical pain score.[22]

According to some data in the literature, inhaled cannabis seems to be more effective in improving pain, quality of life and sleep in patients with fibromyalgia.[21] For example, in a clinical trial in which cannabis was administered by inhalation, a significant 30% reduction in pain scales was found in most patients.[23] In this study, of the different chemotypes tested, the most effective had a THC:CBD ratio of about 1:1.

Another study involved 100 fibromyalgia patients resistant to standard analgesic therapy. After six months of therapy, the results, obtained by evaluating questionnaires, showed that approximately 30 percent of patients achieved an improvement in sleep and quality of life.

In addition, many patients experienced an improvement in anxiety and depression. In this case, Medical Cannabis was administered in the form of an extract in olive oil, with a night-time intake of a variety with 22% THC and < 1% CBD and a variety with 6.5% THC and 8% CBD in the morning. Prescribed doses ranged from 10 to 30 drops per formulation.[24]

Although various studies suggest that Medical Cannabis is a potential treatment for fibromyalgia, the methodological limitations of this evidence currently prevent a definitive conclusion on the use of cannabinoids for pain management in fibromyalgia patients.

Although data in the literature are inconclusive, patients using cannabis or cannabinoids seem to derive many benefits in terms of symptom relief. Indeed, one of the most recent surveys, in line with previous ones, shows that Medical Cannabis, whether used as self-medication or prescribed by a healthcare professional, appears to be a safe and effective therapeutic alternative for the treatment of fibromyalgia symptoms: more than 80% of patients who responded to the survey reported improvements in their condition after using Medical Cannabis.[25]

Cannabis for Nausea and Vomiting Induced by Chemotherapy, Radiotherapy, and HIV Therapies—Antikinetic and Antiemetic Effects

Among the earliest recognized medicinal benefits of cannabis is its efficacy in mitigating nausea and vomiting. THC demonstrates effective antiemetic properties in patients undergoing chemotherapy.

Conversely, pure CBD exhibits biphasic effects: at low dosages, it suppresses the vomiting reflex induced by chemotherapy and radiotherapy, while at high dosages, it lacks beneficial effects and may exacerbate the condition.[26];[27]

When tested in a combined formulation, THC and CBD (e.g. in the spray mixture Sativex®) reduced the incidence of nausea and vomiting in patients undergoing chemotherapy compared to those who used a placebo.[28]

Other non-psychotropic phytocannabinoids such as CBDA, THCA, THCV, CBDV and CBG are also potentially effective in producing similar antiemetic effects.[29]

Below is a list of the main clinical studies carried out.

Table 12.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1975, 1979, 1980, 1982, 1983	7	455	2 mg, 7.5 mg, 10 mg, 15 mg oral THC 3-4 / d Vs. Prochlorperazine 10 mg 3-4 / d;ì.	Different types of cancers.	Antiemetic effect equivalent or superior to Prochlorperazine.	Drowsiness in 2/3 of patients, hallucinations, euphoria.
1979	1	15	Oral THC 10 mg / 5 times per day Vs. Cannabis smoked 1 cigarette / d 1.93% THC.	Sarcoma.	Significant antiemetic effect.	80% sedation patients.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1979, 1981, 1982, 1985, 1987	5	265	Oral THC 1-2 mg 2-3-4 times/ day Vs. Prochlorperazine 5 mg - 7.5 mg-10 mg-20 mg / 2-3-4d.	Various cancers (1 study = paediatric patients).	THC higher anti-emetic effect than Prochlorperazine.	Dry mouth, hypotension, dizziness.
1980, 1988, 1991	3	145	Oral THC 7 mg - 10 mg - 15 mg / 4-7 d Vs. Prochlorperazine 7 mg - 10 mg / 4-7d.	Different types of cancers.	Significantly higher anti-emetic effect. Combination > monotherapy.	Euphoria, dysphoria.
1981	1	36	Oral THC 10 mg / 4-8 d Vs. Haloperidol.	Different types of cancers.	Equivalent antiemetic effect.	Somnolence 58%, vertigo 55%, euphoria 40%.
1980, 1984	2	65	Oral THC 10 mg-12 mg / 3-5 d Vs. Thietylperazine 6.6 mg / 3 d Vs. Metoclopramide 4.5 mg-10 mg / 1-5 d.	Different types of cancers.	Equivalent antiemetic effect between the 3 products or higher when Metoclopramide = 10 mg.	Frequent neuropsychiatric effects, sedation.
1982, 2007	4	208	Oral THC 2 mg / 2d; 1 mg.	Chemotherapy.	Effective.	Well tolerated, sleepiness.
1983	1	20	Oral THC 1 mg / 3 d Vs. Chlorpromazine IM 12.5 mg / 1d.	Gynecological tumours.	Insufficient effect in both products.	Dry mouth and sleepiness.
1983	1	108	Levonantradol IM 0.5 mg / 4d Vs. Levonantradol IM 0.4 mg / 4d Vs. Levonantradol IM 1 mg / 4d Vs. Chlorpromazine IM 25 mg / 4d.	Different types of cancers.	Levonantradol 0.5 mg > Chlorpromazine 25 mg. Higher doses did not increase effectiveness.	0.5 mg Levonantradol well tolerated.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1986	2	56 (20 paediatric).	Oral THC 1 mg - 3 mg Vs. Donperidone 15 mg-60 mg.	Different types of cancers.	Significantly higher antiemetic effects than donperidone.	Well tolerated. sleepiness in 50%.
1986	1	20	Oral THC 2 mg / 2 d Vs Alizapride 150 mg / 3d.	Testicular cancer.	Superior effects of THC.	80% sleepiness. 70% hypotension or tachycardia.
1986	1	32	Oral THC 1 mg / 5d Vs. Metoclopramide IV 1 mg / kg / 5d.	Ovary tumour.	Equivalent but insufficient antiemetic effect.	Drowsiness

Antiemetic Effect (with THC). Summary of the main clinical studies conducted on the antiemetic effects of THC.

Studies consulted.

- Sallan, S. E., et al. (1975). Antiemetic effect of delta-9- tetrahydrocannabinol in patients receiving cancer chemotherapy. New England Journal of Medicine, 293(16), 795-797.
- Herman, T. S., et al (1979). Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. New England Journal of Medicine, 300(23), 1295-1297.
- Sallan, S. E., et al (1980). Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. New England Journal of Medicine, 302(3), 135-138.
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- Frytak, S., et al (1979). Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy: a comparison with prochlorperazine and a placebo. Annals of internal medicine, 91(6), 825-830.
- Johansson, R., et al. (1982). A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory haemesis induced by cancer chemotherapy. Cancer Treatment Reviews, 9, 25-33.
- Ahmedzai, S., et al (1983). Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. British Journal of Cancer, 48(5), 657.
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- Niiranen, A., & Mattson, K. (1985). A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. American journal of clinical oncology, 8(4), 336-340.
- Einhorn, L. H., et al Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. The Journal of Clinical Pharmacology, 21(S1), 64S-69S.
- Chan, H. S., et al. (1987). Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics, 79(6), 946-952.
- Orr, L. E., et al (1980). Antiemetic effect of tetrahydrocannabinol: compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Archives of Internal Medicine, 140(11), 1431-1433.
- McCabe, M., et al(1988). Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Investigational new drugs, 6(3), 243-246.
- Lane, M., et al (1991). Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. Journal of pain and symptom management, 6(6), 352-359.
- Neidhart, J. A et al (1981). Comparative trial of the antiemetic effects of THC and haloperidol. The Journal of Clinical Pharmacology, 21(S1), 38S-42S.
- Colls, B. M., et al (1980). The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. The New Zealand Medical Journal, 91(662), 449-451.
- Gralla, R. J., et al (1984). Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. Cancer treatment reports, 68(1), 163-172.
- Wada, J. K., et al (1982). Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. Cancer Treatment Reviews, 9, 39-44.
- Jones, S. E., et al. (1982). A multi-institutional Phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. Cancer Treatment Reviews, 9, 45-48.
- Levitt, M. (1982). Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treatment Reviews, 9, 49-53.
- Meiri, E., et al (2007). Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Current medical research and opinion, 23(3), 533-543.
- George, M., et al (1983). Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin. Biomedicine & pharmacotherapy= Biomedecine & pharmacotherapie, 37(1), 24-27.
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- Crawford, S. M., & Buckman, R. (1986). Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatinum: a double-blind study. Medical oncology and tumour pharmacotherapy, 3(1), 39.

Table 13.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1981	1	8	Oral THC 2 mg / 2d Vs. Cigarette 1.93% THC / 1d.	Tumours of various kinds.	No antiemetic effect (patients receive cyclophosphamide).	Euphoria, short episodes of tachycardia.
1984	1	20	1 cigarette Vs. Oral THC 15 mg / 4d.	Tumours of various kinds.	Effects in only 25% of patients.	Distorted perception of time.
2010	1	16	THC + CBD spray (1:1).	Chemotherapy.	Significantly improves nausea and vomiting.	-/-

Antiemetic Effect (with full spectrum Medical Cannabis). Summary of the main clinical studies conducted on the antiemetic effects with full spectrum Medical Cannabis.

Studies consulted:

- Shiling, D. J., Stillman, R. C., Chang, A. E., Goldberg, N. H., Seipp, C. A., Barofsky, I., & Rosenberg, S. A. (1981). A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. Cancer, 47(7), 1746-1751.
- Levitt, M., Faiman, C., Hawks, R., & Wilson, A. (1984). Randomized doubleblind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. In Proc Am Soc Clin Oncol (Vol. 3, p. 91).
- Duran, Marta, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. British journal of clinical pharmacology 70.5 (2010): 656-663.

Cannabis in Appetite and Weight Regulation: A Potential Appetite Stimulant for Cachexia, Anorexia, Cancer- or AIDS-Related Appetite Loss, and Anorexia Nervosa

The ability of cannabis preparations to stimulate appetite, particularly for palatable foods, has been documented as far back as 300 BC.[30]
The hyperphagic action of THC (and its degradation product, cannabinol or CBN) is mediated by the stimulation of CB1 receptors, which promote caloric assimilation by amplifying the pleasure derived from food—the hedonistic hunger—resulting in a decreased interval time before starting a new meal.[31]
The stimulation of appetite for therapeutic purposes, using THC and cannabis, has been studied for many decades, especially in relation to:

- cancer-associated cachexia and anorexia;
- acquired immune deficiency syndrome (AIDS)-associated cachexia and anorexia;
- anorexia nervosa.

Cachexia is a term derived from the Greek '*kakos*' (evil) and '*hexis*' (condition), and describes the progressive loss of adipose tissue and body mass due to various chronic debilitating diseases.[31]
Anorexia, in the medical context, refers to a reduced desire to eat, often seen in individuals with chronic illnesses or conditions such as cancer, HIV/AIDS, chronic obstructive pulmonary disease (COPD), heart failure, and other advanced diseases. This loss of appetite can contribute to weight loss and malnutrition, further complicating the management of these conditions. Anorexia nervosa, on the other hand, is a psychiatric disorder characterized by an intense fear of gaining weight and a distorted body image, leading to severe restrictions in food intake and often excessive exercise.
In these conditions, it is possible that patients may lose pleasure or interest in food due to changes in taste perception induced by chemotherapy, or through the development of taste aversions as a consequence of nausea or vomiting resulting from aggressive treatments.[32];[33] Additionally,

elderly individuals experiencing debilitation often encounter a decline in both taste and smell perception.

Cannabinoid preparations stimulate appetite by enhancing the appeal of food pleasure or mitigating the adverse effects on eating habits induced by other therapeutic interventions.[31]

THCV and CBD, in contrast, exert an inhibitory effect on CB1 receptors, resulting in reduced food consumption (THCV is a direct antagonist, whilst CBD a negative allosteric modulator).

To treat cachexia or anorexia, preparations that contain both CBD and THC should therefore maintain a higher proportion of THC to allow CB1 receptor activation (and not 1:1, like Sativex®). In the context of anorexia nervosa, it is hypothesized that combining CBD with other treatments may assist in reducing the anxiety commonly associated with eating.[31]

Here are the main clinical studies carried out in these conditions:

Appetite Control (with THC)

Table 14.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1976, 2002, 2011	3	544	Oral THC 5 mg-22 mg / d; 2.5 mg oral THC Vs. 800 mg megestrol.	Cancer.	THC stimulates the appetite. Weight gain = 0.56kg (placebo = weight loss = 9.6kg). Megestrol more effective than oral THC 2.4 mg.	25% of patients = sleepiness, confusion, dizziness.
1993, 1995, 2003	3	218	Oral THC 2.5 mg; 5 mg; 2.5 mg THC Oral Vs. Smoked Cannabis (3.95% THC).	HIV	Weight gain average 0.5-3.2 kg. Average weight loss placebo of 0.7-1.1 kg.	Generally well tolerated. 3 patients oral THC paranoia and headache.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2006	1	164	THC + CBD (2: 1) Vs oral THC 2.5 mg.	Cancer	No difference with placebo.	-/-

Summary of the main clinical studies conducted on appetite control with THC.

Studies consulted:

- Regelson, et al (1976). Delta-9-THC as an effective antidepressant and appetite-stimulating agent in advanced cancer patients.' The Pharmacology of Marihuana (eds MC Braude, S Szara) pp, 763-776.
- Jatoi, A., et al (2002). Dronabinol versus megestrol acetate versus combinatio therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Journal of Clinical Oncology, 20(2), 567-573.
- Brisbois, T. D., et al (2011). Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomised, double-blind, placebo-controlled pilot trial. Annals of Oncology, 22(9), 2086-2093.
- Struwe, M., et al (1993). Effect of dronabinol on nutritional status in HIV infection.
- Beal, J. E., et al (1995). Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. Journal of pain and symptom management, 10(2), 89-97.
- Abrams, D. I., et al (2003). Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Annals of internal medicine, 139(4), 258-266.
- Strasser, F., et al (2006). Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. Journal of Clinical Oncology, 24(21), 3394-3400.

Appetite Control (with full spectrum Medical Cannabis)

Table 15.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2012	1	7	Cannabis smoked 8% THC-4 cigarettes.	HIV	Significant alteration of appetite hormones.	-/-

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2003	1	67	Cannabis smoked 3.95% THC Vs. 2.5 mg oral THC.	HIV	Weight gain 3-3.2 kg. Equivalent between smoked and oral.	Generally well tolerated.

Summary of the main clinical studies conducted on appetite control with full spectrum Medical Cannabis.

Studies consulted:

- Riggs, P. K., et al (2012). A pilot study of the effects of cannabis on appetite hormones in HIV- infected adult men. Brain research, 1431, 46-52.
- Abrams, D. I., et al (2003). Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Annals of internal medicine, 139(4), 258-266.

Cannabis and Intraocular Pressure: Hypotensive Effect for Glaucoma

Glaucoma is a group of eye conditions that damage the optic nerve, typically due to increased pressure within the eye. This elevated intraocular pressure can lead to progressive vision loss and, if left untreated, can result in irreversible blindness. As early as 1971, studies reported a reduction of 25-30% in intraocular pressure resulting from cannabis smoking, a finding subsequently confirmed by further research conducted on glaucoma patients.[34];[35] Furthermore, several studies have documented the neuroprotective properties of cannabinoids in the retina.[36] To minimize systemic and potential side effects while maximizing the dosage at the site of action, topical administration directly into the eye would be considered ideal for addressing glaucoma. Since cannabinoids are lipophilic molecules, they encounter difficulty penetrating the hydrophilic tear film. Microemulsions and cyclodextrins enhance the corneal penetration of cannabinoids, addressing a significant obstacle. However, these formulations may pose potential inflammatory risks, leading to their limited use across most of Europe.
Here are the main clinical studies carried out.

Glaucoma (with full spectrum Medical Cannabis)

Table 16.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1980	1	18	1 cigarette 2% THC.	Glaucoma	Significant reduction in IOP.	Sensory changes, tachycardia, palpitations.
1981	1	8	Eye drops 0.01% - 0.05%-0.1% THC.	Glaucoma	0.05% - 0.1% THC: significant IOP reduction. 0.01% THC: no effects.	No psychotropic effects but the effects only last a few hours.
2006	1	6	THC + CBD oral extract.	Glaucoma.	significant reduction in IOP.	-/-

Summary of the main clinical studies conducted on glaucoma with full spectrum Medical Cannabis.

Studies consulted:

- Merritt, J. C., et al (1980). Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology, 87(3), 222-228.
- Merritt, J. C., et al (1981). Topical Δ9-tetrahydrocannabinol in hypertensive glaucomas. Journal of Pharmacy and Pharmacology, 33(1), 40-41.
- Tomida, I., et al (2006). Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. Journal of glaucoma, 15(5), 349-353.

Cannabis for the Control of Involuntary Body and Facial Movements: Gilles de la Tourette Syndrome

Gilles de la Tourette syndrome is a neurological disorder characterized by repetitive, involuntary movements and vocalizations called tics. Oral doses of Dronabinol (synthetic THC) in patients with Gilles de la Tourette syndrome have been shown to reduce the frequency of tics over a 6-week period. Despite only few studies on this topic, THC is recommended for the

treatment of Tourette syndrome in adult patients by many experts, when first line treatments failed to improve the tics.[37]
Here are the main clinical studies carried out.

Gilles de la Tourette Syndrome (with THC)

Table 17.

Year	Number of studies	N° of patients	Product and dosage	Results	Side effects
2002, 2003	2	36	Oral THC 5 mg-7.5 mg-10 mg / 1 d.	Significant decrease in tics and OCD improvement (efficacy after 3 weeks).	Anxiety in one patient.

Summary of the main clinical studies conducted on Gilles de la Tourette syndrome with THC.

Studies consulted:

- Müller-Vahl, K. R., et al (2002). Treatment of Tourette's syndrome with Δ9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry, 35(02), 57-61.
- Müller-Vahl, K. R., et al (2003). Δ9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomised trial. The Journal of clinical psychiatry.

Neuroprotective Effects of Cannabis

Current scientific knowledge supports the use of phytocannabinoids for the treatment of both acute and chronic neurodegeneration.
Cerebral ischemia and head trauma are the two main causes of acute neurodegeneration for which Medical Cannabis appears to have potential benefit, as well as for five types of chronic neurodegeneration, for which there is data from clinical use in addition to laboratory studies.[38]

- Multiple Sclerosis (MS);
- Alzheimer's Disease (AD);
- Parkinson's Disease (PD);
- Huntington's Disease (HD);

- Amyotrophic Lateral Sclerosis (ALS).

Robust scientific evidence demonstrates the neuroprotective effects of phytocannabinoids. There are numerous clinical studies indicating the cytoprotective effects of cannabinoids not only on neurons, but also on glial cells, which are non-neuronal components of the brain. These findings reveal the broad spectrum of protection cannabinoids offer against diverse forms of injury or trauma.[39]

The neuroprotective effects of phytocannabinoids are equivalent to those of anti-cytotoxic medications (such as glutamate receptor antagonists), calcium channel blockers (nimodipine), antioxidants (coenzyme Q10), anti-inflammatories (minocycline), or other neuroprotective pharmacological therapies used in individual treatments. Phytocannabinoids combine all these properties, which is a significant aspect for neurodegenerative pathologies, where neuronal damage results from the progressive combination of various cytotoxic events: mitochondrial degeneration, inflammation, and oxidative stress.[40];[41]

Cannabis and Epilepsy

The use of cannabis to manage epileptic seizures is among the earliest known applications of the plant. The first scientific publication in this matter for the Western world was written by William O'Shaughnessy, an Irish physician. In 1840, after years of work in India, O'Shaughnessy documented the administration of hemp tincture for the treatment of infantile epileptic seizures.[42]

In 1890, Queen Victoria's personal physician, Dr J.R. Reynolds, described Cannabis as: "the most useful agent I know of for treating attacks of violent convulsions."[43]

Since 1967, there has been a plethora of medical reports documenting the use of cannabis in treating epilepsy. These reports highlight cases where patients have successfully eliminated all episodes of *petit mal* and *grand*

mal epilepsy, even in cases where the condition had previously shown resistance to conventional anticonvulsant medications.[44]

CBD is definitely a more reliable anticonvulsant molecule than THC, demonstrating clinically significant positive effects in epileptic children who are unresponsive to conventional antiepileptic drugs. Notably, CBD is better tolerated in pediatric patients than traditional antiepileptics and does not elicit motor or neurotoxic adverse effects.[45]

Indeed, Epidiolex® is a CBD-based product that has gained approval for the treatment of Dravet Syndrome and Lennox-Gastaut Syndrome, both of which are highly aggressive forms of epilepsy resistant to conventional drugs, particularly affecting children and adolescents.[46];[47]

The minor cannabinoids CBDV, THCV, and THCA hold potential for greater efficacy as anticonvulsants compared to CBD. However, it's important to note that there is a lack of direct clinical studies comparing the efficacy of these phytocannabinoids.

Here are the key clinical studies conducted.

Epilepsy (with CBD)

Table 18.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
1980, 1986, 1990	3	39	Oral CBD 200 mg - 300 mg/d.	Secondary refractory generalised epilepsy.	55% = without crisis. 30% = clinical improvement.	1/4 = sleepiness.
2017	1	120 children (9.8 mean age).	20 mg/kg/d CBD.	Dravet syndrome.	43% => 50% attack reduction 62% parents rate the child's condition improved.	Somnolence (36%).

Year	Number of studies	Nº of patients	Product and dosage	Pathology	Results	Side effects
2017	2	396 adolescents (16 mean age).	10 mg/kg, 20 mg/kg CBD.	Lennox-Gastaut.	Decreased the frequency of attacks and improved the outcome according to caregivers.	Diarrhoea (18.6%).

Summary of the main clinical studies conducted on epilepsy with CBD.

Studies consulted:

- Cunha, J. M., et al (1980). Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology, 21(3), 175-185.
- Ames FR, et al. (1990). Double-blind clinical study of cannabidiol as a secondary anticonvulsant, presented at: Marijuana'90 International Conference on Cannabis and Cannabinoids; 1990 July 8-11, Kolymbari, Crete. International Association for Cannabinoid Medicines.
- Cross, J. H., et al. (2017). Cannabidiol (CBD) reduces convulsive seizure frequency in Dravet syndrome: results of a multi-center, randomized, controlled trial (GWPCARE1) (CT. 001).GW Pharmaceuticals Announces Positive Phase 3 Pivotal Trial Results for Epidiolex® (cannabidiol) in the Treatment of Lennox-Gastaut Syndrome.
- Thiele, E. A., et al. (2018). Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double- blind, placebo-controlled phase 3 trial. The Lancet, 391(10125), 1085-1096.

Cannabis and Eye Diseases: Retinopathy, Macular Degeneration, and Uveoretinitis

Oxidative stress, often attributed to the presence of free radicals, and inflammation are significant contributors to various eye diseases. These conditions extend beyond glaucoma and encompass, among others:

- Diabetic retinopathy;
- Macular degeneration;
- Uveoretinitis.

In diabetic retinopathy and macular degeneration, oxidative stress is considered the triggering cause, while inflammatory responses are sec-

ondary to oxidative damage and contribute to neuronal death; uveoretinitis, on the other hand, is a disease dominated by inflammation.
Cannabinoids, due to their antioxidant, anti-inflammatory, and neuroprotective properties, have emerged as promising therapeutic agents for the treatment of ocular diseases. In particular, CBD stands out as a promising foundation for the development of therapies targeting degenerative conditions that threaten vision.[49]

Cannabis in Dermatology

The antiproliferative effects of cannabinoids and Anandamide on keratinocytes (skin cells) suggest that the Endocannabinoid System is involved in the etiology of psoriasis.[50] Phytocannabinoids such as THC, CBN, CBD and CBG have demonstrated the ability to suppress the proliferation of human keratinocyte cell lines, a mechanism relevant to the pathophysiology of psoriasis.[51] Furthermore, additional studies have confirmed the ability of phytocannabinoids to inhibit the overgrowth of epidermal skin cells.[52]
Regarding melanoma, studies from 2006 revealed that cannabinoid receptor activators decrease growth, proliferation, angiogenesis and metastasis of human melanoma both in *vitro* and *in vivo*, revealing potential beneficial effects of the Endocannabinoid System in this type of cancer.[53]
Finally, topical application of Adelmidrol®, a palmitoylethanolamide (PEA) analogue (i.e. a PEA-like endocannabinoid), has shown efficacy in treating atopic dermatitis by decreasing mast cell activation and related inflammatory effects.[54]

Cannabis and Cardiovascular Disease

Sufficient scientific evidence from preclinical studies supports the potential of phytocannabinoids to exert beneficial effects in cardiovascular, metabolic and hepatic and renal diseases. In particular, CBD is said to be

beneficial in protecting against damage caused by myocardial ischemia, heart attacks, cardiac arrhythmias, neonatal stroke, and in aiding the recovery of cognitive functions following these traumas or following neonatal hypoxia.[55];[56]

Cannabis in Metabolic Disorders

A substantial amount of evidence, encompassing both preclinical and clinical studies, indicates that the activation of CB1 receptors contributes to the onset and progression of diabetes as well as its major complications. Consequently, the use of cannabinoids that activate CB1 receptors, such as THC, warrants careful evaluation in diabetic patients and those experiencing complications of diabetes, including neuropathic pain arising from the condition.[57]

On the other hand, CBD exhibits promising therapeutic potential for these diseases. Research has explored CBD's efficacy in type 1 diabetes, revealing its ability to decrease the incidence of autoimmune diabetes onset.[58] Additionally, when administered after the manifestation of initial symptoms in non-obese mice with hereditary diabetes, CBD has been observed to arrest disease progression.[59]

Furthermore, in a model of type II diabetes induced in animals through a high-fat diet, researchers demonstrated that while all control mice developed diabetes within an average of 17 weeks, the majority of mice treated with CBD remained free from diabetes until week 26. These findings correlated with reduced inflammation in the insulin-producing pancreatic islets and a lower overall body weight compared to their untreated counterparts.[60]

Tetrahydrocannabivarin (THCV), a constituent of cannabis, behaves differently from THC by acting as a CB1 receptor antagonist and a CB2 receptor agonist. This dual action results in hypophagia, or reduced appetite, while also triggering CB2 receptors, which are believed to confer protective effects against obesity and metabolic disorders.[61]

THCV has been demonstrated to enhance the body's energy expenditure, mitigate glucose intolerance, and improve insulin sensitivity.[62] THC has also shown to attenuate the severity of the immune response and blood glucose levels in type I diabetes, as evidenced in animal studies.[63];[64]

Similarly, prolonged exposure to THC in animals results in decreased weight, reduced food intake, and diminished fat reserves during the duration of drug exposure.[65]

Furthermore, cross-sectional data gathered from a 6-year period in the National Health and Nutrition Examination Survey (NHANES) suggests that cannabis use is correlated with a lower prevalence of Diabetes Mellitus compared to the non-using population.[66]

Given the demonstrated capacity of cannabis, when used acutely, to induce insulin resistance, the collective data mentioned could potentially signify peripheral desensitization of CB1 receptors arising from chronic cannabis consumption.[67]

This mechanism could potentially contribute to the decreased prevalence of obesity among cannabis users in comparison to non-users. This effect remains consistent even after adjusting the statistical data for factors such as tobacco use, gender, age, and hereditary predisposition.[68]

Cannabis and Gastrointestinal Disorders

Cannabinoids decrease gastric acid secretion in animals through activation of CB1 receptors.[69] This activation is also protective in animal models of gastric ulcers induced by aspirin and stress.[70];[71]

THC produces a marked reduction in gastric ulcers, without altering the quiescent production of acid in animals, but only that induced by (pathological) histamine.[72]

Furthermore, cannabinoids that activate CB1 receptors have been shown to reduce motility in the gastric, small intestine, and colon, as well as diminish contractions and peristalsis in intestinal smooth muscles.[73];[74]

Consequently, THC and CBN are implicated in decreasing intestinal transit speed and gastric emptying.

Both CBD and CBC are being recognized for their potential to modulate intestinal motility without diminishing transit, which is a common side effect of many anti-diarrheic agents that can lead to constipation. Additionally, they are observed to normalize intestinal motility following inflammation, owing to their antispasmodic effect.[75]

THC, CBD, CBC and CBG have demonstrated beneficial effects in chronic intestinal diseases, such as IBD.[76]

Clinical trials have evaluated the use of Medical Cannabis in Crohn's disease, revealing improvements in quality of life, weight gain, ability to work, and social interactions, along with a reduction in pain and depression.[77]

Below are the main clinical studies conducted in the field of intestinal disorders.

Intestinal Dysfunctions (with THC)

Table 19.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2006, 2007	2	82	Oral THC 2.5 mg.	Healthy volunteers.	THC relaxes the colon and reduces post-meal motility.	-/-
2011, 2012	3	121	Oral THC 2.5 mg - 5 mg - 10 mg.	IBS	Reduced colon motility IBS-D. No effect on visceral hypersensitivity.	-/-

Summary of the main clinical studies conducted on intestinal dysfunctions with THC.

Studies consulted:

- Esfandyari, T., et al (2006). Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomised, placebo-controlled study. Neurogastroenterology & Motility, 18(9), 831-838.
- Esfandyari, T., et al (2007). Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. American Journal of Physiology-Gastrointestinal and Liver Physiology, 293(1), G137-G145.
- Wong, B. S., et al (2011). Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology, 141(5), 1638-1647.
- Klooker, T. K., et al (2011). The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterology & Motility, 23(1), 30-e2.
- Wong, B. S., et al (2012). Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhoea. Neurogastroenterology & Motility, 24(4), 358-e169.

Intestinal dysfunctions (with full spectrum Medical Cannabis)

Table 20.

Year	Number of studies	Nº of patients	Product and dosage	Pathology	Results	Side effects
2013	1	21	Cannabis smoked 115 mg THC.	Crohn's disease.	Significant and beneficial effects in 10/11. Remission not obtained. Reduction of 100 CDAI points (Crohn's Disease Activity Index).	-/-

Summary of the main clinical studies conducted on intestinal dysfunctions with full spectrum Medical Cannabis.

Studies consulted:

- Naftali, T., et al (2013). Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clinical Gastroenterology and Hepatology, 11(10), 1276-1280.

Cannabis and Cancer Patients

Cannabinoids are acknowledged for their effects in palliative cancer patients.[78]

Their primary application lies in mitigating chemotherapy-induced nausea and vomiting, as well as managing cancer-related pain.

Another potential palliative use of cannabinoids in oncology, supported by Phase 3 clinical trials, includes stimulating appetite and decreasing debilitation (cachexia).[79]

Apart from these uses, the application of cannabinoids in oncology may not be restricted to the palliative actions mentioned above.

Numerous preclinical studies have suggested that THC and other cannabinoids exhibit antitumor effects, which have been observed across a diverse array of animal models of cancer.[80]

These findings prompted the initiation of pilot clinical studies aimed at examining the antitumor effects of THC in patients with glioma. Moreover, the combined administration of CBD and THC has been shown to enhance the antitumor activity of THC and reduce the doses required to induce inhibitory effects on tumor growth.[81];[82];83]

In conclusion, animal studies have demonstrated that cannabinoids induce tumor cell death and inhibit angiogenesis, the aberrant formation of new capillaries that facilitates tumor enlargement and metastasis. There are indications that cannabinoids exert similar effects on patients with Glioblastoma Multiforme (GBM).[84]

Here are the main clinical studies carried out in cancer patients:

Cancer (with THC)

Table 21.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2006	1	9	THC (intra-tumor) 100 mg / 1d.	GBM	Inhibition of tumour proliferation. Decrease in tumour markers.	-/-

Summary of the main clinical studies conducted on cancer patients with THC.

Studies consulted:

- Guzman, M., et al (2006). A pilot clinical study of Δ 9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. British journal of cancer, 95(2), 197.

Cancer (with full spectrum Medical Cannabis)

Table 22.

Year	Number of studies	Nº of patients	Product and dosage	Pathology	Results	Side effects
2013	1	30	THC:CBD (1:1).	GBM	83% 1-year survival (placebo = 44%).	Well tolerated. Vomiting (75%).

Summary of the main clinical studies conducted on cancer patients with full spectrum Medical Cannabis.

Studies cited:

- Sativex Enters Phase III Clinical Programme In Cancer Pain | GW Pharmaceuticals, plc. 2019. Sativex Enters Phase III Clinical Programme In Cancer Pain | GW Pharmaceuticals, plc. [ONLINE].

Cannabis and Bone Diseases

Following the discovery of the skeletal cannabinoid system, significant attention from the scientific community has been directed towards this area.[85] Currently, CB2 receptors appear to play the most promising role. Specifically, CBD (but not THC) appears to enhance healing from fractures.[86] In the future, there is optimism that THCV and β-caryophyllene, a terpene found in the essential oil of black pepper and cannabis, both of which activate CB2 receptors, can undergo further detailed study for the treatment of osteoporosis.[87]

Cannabis and Sleep Disorders

Cannabinoids hold significant therapeutic potential for addressing both insomnia and sleepiness. THC may act as a sedative to promote sleep

induction, while CBD appears to enhance sleep quality in individuals with sleep disorders.[88]

CBD exhibits a biphasic effect on sleep. At low dosages, it promotes wakefulness by increasing alertness and elevating extracellular dopamine levels. However, at higher dosages, CBD can mitigate sleep suppression induced by anxiety states, thereby facilitating rest.[89]

Patients suffering from post-traumatic stress disorder (PTSD), fibromyalgia and chronic pain show significant improvements in sleep duration and quality when treated with a synthetic THC-like drug, Nabilone.[90];[91]

Medical Cannabis in Patients with Psychiatric Issues and Mood Disorders

The treating physician must consistently weigh the risk/benefit ratio in the medical utilization of cannabis. It's crucial to consider that the primary contraindications involve individuals with a personal or family history of psychiatric disorders, including schizophrenia and manic-depressive disorders. This is because cannabis, particularly THC, has the potential to trigger psychotic episodes and transient cognitive symptoms, both positive and negative, associated with schizophrenia.[92]

Schizophrenia

Heavy cannabis use in adolescents and young adults is correlated with an increased likelihood of psychosis diagnosis.[93] Why cannabis causes such effects is still debated nowadays. Evidence suggests that although most people who consume cannabis do not develop schizophrenia, chronic THC consumption can lead to lower levels of Anandamide. The reduction of this endocannabinoid in the cerebrospinal fluid is directly correlated with an increased likelihood of psychosis.[94];[95];[96]

Additionally, it is probable that young individuals who engage in chronic heavy cannabis use, rather than medicinal use, are precisely those who, due to environmental and/or genetic risk factors, are more susceptible to psychosis. This usage pattern may prompt them to experience their first

psychiatric episode approximately two years earlier than if they had abstained from cannabis use.[97]

Below is the main clinical study with THC in patients with schizophrenia:

Schizophrenia (with THC)

Table 23.

Year	Number of studies	Nº of patients	Product and dosage	Results	Side effects
2005	1	13	THC (IV) 2.5 mg-5mg.	Exacerbation of psychotic effects.	-/-

Summary of the main clinical studies conducted on schizophrenia with THC.

Studies cited:

- D'Souza, D. C., et al (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biological Psychiatry, 57(6), 594-608.

Depression

There is evidence associating chronic cannabis use with changes in indices of mental health and well-being.[98] Meta-analyses have suggested a link between heavy cannabis use and depression, and a direct correlation between THC levels in the hair of young chronic users with levels of anxiety and depression.[99];[100]

However, a 2013 epidemiological study indicates that the rise in depression associated with cannabis misuse may not have long-term effects. Additionally, no significant associations were discovered between adolescent cannabis use and depression by the age of 30. It is suggested that the factors predisposing individuals to cannabis use may also elevate their risk for common mental illnesses such as anxiety and depression.[101]

Anxiety and Post-Traumatic Stress Disorder (PTSD)

Patients experiencing post-traumatic stress disorder (PTSD) often find relief from persistent daytime traumatic flashbacks and frequent night-

mares when treated with Nabilone. This synthetic compound, which acts similarly to THC, is commonly utilized in medicine as an antiemetic and analgesic.[102] Clinical reports have confirmed the benefits of cannabis in reducing the severity of PTSD symptoms. In general, the results obtained in clinical practice are consistent with animal studies, where regulation of the Endocannabinoid System has been found to be directly related to the extinction of fear responses following traumatic experiences.[103]

For example, activation of CB1 receptors induces the extinction of trauma/ fear memories, whereas reduction of CB1 activity, by blocking these receptors, prevents the elimination of behaviour reflecting conditioned fears.[104];[105];[106];[107]

CBD, on the other hand, appears to be a very useful anxiolytic. CBD is a cannabinoid that is considered *pleiotropic*, meaning that it acts via several pathways and not just one type of receptor. Several studies, conducted on both animals and humans, have shown that CBD reduces anxiety through its interaction in the brain with serotonin 5-HT1A receptors, helping both patients suffering from anxiety and healthy people under stress (e.g. public speaking).[108];[109] Here are the main clinical studies carried out in anxiety.

Anxiety (with CBD)

Table 24.

Year	Number of studies	Nº of patients	Product and dosage	Pathology	Results	Side effects
2011	2	46	Oral CBD 400-600 mg / 1 d.	SAD	Significant reduction in anxiety, discomfort and cognitive decline correlated with public speaking and associated with impaired activity in limbic areas of the brain.	-/-

Summary of the main clinical studies conducted on anxiety with CBD.

Studies consulted:

- Bergamaschi, M. M., et al (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology, 36(6), 1219.
- Crippa, J. A. S., et al (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. Journal of psychopharmacology, 25(1), 121-130.

Anxiety (with full spectrum Medical Cannabis)

Table 25.

Year	Number of studies	N° of patients	Product and dosage	Pathology	Results	Side effects
2013	1	48	CBD vaporisation 32 mg.	Healthy subjects.	CBD consolidates the extinction of fear.	-/-

Summary of the main clinical studies conducted on anxiety with full spectrum Medical Cannabis.

Studies cited:

- Das, R. K., et al (2013). Cannabidiol enhances consolidation of explicit fear extinction in humans. Psychopharmacology, 226(4), 781-792.

CBD and Psychosis

CBD can attenuate the psychotomimetic effects sometimes associated with THC and exert antipsychotic effects.[110] In 1995, Zuardi and his co-workers found a significant improvement during treatment with CBD in a 19-year-old young woman who had serious side effects with conventional antipsychotics. No side effects were found with CBD.

More recently (in 2006), however, the same research group did not find CBD monotherapy to be effective with treatment-resistant schizophrenia patients.[111];[112] CBD, therefore, appears to have antipsychotic effects especially in patients with non-refractory schizophrenia.

Several clinical studies have compared CBD to atypical antipsychotics and the effects obtained were similar or better for CBD, especially in con-

trolling the 'negative' symptoms of schizophrenia (depression, withdrawal, etc.); CBD has been described as a safe and tolerable drug with significantly fewer side effects than traditional drugs used as antipsychotics.[113]
CBD has also demonstrated efficacy in the treatment of psychotic symptoms associated with Parkinson's disease; in part this may be due to CBD's ability to increase serum levels of Anandamide.[114]
CBD thus demonstrates a similar profile to atypical antipsychotics, but its use is associated with fewer side effects.[115]
Below are the main clinical studies with CBD in psychiatric patients.

Psychosis (with CBD)

Table 26.

Year	Number of studies	N° of patients	Product and dosage	Results	Side effects
2007	1	42	Oral CBD 200 mg-800 mg / 1d Vs. Amisulpride 200 mg - 800 mg / 1d.	Significantly reduces the psychopathological symptoms of acute psychosis. CBD is equivalent to amisulpride but with fewer side effects.	-/-
2012	1	42	Oral CBD 800 mg Vs. Amisulpride 800 mg.	Significant antipsychotic effects and Anandamide increase in serum.	-/-

Summary of the main clinical studies conducted on psychosis with CBD.

Studies cited:

- Leweke, F. M., et al. (2007). Cannabidiol as an antipsychotic. A double-blind, controlled clinical trial on cannabidiol vs. amisulpride in acute schizophrenia. Abstract for oral sessions. European Psychiatry, 22, S14.
- Leweke, F. M., et al (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational psychiatry, 2(3), e94.

Cannabis in Rheumatoid Arthritis

Increasing evidence suggests that the Endocannabinoid System, in particular the CB2 receptors, plays an important role in the pathophysiology

of rheumatoid arthritis. Preliminary data show that specific activation of CB2, in particular, may alleviate rheumatoid arthritis by inhibiting production of autoantibodies, proinflammatory cytokines and metalloproteinases responsible for autoimmune activation.[116]

Studies in humans, however, are limited and the results are not conclusive. A clinical trial with 58 patients showed that Sativex®, compared to placebo, was able to induce statistically significant improvements in pain on movement, pain at rest and sleep quality.[117]

These data should be taken with caution. In fact, a 2021 systematic review of the literature concluded that improvements with the use of cannabis and cannabinoids are modest and central nervous system activation could result in adverse events.[118]

In contrast, surveys on self-medication with cannabis and anecdotal reports indicate that about 20 percent of patients with rheumatoid arthritis use cannabis and report improved pain.[119]

Conclusions

Decades of scientific literature have demonstrated the efficacy of cannabis in treating various pathological conditions. Data from animal models suggest that other pathologies will soon be added to the list.

In the subsequent paragraphs, we will delve into a more detailed analysis of the effectiveness of cannabis in various medical conditions. Included are insights provided by prescribers regarding the practical use of medical cannabis in treating these conditions.

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3.1.1. Case Studies: Fibromyalgia

Here we present four case studies that delve into the use of cannabinoids in the treatment of fibromyalgia, showcasing different approaches and outcomes. The first three cases are provided by Dr. Valeria Giorgi, a specialist in fibromyalgia treatment who has been incorporating cannabinoid therapy into her practice with notable success. The fourth case is contributed by Dr. Sandra Carrillo, known for her pioneering work in medical cannabis research and its application in chronic pain management. Together, these case studies offer valuable insights into the therapeutic potential of cannabinoids in alleviating the symptoms of fibromyalgia, reflecting diverse patient experiences and treatment methodologies.

Fibromyalgia and Depression

Dr. Valeria Giorgi, a medical researcher specializing in fibromyalgia syndrome, currently works as assistant physician in internal medicine at Gruppo Ospedaliero Moncucco, Lugano (Switzerland) and as a research collaborator at the Rheumatology department, IRCCS Galeazzi-S. Ambrogio, Milan (Italy). She has decided to share three compelling cases of patients with fibromyalgia who were treated with medical cannabis.

Dr. Giorgi presents the case of a 42-year-old woman diagnosed with fibromyalgia syndrome and comorbid anxiety-depressive syndrome with panic attacks, previously managed by her family doctor.

Prior to starting cannabinoid treatment, the woman was receiving the following medications:

- Opiates: tramadol and oxycodone + naloxone;
- NSAIDs: paracetamol as needed;
- Antidepressant (SSRI);
- Benzodiazepines: used both as needed and as daily therapy for insomnia and anxiety.

Following the initial consultation, the woman initiated Medical Cannabis therapy, utilizing:

- Bedrocan extract (oil) (THC 22%, CBD 1%), 2 drops in the evening;
- Bediol extract (oil) (THC 6.3%, CBD 8%), 3 drops in the morning.

Both oils were extracted and decarboxylated according to the Romano/Hazekamp method.[1]

Due to side effects (particularly autonomic and increased anxiety), the treatment with Bedrocan oil was discontinued. Subsequently, the dosage of Bediol oil was increased to a maximum of 5/10 drops in the morning and 10/15 drops in the evening. An extract (oil) of Bedrolite (THC 1%, CBD 9%) was introduced into the therapy, although it was not consistently continued. After eight months of therapy, the doctor reported the following outcomes:

- The woman reported immediate improvement in pain.
- There was little to no effect on cognitive dysfunction and fibrofog (cognitive fog, a characteristic symptom of fibromyalgia patients), which was significant in the patient.
- Pain symptom relapses occurred occasionally and were managed with analgesics and increased cannabinoid dosage.
- Overall, there was a substantial reduction in opiate intake (oxycodone was discontinued, and tramadol dosage decreased, primarily for as-needed use), as well as in benzodiazepine usage, although not completely eliminated.

The reported side effects were:

- Dizziness (feeling light-headed), for which it was impossible to increase the morning dosage.
- Anxiety and palpitations (presumably due to THC), so Bedrocan was eliminated.

Fibromyalgia with Migraine, Depression and PTSD

The next case presented by Dr. Giorgi involves a 63-year-old woman presenting with a range of symptoms related to fibromyalgia. She had:

- Fibromyalgia syndrome;
- Chronic migraine;
- Major depression and post-traumatic stress disorder (PTSD), under psychiatric care.

The woman was previously treated with:

- Opiates;
- Indomethacin + Caffeine + Prochlorperazine (anti-migraine), in suppositories;
- Antipsychotic;
- Antidepressants.

Medical cannabis treatment was introduced as an adjunct to the existing therapy, which had been sustained for eight years:

- Bedrocan extract (oil) (THC 22%, CBD 1%), up to 40 drops daily, the dosage was self-administered in consultation with the neurologist at the headache center;
- Bediol extract (oil) (THC 6.3%, CBD 8%), approximately 30 drops daily.

Both oils were extracted and decarboxylated according to the Romano/Hazekamp method.[1] After approximately two years of Medical Cannabis therapy, Dr. Giorgi reports that:

- The patient experienced a drastic reduction in migraine attacks, leading to a reduction in Indomethacin + Caffeine + Prochlorperazine.
- Opioid usage remained largely unchanged, with only a slight reduction noted at the beginning of therapy.

The woman reported no particular side effects during the therapy.

Fibromyalgia and Undifferentiated Connective Tissue Disease

The third case reported by Dr. Giorgi involves a 37-year-old woman diagnosed with fibromyalgia syndrome and undifferentiated connectivitis. The patient was a nurse in the hospital, and, due to fibromyalgia, she had to discontinue her nursing duties and transitioned to an administrative role.
The woman had previously undergone treatment with:

- Low-dose hydroxychloroquine;
- Painkillers as needed (NSAIDs, paracetamol).

The prescribed Medical Cannabis therapy was:

- Bedrocan extract (oil) (THC 22%, CBD 1%), 2 drops in the evening;
- Bediol extract (oil) (THC 6.3%, CBD 8%), 3 drops in the morning.

Both oils were extracted and decarboxylated according to the Romano/Hazekamp method.[1] During the therapy, the patient felt a particular benefit with the Bedrocan extract. However, she noticed a decrease in its effect in the afternoon. To address this, it was decided to administer the dose three times a day. An additional dose was added in the middle of the afternoon, which the patient was able to take at work by bringing an ice bag containing the oil. The new dosing schedule allowed the patient to take 8 drops in the morning, 10 drops in the afternoon, and 15 drops in the evening.
After approximately six months of Medical Cannabis therapy, Dr. Giorgi reports that the patient has significantly decreased her use of NSAIDs (paracetamol is only occasionally used).
The patient reported no particular side effects, apart from a slight increase in asthenia.

Final Remarks

In all three reported case studies, Dr. Giorgi notes that beginning in the COVID-19 lockdown year 2020, there was a significant disruption in the

availability of cannabis preparations. As a result, patients were left without access to their treatment for several months.

Interestingly, Dr. Giorgi points out that in all fibromyalgia patients the effect of cannabis is extremely subjective and depends (also according to some studies) on prejudices about the substance itself and on previous personal experiences with cannabis (some patients already used cannabis independently for pain relief).

Fibromyalgia patients exhibit a particularly strong nocebo (and placebo) effect. Consequently, the doctor refrained from recommending cannabis to patients who had previously experienced negative effects with the substance or had significant ethical and moral prejudices against it. Interestingly, there was a notable age-related difference in these attitudes.

The extraction method has been progressively, where possible, modified from Romano/Hazekamp to the more standardised SIFAP/SIFO (proposed and approved by the Italian Society of Preparatory Pharmacists and the Italian Society of Hospital Pharmacy).

Below is a summary table of the cases reported.

Table 27.

	Patient 1	**Patient 2**	**Patient 3**
Age and gender:	42-years-old, female.	63-years-old, female.	37-years-old, female.
In therapy by:	8 months.	approximately 2 years.	6 months.
Diagnosis:	Fibromyalgia syndrome; Anxiety-depressive syndrome with panic attacks.	Fibromyalgia syndrome; Chronic migraine; Major depression and PTSD.	Fibromyalgia syndrome; Undifferentiated connectivitis.
Possible therapy in place prior to the use of Medical Cannabis or cannabinoids:	Opiates: tramadol and oxycodone + naloxone NSAIDs, paracetamol as needed Antidepressant (SSRI) Benzodiazepines (both as needed and as daily therapy for insomnia and anxiety).	Opiates Indomethacin + Caffeine + Prochlorperazine, in suppositories, at maximum dosage. Antipsychotic Antidepressants.	Low-dose hydroxychloroquine Painkillers as required (NSAIDs, paracetamol).

	Patient 1	Patient 2	Patient 3
Current therapy:	Bedrocan extract (oil) (THC 22%, CBD 1%). Bediol extract (oil) (THC 6.3%, CBD 8%).	Bedrocan extract (oil) (THC 22%, CBD 1%). Bediol extract (oil) (THC 6.3%, CBD 8%).	Bedrocan extract (oil) (THC 22%, CBD 1%). Bediol extract (oil) (THC 6.3%, CBD 8%).
Starting dosage:	Bedrocan oil, 2 drops morning and evening; Bediol oil, 3 drops morning and evening.	Bedrocan oil, up to 40 drops daily, self-administration of dosage in agreement with the neurologist of the headache centre ; Bediol oil, 20/30 drops in the morning and 30 drops in the evening.	Bedrocan oil, 2 drops morning and evening; Bediol oil, 3 drops morning and evening.
Possible corrections in dosage:	Bedrocan oil has been discontinued; The dosage of Bediol oil was increased to a maximum of 5/10 drops in the morning and 10/15 drops in the evening.	None	Increase the dosage of Bedrocan oil to 3 times a day, 8 drops in the morning, 10 in the afternoon and 15 in the evening.
Results obtained with the use of Medical Cannabis (follow-up):	The patient reports immediate improvement in pain. No (or modest) effect on cognitive dysfunction/ fibrofog (which was significant in the patient). Relapses of pain symptoms also occur and are treated with analgesics and increased dosage of cannabinoids. In general, there is a marked reduction in opiates, with oxycodone being eliminated, tramadol used mainly as needed and benzodiazepines being decreased (although these have not been completely eliminated).	The patient reported a drastic reduction in migraine attacks, which was accompanied by a reduction in Indomethacin + Caffeine + Prochlorperazine. Opiates were not decreased, except slightly at the beginning of therapy.	Use of NSAIDs decreased significantly (occasional use of paracetamol).
Any reported side effects:	Dizziness, so it was impossible to increase the dosage in the morning. Anxiety and palpitations (presumably due to THC), so Bedrocan was eliminated.	None	No particular side effects, perhaps a slight increase in asthenia.

	Patient 1	Patient 2	Patient 3
Other considerations:	Since COVID, there has been a significant problem finding cannabis preparations, so for several months patients have been without a preparation. In all fibromyalgia patients the effect of cannabis is extremely subjective and depends (even according to some studies) on prejudices about the substance itself and on previous personal experiences with cannabis (some patients were already using cannabis independently for pain). Fibromyalgia patients suffer from an extremely pronounced nocebo (and placebo) effect, which is why cannabis was not recommended for patients who had had negative effects from previous experiences or those who had major ethical and moral prejudices..		

Case studies in the treatment of fibromyalgia with Medical Cannabis, as reported by Dr. Giorgi.

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Fibromyalgia Management with Medical Cannabis

Dr. Sandra Carrillo, specializing in cannabinoid therapies, shares the case of a 50-year-old female diagnosed with fibromyalgia in 2018. This study demonstrates the substantial benefits and strategic adjustments of cannabinoid-based treatments for managing chronic conditions like fibromyalgia.

Patient Background and Initial Condition

The patient is a 50-year-old female diagnosed with fibromyalgia in 2018. Before transitioning to cannabinoid therapy, the patient was prescribed a variety of medications, which included:

- Gabapentin 300 mg/day;
- Pregabalin 150 mg/day;
- Escitalopram 10 mg/day;
- Clonazepam 2 mg;
- Ketorolac 10 mg/day;
- Ibuprofen 200 mg;
- Esomeprazole 40 mg/day.

These medications were reduced following the introduction of cannabinoid therapies due to adverse side effects.

Cannabinoid Therapy Introduction and Adjustment

Dr. Carrillo prescribed:

- A Cannabis Sativa sublingual extract (oil), with a CBD-dominant profile, namely 100 mg/ml CBD and <20 mg/ml THC;
- A balanced extract, with CBD/THC 1:1 (12 mg/ml CBD and 14 mg/ml THC).

The administration route was sublingual for both extracts. The therapy started with the CBD dominant extract at 0.1 cc in the morning, increasing by 0.1 cc every three days. The balanced extract was introduced at 0.1 cc in the afternoon after two weeks, increasing to 0.3 cc based on symptom control.

Duration of Therapy and Clinical Outcomes

The treatment was carried on for 2 years. Dr. Carrillo reported the following effects:

- Significant reduction in pain, with the Visual Analogue Scale (VAS) score decreasing from 7 to 3;

- the sleep quality enhanced considerably, with sleep onset reduced to 10 minutes and total sleep duration extending to 8 hours;
- a marked improvement in the quality of life: the patient resumed work after resigning two years earlier due to debilitating symptoms;
- a reduction in polypharmacy, thanks to an effective management that allowed for the cessation of most prior medications, focusing solely on cannabinoid therapies.

The reported side effects were dry mouth and mild dizziness, which were non-impairing.

Additional Recommendations

The patient was encouraged to maintain a healthy lifestyle, including regular exercise, proper nutrition, and a sleep hygiene routine.
Here is the summary of this case study:

Table 28.

	Patient 2
Age & Gender:	50 years old, female.
Diagnosis:	Fibromyalgia
Date of diagnosis:	2018
Previous therapy before the use of medical cannabis or cannabinoids:	Gabapentin 300 mg /dia. Pregabalin 150 mg/day. Escitalopram 10 mg/dia. Clonazepam 2mg. Ketorolac 10 mg /day, Ibuprofen 200 mg/day.Esomeprazole 40 mg/day.
Current therapy (whether it has been added to the previous treatment or replaced, details of prescribed medical cannabis or cannabinoids, strains, THC: CBD ratio, starting dosage, etc.):	Cannabis Sativa Sublingual Extract (Oil). 1. Cannabis Sativa L. Ratio: CBD Dominant CBD 100 mg/ml, <2 mg/ml THC. 1ml SL (100mg/am) 2.Cannabis Sativa L. Ratio: CBD/THC 1:1 (12 mg/ml CBD and 14 mg/ml THC). 0.3 ml SL /md 0.5 ml SL /pm Titration protocol: CBD Dominant Sublingual Extract 0.1cc / am, increasing 0.1 cc every three days. After two weeks, we started the 1:1 ratio at 0.1 cc /pm, increasing to 0.1 cc every four days.
Route of administration:	Sublingual

	Patient 2
Any dosage adjustments during therapy:	CBD Dominant Sublingual Extract 0.1 cc / am, increasing 0.1 cc every three days. After two weeks, the 1:1 ratio was started at 0.1 cc /pm, increasing by 0.1 cc every four days. After two months of treatment, an additional dose of 0.1 cc at 1 p.m. was started for better control of symptoms during the day, and when optimum control of symptoms was achieved, it was increased to 0.3 cc.
Length of treatment (how long has been in therapy with cannabis/cannabinoids):	Patient in treatment with cannabinoid therapies for two years.
Follow-up (results obtained with the use of medical cannabis/cannabinoids; describe the ongoing progress or changes observed in the patient's condition after the initiation of therapy; a comprehensive description is appreciated):	1. The patient started treatment with a VAS for Pain (Visual Analogue Scale) score 7. After two years of treatment, the score was 3, (significantly improving). 2. The patient reported significant improvement in the quality of sleep. She used to take 2 to 3 hours to fall asleep at night (sleep onset); now, she takes 10 minutes. She used to wake up at 2 a.m. and have problems sleeping again (sleep maintenance); now, she sleeps 8 hours. 3. The patient reported poor quality of life; actually, she expressed that cannabinoid therapies substantially improved her quality of life. 4. The patient resigned from her job two years ago, due to pain, extreme fatigue, but last year she started working again because she is feeling much better; her energy levels, fatigue, and depression improved significantly. 5. Reduction in Polypharmacy: In a multidisciplinary approach with psychiatry and internal medicine, the patient had a protocol of reduction of the other medications since the patient reported several side effects due the use of the other medications) and now she is only on Cannabinoid Therapies.
Any reported side effects (type, severity, management):	Dry mouth, dizziness. The patient reported it is not impairing.
Additional Considerations:	It is recommended that the patient practice a healthy lifestyle, including an exercise routine, healthy nutrition, and sleep hygiene routine.

Case studies in the treatment of fibromyalgia with Medical Cannabis, as reported by Dr. Carrillo.

3.1.2. Case Studies: Chronic Pain in Adult Patients

Hypertrophic Pulmonary Osteoarthropathy

Dr. Wendy Holden, from the Sapphire Clinic in the UK, presents the case of a 31-year-old patient with complex symptomatology.
The patient has hypertrophic pulmonary osteoarthropathy (HOPA) with swelling and pain, diagnosed in 2021, affecting his ankles and feet, secondary to a congenital heart disease (transposition of the great vessels), corrected by surgery as a child.
Prior to the visit with Dr. Holden, the patient was treated with:

- Paracetamol + codeine.

The patient was unable to take NSAIDs because he was being treated with warfarin (anticoagulant) for life.
Dr. Holden started the therapy by prescribing:

- Adven 20 mg/ml THC full spectrum oil, 0.2 mL at night time, sublingual administration.
- Adven flos EMT1, 19% THC : <1% CBD, 35g monthly, via inhalation.

Subsequently, also due to problems with product availability, the therapy was adjusted in this way:

- Adven flos EMT2, THC 20% : CBD <1%, just over 1g daily – 40g monthly (inhalation).

After 1 year and 3 months of therapy, the patient reports:

- Improvement of pain;
- Improved sleep;
- Feeling more active (going to the gym, swimming);
- Losing 6 kg (desirable).

The only reported side effect is a slight loss of appetite. The doctor reported that the pain occurred mainly in the evening, so the patient did not need THC oil during the day.

Below is a summary table of the treatment carried out.

Table 29.

	Patient
Age and sex:	31-years-old, male.
In therapy since:	June 2021.
Diagnosis:	Hypertrophic pulmonary osteoarthropathy (HOPA) with swelling and pain, affecting ankles and feet secondary to congenital heart disease (transposition of the great vessels) corrected with surgery as a child.
Eventual past medications:	Paracetamol + codeine. Patient cannot take NSAIDs due to lifelong warfarin use.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	Adven flos EMT2, THC 20% : CBD <1%, just over 1g daily - 40g monthly, via inhalation.
Starting dosage:	Adven 20 mg/ml THC full spectrum oil, 0.2 mL at night time, sublingual administration. Adven flos EMT1, 19% THC : <1% CBD, 35g monthly, via inhalation.
Possible corrections in dosage:	Change of variety due to local availability.
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	1 year 3 months.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Pain improved. Improved sleep. Much more active. Lost about 6 kg in weight (desirable).
Any reported adverse effects:	Mild loss of appetite.
Any other consideration:	Never used CBD oil as found that THC controlled his symptoms completely.

Case study in the treatment of hypertrophic pulmonary osteoarthropathy with Medical Cannabis, as reported by Dr. Holden.

3.1.3. Case Studies: Chronic Pain in Elderly Patients

Rheumatoid Arthritis and Colon Cancer

Dr. Mery Peña is a physician who has worked with Medical Cannabis for many years. She was part of the medical team at the Kalapa Clinic in Spain and treats patients from all over Europe.

Dr. Peña decided to share her practical experience with Medical Cannabis and presented a case study on chronic pain of particular interest, a complex case of an 89-year-old woman with multiple symptoms.

The woman is undergoing treatment for chronic pain associated with rheumatoid arthritis and a rotator cuff muscle rupture, with a history of colon cancer now in remission. Additionally, she experiences hearing loss and opioid dependence. Since 2019, she has also been diagnosed with paroxysmal atrial fibrillation and is being treated with anticoagulant drugs due to heart failure.

The woman was first treated with cannabinoids in 2017 for one month, but the therapy was discontinued due to lack of response.

In June 2022, in agreement with his family, she decided to try cannabinoid treatments again, mainly to alleviate the side effects of her prescribed medication. Before starting cannabinoid treatment, the woman was using:

- Fentanyl (transdermal patch), 50 µg every 72 hours;
- Methylprednisolone, 4 mg daily;
- Edoxaban, 1 pill per day;
- Alendronic acid + cholecalciferol 70/5600UI, 1 tablet per week.

To this therapy, Dr. Peña added the following:

- CBD oil 10% (3.3 mg per drop);
- THC extract (oil) 3% (dominant profile: myrcene + beta caryophyllene + linalool).

The THC : CBD ratio of the prescribed therapy was 1 : 8.25.
An omega-3 fatty acid supplement was added to the therapy after the start of cannabinoid intake.
The initial cannabinoid dosage used was:

- 33 mg of total CBD per day divided into 3 administrations: 11 mg during main meals;
- 2 mg THC in the evening.

Following the initiation of therapy, the dosage of CBD and THC was augmented with the aim of reducing the dosage of fentanyl and methylprednisolone. Additionally, the anticoagulant edoxaban, which posed bleeding risks in individuals with atrial fibrillation, was replaced with apixaban, which is considered safer in such cases. After dosage adjustment, the administered cannabinoids were:

- CBD oil at 10%, 3 times a day: 4 drops in the morning, 5 after lunch, 6 after dinner, for a total of 49.5 mg CBD per day, 0.86 mg/ kg/day, for 57 kilos;
- 3% THC oil: 2 drops at lunchtime + 4 drops in the evening, for a total of 6 mg per day.

After 10 weeks of treatment:

- The dosage of methylprednisolone was reduced by half;
- The fentanyl dosage was reduced to 37 µg every 72 hours;
- Edoxaban was replaced by apixaban;
- The woman still experienced low energy and reduced endurance, but her sleep had improved, and nocturnal pain had completely ceased.

Below is a summary table of the treatment carried out.

Table 30.

	Patient
Age and sex:	Female, 89 years old.
In therapy since:	4 months (She tried cannabinoids in Kalapa Clinic in 2017, but decided to stop after a month for lack of response).
Diagnosis:	Chronic pain in the context of rheumatoid arthritis and a rotator cuff muscle rupture, colon cancer in remission, hearing loss, dependence of opioids. Since 2019, the patient has been experiencing paroxysmal atrial fibrillation and was currently under blood-thinning medication due to heart failure.
Eventual past medications:	Fentanyl (transdermal patch), 50 mcg every 72 hours; Methylprednisolone, 4 mg a day; Edoxaban, 1 pill a day; Alendronic acid + cholecalciferol, 70/5600 IUI, 1 table per week.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	CBD 10% oil (3.3 mg per drop). THC 3% (myrcene dominant + linalool + beta caryophyllene profile). THC: CBD ratio - 1 : 8.25.
Starting dosage:	CBD 10% oil, 33 mg a day: 11mg with main meals. THC 3%, 2 mg at nighttime.
Possible corrections in dosage:	Increasing doses of CBD and THC, while reducing dosage of fentanyl and methylprednisolone; swapping edoxaban to apixaban.
Current medications (after corrections in dosage):	CBD 10% oil, 3 times/day: 4/5/6 drops; total CBD/day: 49.5 mg, 0.86 mg/kg/day for 57 kg. THC 3%, 2 drops at lunch time + 4 drops evening; total THC: 6 mg a day.
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	10 weeks.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Methylprednisolone has been halved; Fentanyl decreased to 37 mcg every 72 hours; The patient still has very low energy and low stamina, but is sleeping better and she is pain-free at nighttime.
Any other consideration:	Omega 3 supplement has been added after starting cannabinoids.

Case study in the treatment of rheumatoid arthritis and colon cancer with Medical Cannabis, as reported by Dr. Peña.

Back Pain, Knee Pain and Impaired Mobility

Dr. Wendy Holden is a British physician specializing in the treatment of chronic pain. At Sapphire Clinic in the UK, she has delivered Medical Cannabis therapy to dozens of patients living with chronic pain.
Dr. Holden presents the clinical case of a 66-year-old woman with axial and peripheral spondyloarthropathy, with significant back and knee pain and reduced mobility (she walked with crutches). The woman had been on cannabinoid therapy for approximately 1.5 years and had never used cannabis before. Prior to being treated with cannabinoids, the woman had tried various therapies:

- Multisystemic therapy (MST);
- fentanyl;
- buprenorphine;
- gabapentin;
- pregabalin;
- amytriptyline;
- oral morphine;
- codeine;
- lidocaine patches;
- adalimumab;
- golimumab.

After examination, Dr. Holden prescribed the following therapy:

- Adven 20T 20 mg/mL, THC full spectrum oil (hybrid/indica), 0. 4 mL daily;
- Adven CBD (CM5) broad spectrum oil, 50mg/mL, 0.2 mL 3 times a day;
- Adven flos THC 20% : CBD 0% (variety EMT 2, hybrid), 10g monthly (only in case of severe acute pain).

The initial dosage was:

- THC oil, 0.05 mL at nighttime;
- CBD oil, 0.2 mL twice a day;
- Flos (THC 20%), 10g/month.

Following cannabinoid therapy, the woman reported significant improvements. Pain levels had decreased, sleep quality had improved, and she had become much more physically active. Notably, she had ceased using morphine. Additionally, her C-reactive Protein (CRP) test was normal for the first time since the diagnosis.

Furthermore, there had been a notable improvement in her mood, which is particularly significant given her history of a suicide attempt prior to initiating Medical Cannabis treatment. Additionally, she has been able to resume her job as a nurse. Reported side effects were:

- Severe dizziness (1 day);
- Mild dizziness (1 day);
- Mild concentration disturbances (90 days);
- Mild dry mouth (90 days).

Below is a summary table of the treatment carried out.

Table 31.

	Patient
Age and sex:	Female, 66-year-old.
In therapy since:	April 2021.
Diagnosis:	Axial and peripheral spondyloarthropathy with significant back pain and knee pain and impaired mobility. Walking with crutches.
Past medications:	Multisystemic therapy (MST), fentanyl, buprenorphine, gabapentin, pregabalin, amytriptyline, oral morphine, codeine, lidocaine patches, adalimumab, golimumab.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	Adven THC full spectrum oil (hybrid/indica) 20mg/mL, 0.4 mL daily. Adven CBD (CM5) broad spectrum oil 50 mg/mL, 0.2 mL 3 times a day. Adven hybrid flos, THC 20% : CBD 0% (strain EMT 2), 10 g monthly. Only at needs.

	Patient
Starting dosage:	THC oil, 0.05 mL, nighttime. CBD oil, 0.2 mL, twice a day. Flos, 10 g/month (as need).
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	1 year and 4 months.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Stopped morphine. Pain significantly improved. Much more active. C-reactive Protein (CRP) normalised for the first time since diagnosis. Improved mood—had a suicide attempt prior to starting Medical Cannabis and had to stop work as a nurse. Sleep improved.
Any reported adverse effects:	Dizziness-Severe -(1 days), Vertigo-Mild -(1 days), Concentration impairment-Mild -(90 days), Dry Mouth-Mild -(90 days).
Any other consideration:	Cannabis naïve prior to starting, apart from single use on holiday in Amsterdam.

Case study in the treatment of back pain, knee pain and impaired mobility with Medical Cannabis, as reported by Dr. Holden.

3.2. Cannabis Treatment in Neurological and Neurodegenerative Diseases

3.2.1. Cannabis for Parkinson's Disease

History of Parkinson's

Long before Hippocrates and Galen defined the principles of Western medicine, the Indian physician Charaka—writing around 600 B.C.—compiled the *Charaka Samhita* (The Charaka Collection), a compendium of medical practices that had already been in use in India for centuries and still serves as a cornerstone of Ayurvedic practice today.

In his book, he discussed *Kampa Vata* (Sanskrit terms meaning 'trembling' and 'energizing force of body and mind' respectively) describing what

is now known as Parkinson's disease. Charaka anticipated the observations of English physician James Parkinson by over two thousand years. In his 1817 essay *Shaking Palsy*, Parkinson described a syndrome marked by tremor, rigidity, and slowed movement—features that Charaka had already noted in his ancient medical treatise, long before the condition would come to bear Parkinson's name.

However, Charaka's insights and contributions extended beyond mere descriptions. The Ayurvedic doctor recommended treating his patients with *Mucuna pruriens, known as* Kapikachhu in Sanskrit). This plant, a species of purple pea, produces seeds that, when roasted, are used to make a coffee-like beverage traditionally believed to have aphrodisiac properties. Interestingly, while Charaka could not have known the biochemical basis for the plant's effects, modern science has revealed that its seeds contain levodopa—the very compound that became the cornerstone of Parkinson's treatment in the 1960s. Remarkably, even today, even in the Western medicine, *Mucuna pruriens* is used by patients suffering from this condition.

The origin and exact cause of Parkinson's disease remain elusive to date. While mutations in specific genes have been identified in about 5% of affected patients, the condition is believed to result from a complex interplay of genetic predisposition and yet poorly understood risk factors.

Parkinson's disease typically manifests as a slow-onset neurodegenerative disorder, often emerging around the age of 60, with a higher incidence among men. It is characterized by the progressive accumulation of a protein known as α-synuclein, forming aggregates called Lewy bodies. These Lewy bodies are primarily found in the *substantia nigra*, a specific region of the midbrain responsible for movement control. This accumulation likely leads to a reduction in the synthesis and release of dopamine, a crucial neurotransmitter involved in neuromodulation—the regulation of brain functions.

The hallmark features of Parkinson's disease include both motor symptoms and non-motor symptoms, which may appear at various stages of the disease progression.

The motor symptoms are mainly:

- tremor;
- muscle rigidity;
- bradykinesia;
- postural instability.

Non-motor symptoms include:

- anxiety and depression;
- pain;
- cognitive and language disorders;
- difficulty sleeping.

The treatment of choice involves the use of levodopa (L-dopa) or its analogues, which enhance dopamine bioavailability in the brain, thereby alleviating symptoms. While these medications exhibit high efficacy in the initial stages of therapy, they often encounter a phenomenon of rapid tolerance, leading to a significant reduction in effectiveness over time. Additionally, prolonged use of these drugs has been linked to the emergence of adverse motor symptoms, notably dyskinesia—characterized by involuntary movements.

Dopaminergic agonists and monoamine oxidase inhibitors (MAOI) have also shown efficacy, but the side effects are often unmanageable. In severe cases, surgery, including Deep Brain Stimulation (DBS) or lesional surgery, is used to reduce motor symptoms.

Proper nutrition and rehabilitation interventions are very helpful in treating the symptoms. In this regard, Charaka and James Parkinson—despite being separated by millennia and continents—shared a common conviction: prevention is the most effective remedy for any disease. Yet, a definitive and lasting cure for Parkinson's disease continues to elude us to this day.

Cannabis, Cannabinoids and Neuroprotection

Neurodegenerative diseases—notably Parkinson's and Alzheimer's—are characterized by a progressive loss of neuronal function. In these diseases, inflammation, the immune response and oxidative stress are prominent factors contributing to damage and dysfunction of neurons.
Decades of research have established that cannabis and cannabinoids, particularly THC, CBD, and THCV, possess anti-inflammatory and antioxidant properties. These properties contribute significantly to their neuroprotective effects, offering potential therapeutic benefits in neurodegenerative diseases.[1] Cannabis-induced neuroprotection also occurs through other mechanisms:

- inhibition of glutamatergic transmission in the brain and consequent reduction of excitotoxicity (a phenomenon of neuronal toxicity resulting from exposure to relatively high concentrations of glutamic acid);
- improved function of the blood-brain barrier, which protects the brain from external substances;
- regulation of cerebral blood flow;
- reduction of damage resulting from traumatic brain injury;
- regulation of programmed cell death (apoptosis).

In addition to its neuroprotective properties, cannabis is generally well-tolerated with modest side effects. Consequently, scientific research has been exploring whether Medical Cannabis and its constituents could be utilized to treat symptoms associated with Parkinson's disease.

The Role of Cannabis and Cannabinoids in Controlling Movement

In addition to inducing neuroprotective effects, the Endocannabinoid System is also expressed in many areas of the brain that control movement.

CB1 receptors are found in large quantities in the *substantia nigra* and basal ganglia of the Central Nervous System (CNS). In these brain regions, notably high levels of endocannabinoids, particularly Anandamide, are present. While CB2 receptors are not abundantly expressed in the CNS, they are found in numerous non-neuronal cells like astrocytes and microglia, where they serve immune protective roles.

Researchers at the University of Colorado have recently shown that activating CB1 receptors on astrocytes in the spinal cord reduces tremors in animal models of essential tremors.[2]

THCV, a phytocannabinoid found in smaller quantities in the cannabis plant with anti-inflammatory and antioxidant properties, improves Parkinson's symptoms in animal models, probably through interaction with CB2.[3]

Other receptors of the Endocannabinoid System, such as GPRs and TRPs, are also implicated in neuroprotection and control of body movement.

A 2014 study in an animal model of Parkinson's showed that depletion of the GPR6 receptor, a receptor similar to the cannabinoid GPRs receptors present in the basal ganglia, induces an increase in dopamine in the brain and an improvement in motor activity, especially levodopa-induced dyskinesia.[4] A few years later, CBD was identified as an inverse agonist of GPR6, suggesting its potential as a treatment for Parkinson's disease.[5]

Parkinson's and Cannabis: from Preclinical Studies to Human Trials

Despite a wealth of pre-clinical experimental data on the neuroprotective and tremor-reducing effects induced by cannabis and cannabinoids, human studies have not yielded conclusive results to justify their use in therapy.

A 2001 British pilot study showed that Nabilone, a synthetic THC analogue, was able to reduce levodopa-induced dyskinesia.[6] However, the study was carried out on a small number of patients and did not include a comparison with placebo.[7]

In 2020, researchers from the Parkinson's Disease Working Group at the University of Innsbruck (Austria) showed that four weeks of treatment with Nabilone improved anxiety and sleep disturbances in Parkinson's patients.[11] In contrast, a randomized, placebo-controlled study conducted in UK in 2004 involving 17 participants, showed that cannabis, although well tolerated, did not induce improvements in dyskinesia and parkinsonism.[9] CBD has not demonstrated significant effects in reducing Parkinson's motor symptoms either. However, a study conducted in Brazil with 21 patients showed that those treated with CBD reported an overall improvement in quality of life.[10]

Remaining in Brazil, researchers conducted a study where approximately 20 patients with Parkinson's disease were given either CBD or a placebo before participating in a public speaking test designed to induce anxiety. Those who received a 300 mg dose of CBD showed a decrease in both anxiety and tremors during the simulation.[11]

A study conducted with plant-derived highly purified CBD (Epidiolex®) titrated from 5 to 20-25 mg/kg/day and maintained for 10-15 days, concluded that Epidiolex may be efficacious in patients with Parkinsons' disease, but the relatively high dose used in this study was associated with liver enzyme elevations.[12]

To summarize data on humans, cannabinoids have demonstrated safe and significant potential in addressing both motor and certain non-motor symptoms in Parkinson's disease. However, further large-scale randomized controlled trials focusing on specific forms of cannabinoid treatments are needed to ascertain their overall effectiveness.[13]

The tables below summarize the main clinical studies carried out in patients with Parkinson's disease.

Studies with synthetic THC[6]

Table 32.

Year	No. of patients	Product and dosage	Results	Side effects
2001	7	Oral THC 0.03 mg/kg.	THC has no anti-parkinsonian effects per se, nor contra-indications to Levodopa. Significant reduction in dyskinesia.	Vertigo, postular hypotension.

Summary of clinical study in the treatment of Parkinson's with THC + CBD.

Studies with THC + CBD[7]

Table 33.

Year	No. of patients	Product and dosage	Results	Side effects
2004	19	2.5 mg THC + 1.25 mg CBD capsules.	No anti-parkinsonian effects.	-/-

Summary of clinical study in the treatment of Parkinson's with THC + CBD.

Studies with CBD[9]

Table 34.

Year	No. of patients	Product and dosage	Results	Side effects
2014	21	75-300 mg oral CBD.	Significant improvement in general well-being. No effect on motor functioning.	-/-

Summary of the clinical study in the treatment of Parkinson's with CBD.

The Patients' Point of View

While clinical data may not strongly support the use of Medical Cannabis and cannabinoids in Parkinson's disease, patients' perspectives differ significantly. A cursory Google search reveals ample firsthand evidence of how cannabis has enhanced the quality of life for numerous individuals with Parkinson's disease. Many of these individuals had previously found little relief from traditional medications. While cannabis appears to offer the most significant benefits for non-motor symptoms like anxiety and sleep disturbances, there are also numerous testimonials from patients citing improvements in tremors and postural rigidity.

These anecdotal reports are corroborated by empirical evidence from surveys and polls conducted with methodological rigor, contributing to the growing body of scientific support for the therapeutic potential of cannabis in alleviating symptoms associated with Parkinson's disease. Just to cite one of these surveys, a recent one analyzed the point of view of the German Parkinsonian community. Cannabis use was reported by 8.4% of the patients. Of these, most are younger than non-users, live in large cities, and are more familiar with the legal and clinical aspects of Medical Cannabis. Reduction of pain and muscle cramps was reported by more than 40% of cannabis users. More than 20% reported improvements in rigidity/dyskinesia, immobility, tremor, depression, anxiety and restless legs syndrome. Improvement of symptoms was reported by 54% of users who took CBD orally and 68% who inhaled cannabis containing THC. Compared to CBD intake, inhalation of THC was more frequently reported to reduce akinesia and rigidity. No particular side effects were reported. Sixty-five per cent of non-users expressed interest in the use of Medical Cannabis.[12]

Parkinson's and Cannabis: Conclusions

Preclinical studies, conducted in cellular and animal models, suggest that cannabis and its constituents, including THC, CBD, and THCV, hold significant promise for alleviating both motor and non-motor symptoms associated with Parkinson's disease. While limited randomized, double-blind clinical trials involving small patient cohorts have not shown significant benefits of cannabis and cannabinoids in treating Parkinson's disease, a notable proportion of individuals using these substances for anti-parkinsonian therapy have reported positive outcomes, particularly in terms of enhanced quality of life. This discrepancy highlights the need for further research to reconcile clinical trial findings with patient-reported experiences and to better understand the potential therapeutic effects of cannabis and cannabinoids in managing Parkinson's symptoms, especially in improving the overall quality of life.

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3.2.2. Case Study: Parkinson's Disease

The case study of a patient with Parkinson's disease treated with Medical Cannabis is presented by Dr. Carlo Privitera, an Italian physician. Dr. Privitera, a former surgeon in public healthcare, established a telehealth system called "Progetto MediCOmm—il Medico del Portale accanto" in 2016. Over the years, he has managed a personal caseload of over 4000 cases, and in 2020, he launched the new brand "CAMIT – Cannabis Medica Italia."

He presents the case of a 58-year-old man who has been undergoing treatment for three months for full-blown Parkinson's disease, diagnosed for two years. Before initiating Medical Cannabis therapy, the patient was undergoing treatment with:

- Levodopa 200 mg + Carbidopa hydrate 54 mg, 4 tablets per day;
- Rasagiline, 1 cpr per day.

After a careful analysis of the patient's clinical situation, Dr. Privitera supplemented the existing treatment regimen with:

- Cannabis Flos Billy Button (THC 19% : CBD <1%), 5 g extracts in 200 mL of ethyl alcohol; subsequent dilution in 20 mL of MCT oil; 10 drops in the evening;
- Cannabis Flos Bedica (THC 14% : CBD <1%), 5 g extracts in 200 mL of ethyl alcohol; subsequent dilution in 20 mL of MCT oil; 10 drops in the evening;
- Cannabis Flos Bedrolite (THC <1.0% : CBD 7.5%), 5 g extracts in 200 mL of ethyl alcohol + 1640 mg pure CBD; 10 drops 3 times daily;
- Cannabis Flos Bediol (THC 6.3% : CBD 8%), inflorescence to vaporize; 250 mg x 3 times daily.

The initial dosage was:

- Billy Button extract, 25 mg/day;
- Bedica extract, 44 mg/day;
- Bedrolite extract, 50 mg/day;
- Bediol (vaporised), 3.6-4.8 mg/day.

From the onset of therapy, the patient reported noticeable benefits from the extracts, prompting no significant changes in dosage. However, despite their effectiveness in managing both motor and non-motor symptoms—particularly manic tone—the patient experienced undesirable side effects when the extracts were administered through vaporization.

After approximately three weeks, the vaporized administration was discontinued and treatment continued exclusively with sublingual administration of the extracts.

Dr. Privitera reports that before starting the treatment, the patient experienced constant tremor, with varying degrees of intensity. These symptoms mainly affected the left hemisoma, particularly the left foot, which suffered from painful contraction of the toes.

Initially, the improvement was observed in the upper limb, with subsequent signs of progress also emerging in the lower limb.
Furthermore, to provide a more precise assessment of the therapy's effects, Dr. Privitera performed a 7-day 'load-stop & go' approach, consisting of:

- Doubling the dose for 2 days;
- 2 days of a total suspension;
- Then resuming at initial dosage.

This strategy helped reveal that:

- The patient experienced no side effects from the increased dosage;
- During the two-day withdrawal/washout period, the patient experienced a worsening of motor symptoms, particularly in the lower limb;
- Upon resuming therapy, the patient experienced an immediate reduction in upper limb tremor;
- In the case of the left lower limb, the patient was able to compare the intensity of symptoms with and without cannabis therapy, which further reinforced adherence to the treatment regimen.

As mentioned earlier, the only side effects reported by the patient were associated with inhaling the inflorescences, which caused a sensation of dullness. Although this effect resolved on its own, the patient chose to stop using this method of administration.
Finally, following the observed clinical improvements with cannabinoid therapy, the need for deep brain stimulation (DBS)—a procedure typically reserved for patients who develop resistance to long-term levodopa treatment—was reevaluated.
Below is a summary table of the treatment:

Table 35.

	Patient
Age and gender:	58-yars-old, male.
In therapy by:	3 months.
Diagnosis:	Parkinson's disease diagnosed 2 years ago.
Possible therapy prior to the use of Medical Cannabis or cannabinoids:	- Levodopa 200 mg + Carbidopa hydrate 54 mg, 4 cpr per day; - Rasagiline 1 cpr per day.
Current therapy (type of Medical Cannabis or cannabinoids prescribed):	- Levodopa 200 mg + Carbidopa hydrate 54 mg, 4 cpr per day - Rasagiline 1 cpr per day; - Cannabis Flos Billy Button (THC 19% : CBD <1%), 5 g extracts in 200 mL of ethyl alcohol; subsequent dilution in 20 mL of MCT oil; 10 drops in the evening. - Cannabis Flos Bedica (THC 14% : CBD <1%), 5 g extracts in 200 mL of ethyl alcohol; subsequent dilution in 20 mL of MCT oil; 10 drops in the evening. - Cannabis flos Bedrolite (THC < 1.0% : CBD 7.5%), 5 g extracts in 200 mL of ethyl alcohol + 1640 mg pure CBD; 10 drops 3 times daily. - Cannabis Flos Bediol (THC 6.3% : CBD 8%), inflorescence to vaporize; 250 mg x 3 times daily.
Initial dosage:	Billy Button extract, 25 mg/day; Bedica extract, 44 mg/day; Bedrolite extract, 50 mg/day; Bediol (vaporized), 3.6 - 4.8 mg/day.
Possible dosage corrections:	Vaping was discontinued based on the patient's decision.
Duration of treatment with cannabis or cannabinoids (at the time of the interview):	2 months.
Results obtained with the introduction of Medical Cannabis or cannabinoids in therapy (follow-up):	The treatment effectively managed both motor and non-motor symptoms, particularly the tone of the patient, which improved significantly. A marked improvement was observed in the left upper limb, which had been the limb most affected by the symptoms.
Any reported side effects:	Medium intensity side effects (sense of dullness) due to vaporization of the inflorescences.
Other considerations:	In view of drug resistance, the patient would be a candidate for deep brain stimulation (DBS). After the inclusion of cannabinoid therapy and the experience of clinical improvement, it was decided to re-evaluate the need for this therapeutic tool.

Summary of the treatment of Parkinson's Disease with Medical Cannabis, as reported by Dr. Carlo Privitera.

3.2.3. Cannabis for Alzheimer's and Dementia: A Clinical Protocol

The medical use of cannabis and derivatives among the elderly population has experienced a remarkable 300% increase in recent years. This surge can be attributed, at least in part, to new legislative measures and heightened research focus in this area.
Among the diseases that most commonly affect the elderly, Alzheimer's disease stands out. It is perhaps one of the most devastating diseases, as it slowly yet relentlessly erases a lifetime of memories. It is essential to identify an effective therapy for Alzheimer's disease, and cannabinoid-based treatment may offer a promising and innovative approach.

Alzheimer's Disease

Alzheimer's disease is the most common type of dementia—a generic term indicating a decline in cognitive abilities severe enough to interfere with daily activities. Alzheimer's accounts for at least two-thirds of dementia cases in individuals aged 65 and older. It is a neurodegenerative disease with gradual onset and progressive deterioration of behavioral and cognitive functions, including:

- memory;
- comprehension;
- language;
- attention;
- reasoning.

Onset before age 65 (early-onset) is rare and is observed in less than 10% of Alzheimer's patients. Indeed, Alzheimer's disease is typically an age-related condition. The global prevalence of dementia is reported to be up to 24 million cases and is expected to quadruple by 2050.

The estimated cost for healthcare of Alzheimer's disease is $172 billion per year in the United States alone.
The incidence of Alzheimer's disease doubles every 5 years after the age of 65. The age-specific incidence increases significantly from less than 1% per year before age 65 to 6% per year after age 85.

Pathophysiological and Genetic Features

Alzheimer's disease is a gradual and progressive neurodegenerative condition characterized by the accumulation of neuritic plaques and neurofibrillary tangles in the brain. Neuritic plaques are microscopic lesions resulting from the buildup of protein fragments called beta-amyloid peptides; these plaques develop around cerebral blood vessels and in the gray matter of the brain. Neurofibrillary tangles are composed of the tau protein; they form due to the hyperphosphorylation of tau, leading to a series of negative consequences in nerve cells.
Other distinguishing features of Alzheimer's include degeneration of the pyramidal cells of the hippocampus and neuronal loss in an area of the brain known as the Basal Nuclei of Meynert, leading to reduced levels of acetylcholine.
The potential vascular contribution to the disease, though not yet fully understood, remains an area of active investigation.
At the genetic level, Alzheimer's may be inherited as an autosomal dominant disorder, with mutations in genes such as:

- *APP*;
- *PSEN1*;
- *PSEN2*.

Additionally, the presence of an *APOE* gene variant is associated with an increased risk of Alzheimer's, especially in sporadic and familial forms. Variants in the *SORT1* gene have been observed in both familial and sporadic forms of the disease.

Symptoms

The symptoms of Alzheimer's disease depend on the stage of the disease, which is classified based on the degree of cognitive impairment into the following stages:

- preclinical or presymptomatic;
- mild;
- dementia.

The initial and most common symptom is episodic loss of short-term memory, while long-term memory is relatively spared.
Impairment of short-term memory is followed by:

- difficulties with problem-solving, judgment, and executive functions;
- lack of motivation and disorganization;
- difficulty in completing tasks and abstract thinking.

In the early stages, impairment of executive functions ranges from subtle to significant, followed by language disturbances and visual and spatial skills.
Neuropsychiatric symptoms such as apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are common in the intermediate and late stages.
Other late manifestations include:

- difficulty in performing learned motor tasks (dyspraxia);
- olfactory dysfunctions;
- sleep disturbances;
- extrapyramidal motor signs such as dystonia, akathisia, and parkinsonian symptoms.

These manifestations are followed by primitive reflexes, incontinence, and total dependence on caregivers.

Available Treatments

Currently, there is no cure for Alzheimer's disease, and available treatments mainly aim to manage symptoms. Two categories of approved medications include:

- cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, which work by increasing levels of acetylcholine;
- memantine, a partial antagonist of the N-methyl-D-aspartate (NMDA) receptor, approved for moderate to severe forms.

The benefits of these treatments are limited, and severe side effects often restrict their use. Additionally, it is crucial to address common issues in the advanced stages of Alzheimer's disease in patients, such as:

- anxiety;
- depression and psychosis;
- sleep disturbances.

The Endocannabinoid System in Alzheimer's Disease

- The Endocannabinoid System is involved in multiple biological processes, and its involvement in Alzheimer's disease has sparked interest for its potential therapeutic applications. In the context of this pathology, the Endocannabinoid System appears to play a key role in regulating various factors: anti-inflammatory activity: the Endocannabinoid System is involved in modulating the inflammatory response in the brain. In patients with Alzheimer's disease, chronic inflammation is a common feature. Endocannabinoids act on specific receptors, such as CB2 receptors on astrocytes or glial cells, to reduce inflammation and protect neurons from the accumulation of amyloid plaques.
- neuroprotection: Both THC and CBD can exert neuroprotective effects. This is significant as Alzheimer's is characterized by neuronal

damage and loss of synapses. By activating the Endocannabinoid System, neuronal cell survival can be promoted, and neural damage mitigated.

- control of immune response: the Endocannabinoid System can modulate the immune response, playing a role in balancing inflammatory and anti-inflammatory responses. This ability to regulate immune activity may be crucial in Alzheimer's, where inflammation and the immune system can contribute to disease progression.
- Impact on cognitive processes: Endocannabinoids can influence memory and cognitive functions through interaction with CB1 receptors in the brain. This is particularly relevant in Alzheimer's, where cognitive decline is a key feature.

The use of phytocannabinoids, modulation of the Endocannabinoid System with synthetic compounds like FAAH inhibitors, or the use of cannabis for Alzheimer's, could offer an innovative therapeutic approach, providing a range of benefits from reducing inflammation to neuronal protection and improving cognitive functions.

Preclinical Studies

In cellular models of Alzheimer's disease, anandamide has been shown to prevent neurotoxicity induced by beta-amyloid peptide.[1]
Stimulation of the CB1 receptor in rat microglial cells inhibited the release of nitric oxide (NO), which is associated with the neurotoxic effects of beta-amyloid peptide.[2] Even CBD, which does not bind to the orthosteric site of CB1 and CB2 receptors, has shown protective effects against beta-amyloid peptide-induced neurotoxicity in cellular models.[3]
In mouse studies, blocking the CB1 receptor improved memory deficits induced by beta-amyloid peptide administration, presumably by increasing acetylcholine levels in the hippocampus.[4]

Analysis of brain tissue samples from Alzheimer's patients indicates that the expression of CB1 receptors does not vary much compared to healthy controls, while the expression of CB2 receptors and the enzyme FAAH is increased in microglial cells associated with neuritic plaques.[5]

The hypothesis that beta-amyloid peptide deposition triggers the release of endocannabinoids from neurons and glial cells—thereby activating neuroprotective pathways via CB1 receptors and modulating inflammatory mediator release in microglia through CB2—may help explain the observed benefits of CB1 and CB2 agonists, as well as FAAH antagonists, in Alzheimer's disease.

A pilot study involving patients in advanced stages of dementia also showed significant improvements in behavioral symptoms with the use of dronabinol (synthetic THC), suggesting a potential clinical benefit of cannabinoids.[6]

However, it is important to note that research in this field is still ongoing, and further clinical studies are needed to fully evaluate the efficacy and safety of such therapeutic approaches.

Nevertheless, cannabis and cannabinoids may offer potential benefits such as:

- reducing brain inflammation;
- enhancing cognitive functions;
- improving mood and behavior;
- possible analgesia.

Results of a Prospective Observational Study on Cannabis Use in the Elderly

During the Tenth Conference on Cannabis and Cannabinoids in Medicine (IACM 2019, 31 October–2 November, Berlin, Germany), psychiatrist Ilya Reznik and geriatrician Addie Ron presented data from a prospective observational study involving individuals aged over 75 years (83.2 percent of participants), who were undergoing treatment at geriatric clinic.

The study included a comprehensive evaluation of 184 patients enrolled at the start of cannabis therapy, and then a follow-up after six months of therapy.
The geriatric population enrolled in the study had no previous experience with cannabis and suffered mainly from:

- pain (76.9%);
- sleep disorders;
- cancer-related symptoms;
- mood disorders;
- Parkinson's disease.

The risk of potential adverse effects such as cognitive, cardiovascular and postural stability was assessed. Only 33.6% of the enrolled elderly population reported side effects such as dizziness (12.1%), drowsiness (11.2%) and dry mouth.
The majority of patients (66%) utilized sublingual oil administration exclusively, with half of them (50%) opting for three doses per day.
At the follow-up evaluation after 6 months, 1/3 of the patients discontinued their pain-relieving treatment with opioid analgesics, or with the other previously used painkillers and anti-inflammatory drugs.

Protocol for the Use of Medical Cannabis in the Elderly

At the Berlin conference, Dr. Addie Ron presented the Medical Cannabis protocol designed and successfully used for his study at the Cannabis Clinical Research Institute of Soroka University, Israel.
The primary recommendation from the research group remains to exercise caution before initiating cannabis-based therapy, emphasizing the importance of carefully assessing the risk-benefit profile on an individual basis, particularly among elderly patients.

The study analysed the main risk factors for geriatric patients:

- probable use of several drugs at the same time (polypharmacy) which could interact with each other;
- pharmacokinetic changes induced by cannabinoids;
- dysfunctions of the nervous system;
- increased cardiovascular risk.

Overall, before starting cannabis therapy, the advice is to adhere to the principle '*Primum non nŏcēre*' (First, do no harm). To meet this fundamental requirement of medicine, it is recommended a gradual titration of cannabis, increasing the dose by 5 mg every 7 days until the desired effects are achieved. This approach also allows for better management of potential side effects and the possibility of discontinuing therapy, even at lower dosages, if they are not well tolerated. The proposed protocol is as follows:

- days 1-3: 5mg THC + 5mg CBD;
- days 4-6: 10mg THC + 10mg CBD;
- days 7-14: 15mg THC + 15mg CBD.

During this study, patients were constantly monitored to assess both side effects and treatment efficacy; once the desired effect was achieved, the dose was stabilised, with no need for further increase.
As shown above, oil was the preferred method of administration for most patients, administered sublingually. This approach yielded positive outcomes for all individuals involved.
Summarizing the results obtained, a dose of between 0.75 mg and 1.5 mg THC + CBD, twice daily, was well tolerated by elderly patients.
Here are the major benefits reported:

- general improvement of functionality;
- increased body weight;
- improved cognition;

- reduction of constipation;
- improving mobility.

Cannabis for an Aging Population

The longevity of the world's population, especially in developed countries, has a worrying downside: the older one gets, the more one is exposed to the development of neurodegenerative disorders.

We are thus faced with the terrible prospect of 35 million elderly people currently diagnosed with Alzheimer's disease, one of the most widespread neurodegenerative conditions worldwide. A condition for which, unfortunately, the only available remedies are symptomatic, and fail to halt the progress of the disease.

Against this alarming background, the scientific community is turning its efforts to seek more effective treatments. Indeed, there are many aspects of the Endocannabinoid System that could be exploited for this purpose.

As demonstrated by Professor Javier Fernandez-Ruiz, from the Complutense University of Madrid, cannabinoid receptors are affected by the neurodegeneration typical of Alzheimer's disease; they are also involved in the processes of preservation, repair and/or replacement of neural and glial cells.[7]

In the brains of Alzheimer's patients, there is a sharp decrease in acetylcholine, a neurotransmitter essential for memory and cognition. The progressive reduction in acetylcholine release is often counteracted in clinical practice with the prescription of drugs such as Donepezil®, which is able to inhibit the enzyme that degrades acetylcholine (acetylcholinesterase), increasing its bioavailability.

Cannabinoids may act in a similar way, as they too inhibit acetylcholinesterase, as well as possibly offering other additional benefits, such as increased appetite and weight, and reduced anxiety and aggression.[8]

CBD for Managing Aggression in Dementia and Alzheimer's

A randomized, double-blind, placebo-controlled phase II study investigated the safety and efficacy of a CBD-rich plant oil for the treatment of individuals with dementia-induced agitation, one of the most common symptoms in patients with severe dementia and Alzheimer's disease.[8] 64 patients were enrolled in the clinical study, which lasted 16 weeks (6 weeks of titration and 10 weeks of stable dose assessment).
During the evaluation period, patients underwent 10 visits. Here are the parameters taken into account:

- physical and vital parameters;
- height/weight;
- temperature;
- blood pressure;
- behavioural disorders (based on the Cohen-Mansfield agitation scale);
- scale of neuropsychiatric disorders;
- CGI-S (Clinical Global Impression-Severity) rating scale to analyse the risk/benefit ratio of treatment in psychiatric patients;
- tests for the assessment of intellectual efficiency disorders and the presence of cognitive impairment (Mini-Mental State Examination);
- mood (based on the GDS questionnaire);
- security tests;
- concomitant drugs;
- adverse events.

The average age of patients eligible for the study was 79 years. At the end of this study, in which there were no significant adverse effects to report, 71.9% of patients in the treatment group and 30% in the placebo group experienced relief from dementia-induced agitation. The authors therefore concluded that CBD from Medical Cannabis oil is a safe treatment that can reduce agitation and behavioural symptoms in dementia.

Microdoses of Cannabis Extracts for Alzheimer's: a Case Report

In 2022, an interesting clinical case was published on the micro-dosing of cannabis in a 75-year-old patient diagnosed with Alzheimer's 2 years preceding the publication.[9] The patient showed the main signs of the disease and was unable to live on his own.

The patient was treated for 22 months with microdoses of cannabis extracts (average dose 500 ug) containing THC : CBD in a ratio of 8 : 1.

The treatment described attenuated the symptoms of Alzheimer's, with rapid onset and long-term consequences. The improvement in cognitive abilities and memory lasted for more than 1 year after the start of treatment, and remained stable throughout the follow-up period (up to 42 months after the start of treatment).

Cannabis for the Elderly: Conclusions

Data from studies and case reports have confirmed the safety profile of cannabis-based medicines for the elderly population, especially when using remedies that maintain THC levels balanced by high levels of CBD, and when taking the products sublingually. The results on the use of cannabis-based medicines reported by doctors and scientists have proved very promising for elderly patients, who can benefit from this therapy to address many age-related diseases, as well as for an overall improvement in quality of life. With cannabis therapy, elderly patients can benefit from a general improvement in body functions, weight gain, improved cognition, reduced constipation and increased mobility.

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3.2.4. Cannabis, CBD and Epilepsy

Epilepsy stands as one of the prevalent neurological conditions, especially in childhood. Approximately thirty percent of pediatric epilepsy instances are classified as drug-resistant, signifying that conventional medication fails to adequately manage the condition. In such scenarios, cannabis and cannabinoids emerge as promising therapeutic options.

What is Epilepsy

Epilepsy—derived from the Greek *epilambanein*, meaning "to seize, possess, or afflict"—is a neurological disorder marked by the sudden onset of seizures, often convulsive in nature and typically occurring without an identifiable cause.

Epileptic seizures originate from irregular electrical activity within specific neurons, typically situated in the cerebral cortex. These neurons, known as epileptogenic foci, initiate abnormal electrical discharges that spread

to neighboring neurons, resulting in various types and durations of convulsions or absences (brief loss of consciousness). A single seizure does not warrant a diagnosis of epilepsy. Instead, for a diagnosis to be made, one of the following criteria must be met:

- two or more convulsive seizures without known cause, occurring more than 24 hours apart;
- a convulsive seizure of unknown cause is observed, and there is a 60 % increased likelihood of experiencing another seizure; this probability is determined based on factors such as family history, general population risk rate, the presence of possible risk factors, such as head trauma, etc.

Epilepsy is termed symptomatic when identifiable brain abnormalities are responsible for its onset. These abnormalities can be categorized as:

- congenital: present from birth;
- acquired: resulting from factors such as head trauma, brain hemorrhage, bacterial or viral infections, or tumors.

The precise causes of epilepsy are frequently unidentified even if one third of epilepsies are of genetic origin. Epilepsy impacts approximately 0.6 - 1% of the global population, with 60% of cases manifesting in childhood, particularly during the early years of life when the brain is still developing. This form is referred to as childhood epilepsy. Among the most severe forms of childhood epilepsy are those classified as epileptic and developmental encephalopathies. In these conditions, epileptic activity itself contributes to cognitive and behavioral deficits, negatively impacting a child's development. These include:

- infantile spasms;
- Lennox-Gastaut syndrome;
- Doose syndrome;
- partial malignant childhood crises;
- Dravet syndrome.

Children diagnosed with epilepsy typically experience higher rates of mental health issues linked to developmental comorbidities, such as depression, anxiety, learning disabilities, developmental delays, and autism. Moreover, epilepsy diagnosis in children is correlated with an elevated risk of challenges in areas like independence, social behavior, and academic performance.

To try to keep these problems under control, it is necessary to prevent the onset of seizures and convulsions with pharmacological treatments.

Epilepsy places a significant financial burden on both the healthcare system and affected individuals, especially in cases where the condition is resistant to medical treatment, resulting in substantially higher costs.

Seventy percent of childhood epilepsy cases respond well to pharmacological treatment, with one of the various available drugs often completely eliminating seizure recurrence from the first treatment. The remaining 30 percent of children are classified as having drug-resistant (also known as refractory or intractable) epilepsy, as defined by the International League Against Epilepsy. This occurs when two or more anti-epileptic treatments, administered at appropriate dosages, fail to control seizures, resulting in frequent recurrence.

In such cases, treatment options may involve epileptic surgery, vagus nerve stimulation, or the ketogenic diet. However, for many patients who are ineligible for surgery or unresponsive to these treatments, medical cannabis may offer more promising prospects for reducing seizures compared to other pharmacological interventions.

Cannabis and Epilepsy in History

The earliest recorded use of cannabis for treating epileptic seizures dates back to 7th century BC Babylonia. A cuneiform tablet housed in the British Museum in London bears inscriptions indicating that cannabis was employed during that period to address various types of convulsive seizures,

including those occurring at night. Moving forward in history, around 1464, a writing on hashish attributed to the Persian physician Abu Bakr Muhammad ibn Zakariya al-Razi emerged. In this document, it is recounted that the poet Ali ben Makki utilized hashish to effectively manage the seizures of the son of the chamberlain of the Caliphate Council. In the 1840s, Dr. William Brook O'Shaughnessy, in his famous treatise *On the Preparations of the Indian Hemp, or Gunjah*, described how he successfully treated the infantile spasms of a 40-day-old baby in Calcutta, by administering a cannabis extract. Upon his return to Britain, O'Shaughnessy introduced his medical colleagues to the use of cannabis to treat various disorders, including epilepsy. Subsequently, in 1851, cannabis was included in the U.S. Dispensatory, the forerunner of the official pharmacopoeia. From then on, the therapeutic use of cannabis became a common practice for physicians in the late 18th and early 19th centuries, and reports of its efficacy in treating various conditions, including childhood epilepsy, multiplied worldwide. At least until 1937, when the Marihuana Tax Act made the use of cannabis illegal in the US and worldwide. Despite the prohibition, subsequent reports emerged on the efficacy of cannabis in treating childhood epilepsy, prompting scientific research to cautiously explore these findings despite various challenges. Thus, in 1978, the first placebo-controlled study was carried out by Mechoulam and colleagues on the use of CBD in patients with refractory epilepsy. In this study, two of the four patients treated with CBD had a complete resolution of their seizures, whereas this did not occur in any of the patients in the placebo group.[1]

In 2013, Dr. Sanjay Gupta, the medical correspondent for the US television station Cable News Network, reported the case of a child with drug-resistant Dravet Syndrome who had been effectively treated with a CBD-rich cannabis extract. This led to a considerable increase in interest, from both patients and researchers, in cannabis and CBD, particularly as a potential anti-epileptic treatment.

The Endocannabinoid System and the Role of Cannabinoids in Epilepsy

CB1 receptors are widely expressed in the presynaptic terminals of brain neurons. The two main endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), on the other hand, are produced by the postsynaptic membranes of neurons when these are depolarised (activated). When this occurs, the binding of endocannabinoids to CB1 receptors decreases the release of additional neurotransmitters from presynaptic neurons.

This mechanism may underlie the anti-epileptic action of cannabinoids, as the hyperactivation of neurons during a seizure is sustained by an excessive release of the neurotransmitter glutamate from presynaptic neurons. CB1 activation prevents the release of glutamate and this would explain the anti-epileptic effect due to CB1 activation.

Supporting this notion, analysis of brain tissue from patients with refractory epilepsy who underwent surgical resection revealed reduced CB1 expression in glutamatergic neurons, indicating a lower receptor density and increased glutamate release, which in turn heightens neuronal excitability. Conversely, an increase in CB1 expression was observed in GABAergic neurons, which are responsible for the release of GABA—the principal inhibitory neurotransmitter in the mammalian nervous system. This upregulation of receptors resulted in decreased GABA release and heightened neuronal excitability.[2]

Activation of CB1 receptors, however, may only represent a secondary mechanism of the anti-epileptic action exerted by phytocannabinoids.

Regarding Δ9-tetrahydrocannabinol (THC), several animal studies have tested its efficacy, both alone and in combination with other anti-epileptic drugs. The anticonvulsant action observed seems to primarily stem from one of its metabolites, 11-OH-Δ9-THC.[3]

It's important to note that while THC has demonstrated an anticonvulsant effect in some animal studies, it has also been reported to act as a proconvulsant in certain cases. While this effect has not been observed in

humans, the potential for it to occur, along with the psychoactive effects of THC, restricts its therapeutic use in children with epilepsy.

The phytocannabinoid that has garnered the most attention in anti-epileptic studies is undoubtedly cannabidiol (CBD). Conversely, CB1 expression was found to be elevated in GABAergic neurons, which mediate the release of GABA, the primary inhibitory neurotransmitter in the mammalian nervous system. Unlike THC, CBD's effects are not attributed to a direct action on CB1 receptors. Instead, CBD seems to interact with neuronal calcium channels or other receptors, such as vanilloids.[4] Furthermore, it has been ruled out that the anticonvulsant action is due to one of its metabolites.

According to recent data, CBD exerts potential anti-seizure effects by blocking the pro-excitatory actions of an endogenous membrane phospholipid, lysophosphatidylinositol (LPI), thus dampening neuron's hyperexcitability.[5]

Recently, other phytocannabinoids have garnered interest in the context of anti-epileptic therapy, particularly Δ9-tetrahydrocannabivarin (THCV) and cannabivarin (CBV). Both compounds exert their effects through direct and indirect modulation of CB1 receptors.

Clinical Studies on Cannabis and Epilepsy

Studies with Epidiolex®

The first study with Epidiolex® was conducted in 2016.[6]

This was an open-label study with 162 participants with drug-resistant epilepsy, including both adults and children, many of whom had either Dravet or Lennox-Gastaut syndrome. The authors reported a median reduction in motor seizures of 36.5%.

Another study with 120 children or young adults with Dravet syndrome reported a 50% reduction in convulsions in 47% of patients treated with CBD and 27% treated with placebo.[7]

In 2018, a double-blind, placebo-controlled study with 225 participants showed that 41.9% of patients treated with pure CBD had a reduction in

atonic seizures, compared to 17.2 percent of patients in the placebo group. Ultimately, two comprehensive systematic reviews of the literature, encompassing all studies conducted with Epidiolex®, consistently demonstrated its efficacy in treating drug-resistant childhood epilepsy, notably in Lennox-Gastaut and Dravet syndromes.[8];[9]

Studies on Extracts derived from Cannabis Varieties high in CBD Content

Many patients around the world, unable to access Epidiolex® due to legal restrictions or financial constraints, have turned to CBD extracts and homemade remedies to manage drug-resistant childhood epilepsy, often reporting positive outcomes. An analysis conducted in Australia revealed that the majority of these products contained low levels of CBD and consistently included THC in all formulations. Despite this, various studies utilizing cannabis extracts with high CBD concentrations have demonstrated efficacy in managing epileptic seizures. In particular, a 2016 study showed that 39% of patients treated with CBD extracts (THC:CBD 1:20) experienced a 50% reduction in seizures, with complete cessation observed in 10% of cases. Some participants (5 out of 74), however, discontinued the study due to side effects.[10]

A multicentre clinical study on *Cannabidiol in Children with Refractory Epileptic Encephalopathy (CARE-E study)* started in 2018. Initial findings published in 2019 showed that an extract containing THC and CBD in a 1:20 ratio was effective in reducing the frequency of seizures in all 7 participants analyzed so far.[11]

In a case report from Italy, published in Neurological Sciences in 2020, five patients with epilepsy resistant to conventional drugs were followed. They were prescribed Medical Cannabis only after standard therapies had failed and, in some cases, after non-tolerable side effects had occurred. The treatment consisted of taking a pharmaceutical-grade cannabis extract (THC:CBD, 1:9) diluted in olive oil. After undergoing this treatment, all patients reported a reduction in both the frequency and severity of seizures. Additionally, they experienced improvements in mood and sleep quality,

leading to an overall sense of well-being, with no significant side effects reported.[12]

To summarize, a systematic review of six randomized clinical trials (RCTs), involving a total of 1,034 individuals with Dravet syndrome, Lennox-Gastaut syndrome, or tuberous sclerosis complex—a rare genetic disorder associated with epilepsy and poor seizure control—supported the use of CBD for patients with treatment-resistant seizures, demonstrating satisfactory seizure reduction and an acceptable safety profile.[13]

Side Effects of Cannabis and CBD

Regarding the potential side effects of cannabis use in children, the primary concerns revolve around the potential contamination with THC and its impact on a developing brain, particularly in children.

The majority of side effects noted during various studies, while common, are generally described as mild or moderate and encompass:

- drowsiness;
- fatigue;
- gastrointestinal symptoms such as nausea, diarrhea and decreased appetite.

Serious side effects reported, although very rare, include:

- elevation of liver enzymes, particularly in children concurrently taking valproic acid;
- exacerbation of convulsions;
- dyscrasias (altered blood chemistry).

Regarding Epidiolex® specifically, the most common side effects observed in the treatment of Dravet and Lennox-Gastaut syndrome are:

- drowsiness;
- decreased appetite;
- diarrhea;

- increased transaminases (always to be monitored with CBD therapy);
- fatigue, weakness and asthenia;
- skin rashes;
- insomnia and sleep disorders;
- infections.

Interestingly, side effects were observed to a greater extent in those taking Epidiolex® compared to those treated with CBD-rich extracts in various studies. This discrepancy could be attributed to the entourage effect of cannabis, which refers to the synergistic interaction among all components of the plant's phytocomplex. This phenomenon may potentially reduce side effects while maintaining therapeutic benefits.[13]

Conclusions

Throughout history, cannabis has often been used across cultures to treat various disorders, including epilepsy. In the late 1800s and early 1900s, it was one of the treatments most recommended by physicians around the world, and reports on its efficacy were numerous. Currently, aided by more permissive legislation, the use of cannabis and its derivatives for treating epilepsy—including drug-resistant forms in children—has regained attention and interest in the medical community. Recent clinical studies have highlighted CBD as the primary active component of cannabis in anti-epileptic properties. However, it's worth noting that other phytocannabinoids like THCV and CBDV may also demonstrate positive effects on epilepsy. CBD's efficacy was observed in both licensed medications, such as Epidiolex®, and in cannabis extracts with high CBD content.
CBD dosages used in the studies ranged from 1 to 50 mg/kg per day, with doses around 5-10 mg/kg being the most commonly used.

Notwithstanding these advances, uncertainties persist regarding the pharmacokinetics, long-term adverse effects, suitable types of epilepsy and seizures for treatment, as well as the optimal dosage of CBD and

other phytocannabinoids. The data available in the literature, alongside numerous anecdotal reports, suggest promising prospects for considering cannabis and its derivatives as a therapeutic option for childhood epilepsy. This is especially relevant when other conventional pharmacological treatments have proven ineffective or intolerable.

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3.2.5. Case Study: Drug-resistant Epilepsy in Adults

Dr. Carlo Privitera, a surgeon who left the public healthcare system in 2015, founded *Project MediCOmm* in 2016, pioneering the use of a telehealth system. Over the years, this initiative has managed a caseload exceeding 4000 treated patients. In 2020, Dr. Privitera launched the new brand 'CAMIT – Cannabis Medica Italia.' He presents the case of a 43-year-old man with drug-resistant epilepsy and intellectual disability, who has been undergoing treatment with Medical Cannabis since January 2019. Before commencing treatment under Dr. Privitera's supervision, the patient was prescribed:

- Levetiracetam, 500 mg, twice daily;
- Carbamazepine, 400 mg, 3 times daily.

Dr. Privitera adjusted the treatment regimen by substituting levetiracetam with valproic acid. Furthermore, the therapy was fine-tuned through the testing of eight distinct combinations of Medical Cannabis and CBD before settling on the optimal therapeutic regimen, structured as follows:

- Carbamazepine, 400 mg, 3 times daily;
- Valproic acid, 150 mg, 3 times daily;
- Cannabis Flos Bedica extract (oil) (THC 14% : CBD <1%) 1000 mg + pure CBD 2000 mg, 10 drops 3 times a day + 30 drops in capsule before going to sleep;
- Cannabis Flos Bedica extract (oil) (THC 14% : CBD <1%), 10 g in 400 mL ethyl alcohol, subsequent dilution in 100 mL MCT oil, 10 drops in the evening;
- Flos Bedrolite Cannabis extract (oil) (THC 1% : CBD 9%), 10 g + 3500 mg pure CBD, 15 drops twice daily.

After a gradual escalation, the initial CBD dosage was increased from 0.5 mg/kg/day to the final dosage. Following 3 years and 10 months of therapy, Dr. Privitera observed the following outcomes:

- Before initiating treatment, the patient experienced a severe generalized seizure every week, along with frequent small seizures (partial, myoclonic) throughout the day and particularly at night;
- currently, the patient has attained clinical stabilization with the administered treatment, experiencing only one monthly seizure, which is of lower intensity compared to previous episodes and resolves spontaneously. Additionally, daily seizures have ceased entirely.

Dr. Privitera notes that during the initial phase, the clinical presentation included not only the customary signs and symptoms of epilepsy but also behavioral disturbances, likely stemming from interactions between cannabinoids and other medications. These manifestations decreased following adjustments to the treatment regimen, notably the discontinuation of levetiracetam. The addition of valproic acid, at a minimal dosage, played a role in stabilizing the clinical presentation. The patient currently competes regularly in equestrian competitions and has also participated in international competitions.
Below is a summary of the treatment conducted.

Table 36.

	Patient
Age and gender:	47-years-old, male.
In therapy since:	January 2019.
Diagnosis:	Drug-resistant epilepsy and intellectual disability.
Possible therapy in place prior to the use of Medical Cannabis or cannabinoids:	Levetiracetam, 500 mg, twice daily; Carbamazepine, 400 mg, 3 times daily.
Current therapy, dosage:	- Carbamazepine, 400 mg, 3 times daily; Valproic acid, 150 mg, 3 times daily; - Cannabis Flos Bedica extract (oil) (THC 14% : CBD <1%) 1000 mg + pure CBD 2000 mg, 10 drops 3 times daily + 1 capsule before going to bed; - Cannabis Flos Bedica extract (oil) (THC 14 : CBD <1%), 10 g in 400 mL ethyl alcohol, 10 drops in the evening; - Flos Bedrolite Cannabis extract (oil) (THC 1% : CBD 9%), 10 g + pure CBD 3500 mg, 15 drops twice daily.

	Patient
Initial dosage:	CBD 0.5 mg/kg/day.
Possible dosage corrections during therapy:	The initial dosage of CBD was gradually increased to the final dosage.
Length of treatment (since or how long he has been in therapy):	3 years and 10 months.
Results obtained with the use of Medical Cannabis:	The patient has achieved clinical stabilisation with the treatment undertaken and reports only one monthly seizure (of lower intensity than before, with spontaneous resolution) and the disappearance of daily seizures.
Any reported side effects:	Behavioural disorders, probably attributable to interactions between cannabinoids and other drugs. These manifestations decreased in relation to the changes in therapy, particularly levetiracetam. The inclusion of valproic acid, at the lowest dosage, contributed to the stabilisation of the clinical picture.
Other considerations:	Cannabis-naïve patient.

Summary of the treatment of drug-resistant epilepsy with Medical Cannabis, as reported by Dr. Carlo Privitera.

Management of Epileptogenic Encephalopathy and Bannayan-Riley-Ruvalcaba Syndrome

This peculiar case study has been presented by Dr. Valeria Giorgi, a medical researcher specializing in fibromyalgia syndrome, currently assistant physician in Internal Medicine, at Gruppo Ospedaliero Moncucco, Lugano (Switzerland) and research collaborator at the Rheumatology department, IRCCS Galeazzi – S. Ambrogio, Milan (Italy). This case highlights the importance of personalized, closely monitored therapeutic strategies in managing complex neurodevelopmental disorders with cannabinoid-based therapies, demonstrating significant improvements in quality of life for both the patient and their caregiver.

The case details the clinical profile and therapeutic approach for a 37-year-old male diagnosed at birth with epileptogenic encephalopathy and Bannayan-Riley-Ruvalcaba syndrome, a complex condition characterized by

intellectual disability, macrocephaly, absence of speech, motor clumsiness, scoliosis, morphoeic epilepsy, and pathological sleep rhythm disorders. These symptoms include frequent nocturnal awakenings and occasional awakenings with generalized clonus lasting 10-15 seconds.

Prior to cannabis therapy, the patient was treated with a range of medications including:

- Carbamazepine 1200 mg/day;
- Sodium Valproate 950 mg/day;
- Clonazepam 2.5 mg (evening);
- Melatonin 2 mg (evening);
- Trazodone 150 mg (evening);
- Alprazolam 0.75 mg/mL (morning, if anxious);
- Diazepam 10 mg (rectal use for seizures).

The Addition of Cannabinoid Treatment

In the final week of August 2023, cannabinoid therapy was introduced alongside the existing treatment regimen, beginning with CBD oil in MCT oil at a 20% concentration. The dosage started at 3 drops in the evening and was gradually increased by 5 drops per day, reaching a total of 19 drops. This initial approach did not yield significant improvements, as nights remained restless with frequent awakenings.

In September 2023, an attempt to increase the dosage more effectively led to the prescription of 200 mg CBD capsules. However, this caused a deterioration in symptoms, including more disturbed sleep and increased limb clonus, indicating a dose-dependent adverse effect. Consequently, the capsules were discontinued in October 2023, and the regimen reverted to solely using 20% CBD MCT oil, with dosage adjustments leading to gradual improvements.

By February 2024, a galenic preparation of Bedica variety oil (14% THC, <1% CBD) was incorporated into the treatment to improve anxiety management

and sleep quality. The introduction began with minimal doses, followed by careful titration to ensure tolerability and effectiveness.

Current Cannabinoid Therapy Regimen (in addition to prior non-cannabinoid treatment)

- Morning: 29 drops of 20% CBD MCT oil and 2 drops of BEDICA oil.
- Evening: 39-40 drops of CBD oil and 4 drops of BEDICA oil.

Treatment Duration and Outcomes

The treatment began in September 2023 and remained ongoing as of March 2024. By that time, remarkable improvements had been observed:

- the patient experienced uninterrupted sleep for the first time since birth, achieving 7-8 hours of rest;
- nocturnal seizures and limb clonus were absent;
- The patient's mother reported significant relief as it was the first time in 37 years that she could sleep through the night due to the stabilization of her son's condition;
- The daytime use of Alprazolam was discontinued, replaced by the consistent use of CBD + Bedica oil, further stabilizing the patient's symptoms;
- After starting cannabis therapy, the patient discontinued Trazodone, under close neurological supervision.

Side Effects

The treatment with CBD capsules initially worsened seizures and sleep quality, indicating a critical need for careful dose management in cannabinoid therapies.
Below a table summarizing this case study.

Table 37.

	Patient
Age & Gender	37-years-old, male
Diagnosis	Epileptogenic encephalopathy. Bannayan-Riley-Ruvalcaba syndrome which results in mental retardation, macrocephaly, absence of speech, motor clumsiness, scoliosis, morpheic epilepsy, and pathological sleep rhythm disorders. Numerous awakenings every night and, less frequently, awakenings with sitting up, generalized clonus for 10-15 seconds.
Date of diagnosis	Birth.
Previous therapy before the use of medical cannabis or cannabinoids:	- Carbamazepine 1200 mg/day: 600 mg in the morning + 600 mg in the evening - Sodium Valproate 950 mg/day: 500 mg 1 tablet in the morning + 450 mg 1 tablet + ½ tablet in the evening - Clonazepam: 2.5 mg 20 drops in the evening - Melatonin: 2 mg 1 tablet in the evening - Trazodone: 150 mg in the evening - Alprazolam 0.75 mg/mL 15/19 drops in the morning if anxious - Diazepam 10 mg for rectal use if seizure occurs.
Current therapy (whether it has been added to the previous therapy or replaced it, details of prescribed medical cannabis or cannabinoids, strains, THC:CBD ratio, starting dosage, etc.):	Added to previous therapy: - In the morning: 29 drops of 20% CBD MCT oil and 2 drops of Bedica variety oil (14% THC, <1% CBD). - In the evening: 39-40 drops of CBD oil and 4 drops of Bedica variety oil (14% THC, <1% CBD).
Route of administration:	Mouth.
Any dosage adjustments during therapy:	In September 2023, to facilitate an easier dosage increase, 200 mg CBD capsules were prescribed. However, the introduction of just one capsule led to a deterioration in symptoms within a week, with much more disturbed sleep and awakenings accompanied by limb clonus, indicative of dose-dependent symptom exacerbation. In October 2023, the CBD capsules were discontinued, and the use of 20% CBD MCT oil was resumed. The dosage started at 24 drops, increasing by 5 drops every 2-3 days. This adjustment gradually improved the quality of sleep and reduced the frequency of awakenings and minor seizure episodes. After one month, the final dosage was established as 29 drops of 20% CBD MCT oil in the morning and 39 drops in the evening. Starting February 2024, Bedica oil (14% THC, <1% CBD) in MCT oil was introduced for further control of anxiety and sleep quality, beginning with 1 drop in the afternoon and 1 drop in the evening, with increases of 1 drop every 2-3 days.
Length of treatment (how long has been in therapy with cannabis/ cannabinoids):	September 2023 - ongoing as of March 2024.

	Patient
Follow-up (results obtained with the use of medical cannabis/ cannabinoids):	In March 2024, the mother reported: "the patient is experiencing peaceful sleep uninterrupted by awakenings, free from minor seizure episodes, and without limb clonus. For the first time since birth, the patient sleeps peacefully for the initial 7-8 hours, without any awakenings." Consequently, for the first time since the birth of her child 37 years ago, the mother also managed to sleep. The daytime Alprazolam drops for anxiety have been eliminated, consistently replaced by the 20% CBD + Bedica oil. After starting cannabis therapy, the patient also discontinued Trazodone, under close neurological supervision.
Any reported side effects (type, severity, management):	Worsening of seizures and sleep quality with CBD capsules, which was dose-dependent.
Additional Considerations	None.

Summary of treatment of Epileptogenic Encephalopathy and Bannayan-Riley-Ruvalcaba Syndrome with Medical Cannabis, as reported by Dr. Valeria Giorgi.

3.2.6. Cannabis for Multiple Sclerosis

Brief Description of Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic autoimmune neuroinflammatory disease that affects neurons in the brain and spinal cord.[1]

Every neuron has an axon, a structure specialized for transmitting nerve impulses. Under normal physiological conditions, axons are encased by glial cells that provide protection and form the so-called *myelin sheath*. In MS, an autoimmune process—often of unknown origin—triggers a degenerative response that leads to the formation of so-called *demyelinated plaques*. These are areas where the myelin sheath is no longer intact around the axon, resulting in impaired neuronal function.[2] In some cases, a remyelination process may occur early in the progression of the disease, but over time this inflammatory process leads to progressive neuro-axonal loss and increased disability. The various signs and symptoms of MS depend on the site of the lesions in the brain and spinal cord. Common symptoms and signs include:

- spasticity;
- weakness;
- sensory disturbances;
- painful spasms;
- ataxia;
- tremor;
- optic neuritis and complex ophthalmoplegia;
- fatigue and dysphagia.[3]

The course of multiple sclerosis (MS) varies greatly between individuals, resulting in a wide range of symptoms and disease progressions. Consequently, treatment strategies must be personalized to target the specific symptoms that most significantly affect each patient's quality of life.[4] Among these, spasticity—characterized by involuntary increases in muscle tone or sudden muscle contractions—is one of the most common and challenging symptoms to manage.

Classic Treatments

Current drug therapies for MS can be grouped into two categories:

A) disease-modifying therapies;
B) symptomatic therapies.

Disease-modifying therapies aim to reduce the number, severity and duration of relapses, maintaining periods of remission and slowing down disease progression.
These treatments are generally based on immunomodulators and/or immunosuppressants, such as interferon beta, copaxone, fingolimod, natalizumab or alemtuzumab.[5] Although these drugs are effective in improving certain aspects of MS and delaying the progression of various symptoms, they often cause severe side effects that restrict their long-term use.

Symptomatic therapies, designed to relieve the disabling symptoms of MS, include anticonvulsants for neuropathic pain, anticholinergic drugs for bladder dysfunction and dysphagia, and botulinum toxin injections for spasticity.[6] Again, the use of these drugs may in many cases be limited by their side effects.[7]

Starting in the 1970s, following various anecdotal reports of MS patients experiencing symptomatic relief after smoking cannabis, scientific research began to investigate the efficacy of cannabinoids in managing MS symptoms.[8]

Clinical Studies on Cannabis as a Remedy for Spasticity

In a 1999 German study involving 170 patients who used cannabis for self-medication, 11% of whom had multiple sclerosis (MS), 71% reported experiencing improvements in spasticity without encountering notably severe side effects.[9]

For a summary of more recent research, the studies conducted by Karst *et al*. and Correia de Sá *et al.* provide valuable insights.[10];[11]

In 2003, a major study compared the effects of cannabis extract (2.5 mg THC + 1.25 mg CBD + 5% other cannabinoids per day, with the first 4 weeks in which the contents were titrated and doses adjusted for side effects, up to a maximum of 25 mg THC per day, depending on body weight), THC alone (Marinol® capsules for oral administration) and placebo, in a population of 630 MS patients at different stages of development.[12] The effects of cannabis treatments on muscle spasticity were examined for 15 weeks and the study reported several beneficial effects of cannabinoids on pain and spasticity; there was also a significant improvement in sleep quality and depression compared to the placebo group. However, according to the Ashworth scale (the method then used to measure muscle tone) the differences in the degree of spasticity before and after treatment were low and insignificant; this was due to the high subjectivity of the test, which

was later abandoned as a measure of spasticity. A significant improvement in the 10-minute walk was also recorded in this study, but only after long-term use of cannabis medication.[13]

Due to the promising yet inconclusive initial results, the study was extended for an additional 12 months, with 80% of the original participants continuing. During this follow-up, the results of the *Rivermead Mobility Index* (RMI)—a more modern tool for assessing spasticity—demonstrated a significant improvement in spasticity scores. In contrast, the Ashworth scale showed only moderate improvement in both groups.[14]

The inconsistent results of the initial study were attributed to the limitations of the measurement parameters initially selected.

In 2006, Wade and colleagues published another important study analysing the efficacy of a cannabis-based spray (Sativex®) in the treatment of Multiple Sclerosis symptoms. Sativex® is a mixture of THC and CBD (1:1), which was administered daily for over 10 weeks to 137 patients.[15] The change in spasticity was measured exclusively on a visual scale and the effects on spasticity were promising. Compared to placebo, the average reduction in spasticity in patients treated with Sativex® was 54.6% greater. These results were later confirmed by a 74-week follow-up study that also showed that the patients' progress was maintained over time.[16] Very intriguing, 88% of the patients voluntarily began using cannabis treatments again at the end of the study. In 2007, Collins and colleagues employed a more reliable assessment method—the Numerical Rating Scale (NRS)—to evaluate the antispastic effects of Sativex® in 189 patients with multiple sclerosis.[17] Over the course of the 6-week study, participants were allowed a maximum daily dose of 48 sprays. This regimen resulted in a notable reduction in spasticity, as reflected by the NRS scores. By the end of the study, 40% of participants had reported improvement in the majority of their symptoms.

Furthermore, in 2010, Wade and colleagues evaluated the effects of Sativex® in 666 patients with multiple sclerosis, using a visual analogue scale, a numerical rating scale, and the *Global Impression of Change*—a

measure reflecting patients' perceived changes in their pain experience. The study concluded that Sativex® effectively reduces spasticity and is generally well tolerated by patients.

A separate study was conducted by the Novotna group in the Czech Republic.[19] To select participants for this research, an initial 4-week trial was conducted during which all enrolled subjects received the spray treatment. Only those who demonstrated more than a 20% improvement in spasticity during the initial phase were selected to continue the study for an additional 12 weeks. Of the 572 individuals initially enrolled, 272 were identified as 'early responders' and proceeded to the extended phase of the study. Although the permitted daily dose was only a quarter of that used in the Collins study, the NRS scores for spasticity decreased by an average of 3.01 points (from a baseline of 6.91 to an endpoint of 3.9), indicating a substantial reduction in subjective spasticity symptoms. Additionally, the frequency of spasms and sleep disturbances also declined with the use of Sativex®.[20]

This study, a phase III trial, was the first to identify a clinically significant reduction in spasticity induced by Sativex®.[21] A subsequent 5-week randomized, placebo-controlled study examined the effects of discontinuing Sativex® in patients who had previously benefited from the treatment. The results confirmed the positive impact of Sativex.[22]

In 2015, a Canadian research group conducted a double-blind study involving MS patients with neuropathic pain who were unresponsive to gabapentin treatment. Participants received either Nabilone (synthetic THC) or a placebo in addition to gabapentin for a duration of five weeks. The group of patients who received Nabilone experienced a reduction in pain with minimal side effects. Based on these findings, the researchers concluded that Nabilone could be a viable adjunct to gabapentin in the treatment of neuropathic pain in patients with multiple sclerosis.[23]

Conclusions from Clinical Studies on Cannabis Use in Multiple Sclerosis

In addition to the studies mentioned, numerous other research investigations have examined the effects of cannabis cannabinoids in MS, with findings generally pointing to similar conclusions. In 2014, the *American Academy of Neurology* opted to consolidate the results of all clinical studies on cannabis-based treatments for neurological conditions, including MS, into a comprehensive publication analyzing all the available literature.[24] This review analyzed 34 clinical studies and, with regard to multiple sclerosis, arrived at the following conclusions:

- For spasticity in MS, both cannabis extract preparations and pure THC (whether synthetic or natural) have been shown to significantly reduce subjective symptoms though their efficacy in objective assessments remains limited. The effectiveness of inhaled cannabis continues to be uncertain.
- Cannabis extract preparations are effective in alleviating neuropathic MS pain or painful spasms, while THC (pure and synthetic) is likely effective. Inhaled cannabis also demonstrates some efficacy in reducing neuropathic pain.
- In bladder disorders, only isolated THC was found to be effective.
- In MS-induced tremor, the tested cannabinoid preparations were ineffective or only moderately effective.

Side Effects of Cannabinoid Preparations

As evidenced by numerous studies, cannabis-based medicines generally have a favorable tolerance profile, with occasional adverse effects, all of which are typically categorized as “mild or moderate.” These include:

- dizziness;
- dry mouth;
- disorientation;

- loss of concentration and coordination;
- to a lesser extent, psychiatric symptoms such as psychosis or depression.

To explore these aspects, an extensive study by Wade and colleagues examined 137 MS patients who used up to 48 sprays of Sativex® per day and found that, compared to the placebo group, cannabinoid therapy resulted in mild to moderate side effects, all of which resolved with cessation of treatment.[25] To minimize the risk of side effects, it is recommended to initiate treatment with very low doses and gradually titrate upward to the minimum effective dose. If necessary, alternative administration methods other than oro-mucosal spray should be considered.

The main concern in MS patients is vulnerability to psychiatric symptoms such as depression, cognitive decline and asthenia. In addition, reduced information processing speed and verbal memory are often impaired as the disease progresses. A number of studies focusing on the neuropsychological effects of Medical Cannabis in patients with Multiple Sclerosis have shown that the treatment worsens verbal memory compared to placebo. However, it has also been shown that the use of cannabis extracts in the short to medium term does not induce cognitive decline.[26]

In a meta-analysis of all published studies on Sativex®, euphoria was reported in 2.2% of patients, depression in 2.9%, and no episodes of tolerance or withdrawal were recorded even when therapy was suddenly discontinued.[27] In addition, there were only three reported cases of psychosis and ten cases of hallucinations. In all instances, symptoms remitted upon discontinuation of therapy.[28] In any case, it is crucial to assess the patient's personality traits before initiating this therapy, especially since it is contraindicated in individuals with psychiatric disorders or addictions.

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3.2.7. Case Study: Multiple Sclerosis

Dr. Sandra Carillo is a Professor at the Faculty of Medicine at the University of Panama, a practicing clinician, and Co-Founder of Medicann Cannabis Clinics. She also serves as President of the Colombian Medical Cannabis Association, in addition to her roles as an international speaker and presidential advisor.

She is also a prescribing physician and has chosen to share with us an intriguing clinical case involving a woman diagnosed with multiple sclerosis who was treated with Medical Cannabis extracts.

The patient, aged 48, before the therapy with cannabinoids, was treated with:

- Ocrelizumab IV;
- Gabapentin, 600mg/day;
- Clonazepam 2.5 mg/day;
- Escitalopram 10 mg/day;
- Ketorolac 10mg (if needed in case of pain).

The woman has been under Dr. Carrillo's care for approximately two years. To alleviate her symptoms and reduce reliance on previously prescribed medications, Dr. Carrillo introduced a therapy based on Medical Cannabis extracts alongside the existing treatment regimen, specifically:

- *Cannabis Sativa L.* Magistral Preparation, CBD-rich extract (THC <2.0 mg/ml : CBD 100mg/mL), sublingual extract;
- *Cannabis Sativa L.* Magistral Preparation, THC:CBD, 12:14 (THC 12 mg/ml: CBD <15.4 mg/mL), sublingual extract.

The initial dosage was:

- CBD-rich extract, 2.5 mg /day;
- THC:CBD, 12:14 extract, 2.5 mg /day.

Starting with a low initial dose, the doctor recommended titrating the extracts every three days, increasing the dosage by 2.5 mg at each interval until symptom control was achieved with minimal side effects.

The optimal dosage for the patient was:

- CBD-rich extract: 1 mL in the morning (corresponding to 100 mg CBD) and 1 mL in the evening (corresponding to 100 mg CBD), sublingually;
- THC:CBD, 12:14 extract, 0.3 mL in the morning (corresponding to 3.6 mg THC, 4.6 mg CBD) and 0.6 mL in the evening (corresponding to 7.2 mg THC, 9.2 mg CBD), sublingually.

After two years of therapy, the doctor reported:

- significant improvement in pain scales scores (VAS);
- significant improvement in quality of life (QoL) questionnaires;
- significant improvement in Modified Ashworth Scale (MAS) for spasticity;
- discontinuation of clonazepam;
- discontinuation of gabapentin and ketorolac.

The patient reported that Medical Cannabis therapy has resulted in an improvement in anxiety and sleep quality. Reported side effects were dry mouth and, occasionally, dizziness. Below is a summary of the case study:

Table 38.

	Patient
Age and sex:	48-year-old, Female.
In therapy for:	2 years.
Diagnosis:	Multiple Sclerosis.
Medications that were eventually discontinued:	- Ocrelizumab IV, - Gabapentin 600 mg/day, Clonazepam 2.5 mg/day, - Escitalopram 10 mg/day, Ketorolac 10 mg (in case of pain).
Current medications (type of Medical Cannabis or cannabinoids prescribed):	- Cannabis Sativa L. Magistral Preparation, CBD-rich sublingual extract (THC <2.0 mg/mL : CBD 100 mg/mL), 1 mL sublingual (100 mg/am), 1 mL sublingual (100 mg/pm). - Cannabis Sativa L. Magistral Preparation, sublingual extract, THC:CBD, 12:14 (THC 12 mg/mL : CBD < 15.4 mg/mL), 0.3 mL sublingual in AM, 0.6 mL sublingual in PM.
Starting dosage:	- CBD-rich extract, 2.5 mg/day; - THC:CBD, 12:14 extract, 2.5 mg/day.
Possible corrections in dosage:	Titration was performed every third day, with the dose increased by 2.5 mg at each interval, until symptom control was achieved with minimal side effects.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	- Significant improvement in pain scales scores (VAS); - significant improvement in quality of life (QoL) questionnaires; - significant improvement in Modified Ashworth Scale (MAS) scores for spasticity; - no longer using Clonazepam; - discontinued Gabapentin and Ketorolac.
Any reported adverse effects:	Dry mouth, occasionally dizziness.
Any other consideration:	Patient reported improvement in anxiety and sleep quality.

Summary of the treatment of Multiple Sclerosis with Medical Cannabis, as reported by Dr. Valeria Giorgi.

3.3. Cannabis Therapy for Musculoskeletal Disorders

3.3.1. Cannabinoids and Musculoskeletal Health

Introduction

Bone pain, classified as musculoskeletal pain, is one of the leading contributors to chronic pain worldwide. Conditions such as arthritis, joint inflammation, and lower back pain impact millions of people each year across the globe.

Work-related injuries, sports-related trauma, and motor vehicle accidents are among the leading causes of these conditions. Additionally, chronic pain resulting from musculoskeletal issues can develop as a result of aging, immune system disorders, or sedentary lifestyles.

In managing these conditions, healthcare providers can choose from a variety of treatment options; however, some of these therapies may carry undesirable or even potentially harmful side effects.

One alternative treatment option that has gained considerable attention is Medical Cannabis. Extensive research has investigated its potential to alleviate chronic pain symptoms, suggesting that cannabis-derived products may provide a viable therapeutic approach for musculoskeletal pain affecting millions worldwide.

Bones and the Musculoskeletal System

The musculoskeletal system ensures shape, stability and movement to the human body. It consists of the bones, which make up the skeleton and on which the muscles, tendons, ligaments, joints, cartilage and other connective tissue 'rest.' The latter is the tissue that supports and binds tissues and organs together and is mainly composed of collagen and elastic fibers.

Bone Cycles

In humans and other vertebrates, bone structure undergoes significant changes throughout life. These changes include:[1]

- a rapid skeletal growth phase, leading to the attainment of peak bone mass; typically occurs during childhood and adolescence and is essential for establishing strong and healthy bones;
- a steady state phase, where bone remodeling processes continue to occur but are balanced, resulting in maintenance of bone density and strength. This phase typically encompasses adulthood;
- age-related bone loss, characterized by a gradual decline in bone density and strength, leading to an increased risk of osteoporosis and fractures, particularly in older adults.

These changes are the consequence of an ongoing process of resorption/formation of the mineralized bone matrix, known as remodeling. The bone remodeling cycle begins with the relatively rapid resorption of the existing mineralized matrix by specialized bone cells called osteoclasts. This resorption phase typically occurs over a few weeks.[2] Following resorption, there is a slower phase of bone formation, primarily orchestrated by bone-specific cells known as osteoblasts. This formation phase lasts several months as new bone tissue is synthesized and deposited.[3] Once the formation process is complete, osteoblasts mature into osteocytes, which are the mature cells of adult bone tissue responsible for maintaining bone structure and function.

Osteoporosis

It is important that all stages of the remodeling process remain well balanced to preserve skeletal integrity. Additionally, osteoblasts play a vital role in repairing damaged bone tissue. A classic example of imbalance in the bone remodeling process is osteoporosis, one of the most common degenerative diseases in Western societies. Osteoporosis results from a

marked increase in bone resorption that surpasses bone formation. This imbalance leads to bone loss, skeletal weakening, and an elevated risk of fractures. Although it primarily affects women, men can also be affected.[4]
The bone remodeling process is regulated by a complex network of endocrine, autocrine/paracrine and systemic interactions.
In this context, the Endocannabinoid System is implicated in the control of bone remodeling.
The discovery of the skeletal cannabinoid system has drawn significant attention from the scientific community.[5] CBD (but not THC) has shown potential in promoting fracture healing.[6] Currently, CB2 receptors are believed to hold the most promising role. Looking ahead, there is anticipation for further investigation into THCV and β-caryophyllene, both CB2 receptor activators—for their potential applications in the treatment of osteoporosis.[7]

The Endocannabinoid System in Bones

Recently, an emerging body of evidence suggested the Endocannabinoid System (ECS) may play essential roles in bone formation.
The osteoblast, which originates from osteoprogenitor cells, initially expresses little or no CB1 and CB2 cannabinoid receptors. As these cells mature, the expression of CB1 receptors remains low, while CB2 receptor expression increases progressively throughout the osteoblast differentiation process.
In osteoclasts, CB1 is expressed at low levels while CB2 is expressed abundantly. Therefore, CB2 is the most highly expressed cannabinoid receptor in the bone system, while CB1 is present in smaller amounts. However, CB1 is highly expressed in skeletal sympathetic nerve endings.[8]
GPR55, an atypical ECS receptor, is also expressed on both osteoclasts and osteoblasts.[9]

The Endocannabinoid System and Osteoporosis

The ECS influences the regulation of bone mass maintenance through CB1 and CB2 receptor activity. GPR55 also influences bone mass and increases bone resorption, although its physiological function is still largely unknown.[10]

CB1 receptor activity appears to play a protective role in the regulation of bone mass and osteoporosis through the differentiation of adipocytes and osteoblasts as well as the expression of multiple intracellular signaling proteins.

Administering cannabinoids to mice with osteoporosis, researchers showed that while bone damage improved in normal mice, it remained unaffected in those lacking cannabinoid receptors. This underscores the crucial role of cannabinoid receptors in modulating bone density.[11]

Indeed, knockout mice, where the CB1 receptors have been genetically inactivated, exhibit bone loss and osteoporosis, likely attributed to abnormalities in the differentiation process of osteoblasts.[12];[13]

A subsequent study by a group of German researchers revealed that activation of the CB2 receptor inhibits the formation of bone-resorbing cells (osteoclasts) by down-regulating osteoclast precursors. This shift in balance favors osteoblasts, the cells responsible for bone formation.[14]

Activation of the CB2 receptor also plays a role in maintaining bone mass. Studies on laboratory animals lacking CB2 expression have shown a decrease in bone mass, resembling the findings in CB1 knock-out mice.[15]

The effects of cannabinoid receptor ablation in animal models are highly dependent on the sex and age of the animal.

CB2 receptor activation increases bone mass by increasing the number and activity of osteoblasts, inhibiting the proliferation of osteoclasts and stimulating the formation of fibroblastic colonies by bone marrow cells.[16]

Effects of THC on Bone Mass

While tetrahydrocannabinol (THC) primarily activates CB1 receptors, it has been found to potentially hinder bone healing. THC inhibits osteogenesis and induces cell death in various types of bone cells, which may impede the healing process.[17] However, despite its potential negative impact on bone healing, THC is being investigated for its potential application as an anti-cancer agent, as it inhibits the proliferation of cancerous bone cells.[18];[19]

The inhalation of cannabis smoke, similar to tobacco smoke, appears to reduce bone healing in animal models. Specifically, the influence of THC on mesenchymal stem cell differentiation suggests a negative effect on their ability to develop into bone-forming cells, known as osteoblasts. This impairment in osteogenic potential may subsequently impede the process of bone healing.[20]

Heavy cannabis consumption has been linked to several factors indicative of compromised bone health, including low bone mineral density, low body mass index, high bone turnover and increased risk of fractures.[21] However, the extent to which these effects are solely attributable to THC ingestion remains unclear.

Effects of CBD on Bone Mass

Cannabidiol (CBD) antagonises the GPR55 receptor, is a CB2 receptor inverse agonist and has low affinity for CB1.

In vivo studies have shown that CBD can inhibit bone resorption through modulation of GPR55 signalling and activation of CB2 receptors.[22] It is not known whether THC also acts on the GPR55 receptor and, if so, whether it has similar or opposite effects to CBD.

The impact of CBD on fracture healing was investigated in a rat model of femur fractures.[23] The study revealed enhanced biomechanical properties of femur fracture healing in rats treated with CBD compared to the control group. Interestingly, this effect was not observed in rats treated solely with THC. Additionally, when rats were administered equal amounts of CBD and

THC, there was a dampening of the osteogenic effect previously observed with CBD alone.[24]

CBD and cannabigerol (CBG) have been recently investigated in a mouse model for tibial fracture. Data from this study suggest CBD and CBG as therapeutic agents that can replace NSAIDs in managing post-fracture pain as both cannabinoids exert potent analgesic effects and, at the same time, promote bone healing.[41]

Clinical Investigations on the Effects of Cannabis Use on the Outcomes of Orthopaedic Surgery

A retrospective review of the literature conducted in 2015 assessed patients undergoing primary total joint arthroplasty. The study revealed that individuals who abused substances before surgery, including not only cannabis but also opioids, cocaine, amphetamines, inhalants, and sedatives, exhibited higher rates of surgery-related complications.[25]

Conversely, a recent retrospective study of patients who used only cannabis found no difference in complications after primary knee arthroplasty, in patients who used cannabis compared to non-users.[26] In a 2018 study, the impact of cannabis use among orthopaedic patients on hospital mortality, heart failure, stroke, and heart disease was assessed. The findings revealed a reduced mortality rate among patients who used cannabis compared to those who did not.[27]

Cannabinoids in the Treatment of Musculoskeletal Pain

Opioid overuse among patients with musculoskeletal pain is a major concern for orthopaedic surgeons, given recent trends in morbidity and mortality associated with chronic opioid use.[28] As a result, alternatives to opioid have recently gained considerable attention.

Patients with complex surgical histories involving extensive procedures or multiple comorbidities often require the use of multiple painkillers.[29] Cannabinoids have the potential to decrease the opioid burden in these surgical patients.[30];[31]

Several preclinical studies indicate that the ECS exhibits a key role in the nociceptive system, and that CB1 and CB2 receptor agonists have antinociceptive properties. However, clinical trials in patients with bone issues have yielded conflicting data.[32] Indeed, as pointed out by a recent systematic review of the orthopaedic literature, "there is a relative paucity of high-quality evidence available on the use of cannabinoids for the management of musculoskeletal pain, particularly with regard to the major orthopaedic injuries, namely arthritis, back pain, postoperative pain and trauma-related pain."[33]

This literature review appears to contradict other data, primarily anecdotal evidence cited in a publication by Professor Di Marzo in 2020, which discussed the use of CBD in athletes: "Despite the lack of studies on the use of CBD in the management of sports injuries, some data suggest its potential use in osteoarthritis, Delayed Onset Muscle Soreness (DOMS) and so-called 'overuse injuries' associated with neuropathy, pain and concussion."[34]

Moreover, several clinical and observational studies support the efficacy of cannabis treatment on patients with chronic pain resistant to traditional treatments.[35]

A significant reduction in pain was observed in a 2011 study examining the interaction between cannabinoids and opioids in chronic pain.[36] According to this research, vaporized cannabis allowed the use of lower doses of opioid drugs to achieve a satisfactory analgesic effect.

A 2015 review of all previously conducted clinical trials concluded that cannabis is an effective treatment for chronic pain, including back pain.[37]

A recent study describes the use of CBD for the symptomatic relief of a lumbar compression fracture, addressing acute pain, as well as for the

mitigation of chronic chest pain and dysesthesia (an unpleasant, abnormal sense of touch) secondary to a surgically treated meningioma.[38]

Although data in the literature are inconclusive, many patients suffering from chronic musculoskeletal pain use cannabis to alleviate their condition. A 2022 survey of 184 patients reported that the use of cannabis, both inhaled and oral, induced a decrease in chronic pain in all study participants. In addition, 89% of participants felt that Medical Cannabis was more effective than opiates for adequate pain management.[39]

Other convincing results were found for myofascial pain syndrome, a painful condition of muscular origin that is not easy to classify; myofascial pain syndrome often affects the masticatory muscles, especially in the temporomandibular region, causing facial and neck pain, headaches and ear pain. This condition is commonly referred to as temporomandibular pain (TMD).

Conclusions

Preclinical studies show that the Endocannabinoid System plays an important role in bone healing and homeostasis.

Recent data indicate that CBD may enhance bone healing, whereas THC is believed to potentially impede bone metabolism and repair. Nevertheless, existing animal models exhibit age and sex dependency, which restricts the broad applicability and generalizability of cannabinoid research findings to humans.[40] It is currently unclear whether preclinical data on bone formation and homeostasis can be replicated in humans.

An association between heavy cannabis consumption and decreased bone density has been reported. However, it is not considered the fact that heavy cannabis users often combine cannabis with tobacco. When cannabis is smoked with tobacco, it exposes individuals to carcinogens similar to those found in cigarette smoke, which could potentially lead to long-term surgical complications. Considering all available literature, it appears that consumption of CBD alone or in combination with THC might have beneficial effects on bone metabolism and the healing of fractures.

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3.3.2. Cannabis for Muscular Dystrophy

History of Muscular Dystrophy

The term “muscular dystrophy” is commonly used to describe a group of hereditary conditions, typically of known genetic causes. These conditions are characterized by a progressive and irreversible decline in skeletal muscle function, known as atrophy. Individuals with muscular dystrophy often experience a pervasive sense of weakness and find it increasingly difficult to perform certain movements.

One of the first scientific reports describing muscular dystrophy dates back to 1836 and was authored by two italian doctors, Gaetano Conte and Luigi Gioja.[1] They reported the clinical case of two brothers, afflicted with progressive muscle weakness, which started around the age of 10 and eventually resulted in a general weakening of the body and generalised muscular hypertrophy. At the time of the publication, many doctors misinterpreted the symptoms as tuberculosis, leading to limited follow-up of the case.

In 1861, Guillaume Benjamin-Amand Duchenne, a French neurologist who was already famous for using electricity to stimulate muscles and nerves, described the case of two boys suffering from ‘hypertrophic paraplegia of infancy of cerebral cause’—as he called the disease in his first article.[2]

The following year he published a series of photos featuring these boys, and in 1868, he documented 13 additional cases with similar characteristics. As a result, muscular dystrophy came to be recognized as a distinct and legitimate medical condition. In tribute to the French doctor’s contributions to the understanding of this condition, one of the most severe forms of dystrophy is now known as Duchenne muscular dystrophy.

Genetic Inheritance in Muscular Dystrophy

Muscular dystrophy can manifest in various forms, affecting individuals of any gender and age. Most forms of dystrophy are inherited and in-

volve mutations in one or more genes that produce proteins crucial for muscle function.[3] These mutations result in the production of proteins that cannot effectively carry out their function within the muscles, leading to a generalized defect. This can cause muscle degeneration, progressive weakness, dysfunction of muscle fibers, uncontrolled breakdown of muscle cells (phagocytosis), reduced thickness of tendons and muscles, and loss of strength and functionality in affected muscle fibers and tendons, which are often replaced by connective tissue.[4]

The various forms of muscular dystrophy can be inherited in three main ways:

- autosomal dominant inheritance, when an individual inherits a normal gene from one parent and a defective one from the other, which is dominant so the disease manifests itself;
- autosomal recessive inheritance, when both parents have an altered gene and pass it on to their offspring;
- *X-linked* inheritance, when the defective gene is located on the X chromosome, present in both sexes and is passed on to offspring.

Most Frequent Forms of Muscular Dystrophy

The US National Institute of Neurological Disorders and Stroke (NINDS) has identified 9 main forms of muscular dystrophy—sometimes also classified as myopathies (i.e. dysfunction of the voluntary muscles):[5];[6]

1. *Duchenne's*

As the most common form of childhood muscular dystrophy, this severe type accounts for nearly half of all diagnosed cases. It primarily affects males and is attributed to a defect in a gene located on the X chromosome. This genetic anomaly leads to the absence of dystrophin, a crucial protein essential for normal muscle function. Typical symptoms include weakness in the pelvic and upper leg muscles, difficulty with activities

such as running, jumping, and walking, fatty tissue accumulation in the calf muscles, and frequent falls. Symptoms typically manifest around the age of 3, with hospitalization often not necessary until around 12 years old. Unfortunately, life expectancy for individuals with Duchenne muscular dystrophy is typically around 20 years.

2. *Becker*

Similar to Duchenne muscular dystrophy but less frequent, Becker muscular dystrophy is caused by a defect in the Xp21 gene on the X chromosome. This genetic abnormality results in the production of a flawed form of dystrophin, with the terminal portion missing. Unlike in Duchenne dystrophy, the dystrophin protein in Becker dystrophy is partially functional, leading to a milder phenotype. Common symptoms include difficulty standing up, frequent muscle cramps, walking on tiptoes, and frequent falls. Becker muscular dystrophy typically manifests between the ages of 11 and 20, predominantly in males. Hospitalization is usually not necessary before the age of 30 for individuals with Becker muscular dystrophy.

3. *Congenital*

Congenital muscular dystrophy encompasses a group of rare diseases characterized by defects in muscle fiber proteins or dysfunctions of the central nervous system. Typical symptoms include scoliosis, shortened muscles leading to joint stiffness, impaired muscle control from birth, foot deformities, intellectual disability, and difficulties with breathing and swallowing. It affects both males and females from the age of 2 years onwards. If the condition extends beyond childhood, hospitalization may not be necessary.

4. *Distal*

Distal muscular dystrophies represent a group of diverse disorders characterized by progressive weakening of the muscles in the limbs, such as the hands, forearms, feet, and calves. These conditions result from defects or

deficiencies in specific proteins essential for proper muscle function, with approximately fifteen genes identified as responsible. Common symptoms include motor defects, difficulty in gesturing, and walking problems, varying depending on the specific subtype of distal dystrophy. Importantly, these disorders typically do not affect lifespan.

5. *Emery-Dreifuss*

Emery-Dreifuss muscular dystrophy is attributed to defects in specific proteins surrounding the cell nucleus, stemming from genetic alterations on the X chromosome. This condition is characterized by muscle weakness and atrophy, tendon contractures, and cardiomyopathy. Typical symptoms include difficulty in bending the neck forward, raising the arms above the head, lifting objects, walking or climbing stairs, and cardiac dysfunction. Onset typically occurs in adolescence, while cardiac issues may arise after the age of 20, potentially leading to sudden death.

6. *Facioscapulohumeral (FSHD)*

Facioscapulohumeral muscular dystrophy (FSHD) ranks as the third most common genetic disorder of the musculature. While the exact genes responsible for this condition have yet to be definitively identified, there is a hypothesis suggesting that a typically dormant gene can be activated, leading to the disease. Symptoms of FSHD encompass reduced muscle strength (hyposthenia), difficulties in opening and closing the eyes, facial muscle impairments, abnormalities in biceps and triceps muscle reflexes, hearing issues, spinal curvature, and muscle wasting around the shoulders. Both males and females are affected, typically by the age of 20. Although severely debilitating, FSHD does not typically affect life expectancy.

7. *Limb-Girdle (or caterpillar)*

Limb-girdle muscular dystrophy, also known as caterpillar muscular dystrophy, primarily affects the muscles of the pelvic and scapular girdles.

It encompasses a group of rare diseases caused by mutations in various genes. One specific variant, known as F1, arises from mutations in the TNPO3 gene, resulting in dysfunction of the protein transporter 3.[7] Individuals with the F1 variant are predominantly found in Spain or Italy and often belong to a single-family lineage spanning at least eight generations, where the disease has been carried. Common symptoms include frequent falls, weakness in the hips spreading to the shoulders, legs, and neck, an unsteady gait, stiffening of the spine, and difficulty climbing stairs. Typically, symptoms emerge during adolescence and progress to more severe manifestations over time.

8. *Myotonic*

Myotonic dystrophy is one of the most prevalent forms of dystrophy in adults, stemming from a faulty gene located on chromosome 19q13.3. This genetic anomaly involves a trinucleotide sequence (CTG) that repeats an excessive number of times, ranging from 50 to 40,000 repeats, in contrast to the normal range of 5 to 35 repeats in non-defective genes. A distinctive characteristic of myotonic dystrophy is myotonia, marked by prolonged muscle contractions and delayed relaxation. Common symptoms include difficulty swallowing, fatigue, weight loss, cataracts, vision impairments (due to involvement of eyelid muscles), and heart abnormalities. Onset typically occurs in both males and females between the ages of 20 and 30, and hospitalization is generally unnecessary unless complications arise, such as cardiac failure, which can be fatal.

9. *Oculo-pharyngeal*

Oculo-pharyngeal dystrophy is defined by a gradual decline in the strength of the eye and throat (pharynx) muscles, attributed to a flaw in the PABPN1 gene. This anomaly involves an abnormal repetition of the GCG triplet, leading to erroneous mRNA transfer from the nucleus. Typical symptoms encompass heart irregularities, ptosis (drooping eyelids), muscle wasting

in the shoulders and neck, and swallowing difficulties. It predominantly affects specific populations such as French Canadians, US Hispanics, and Ashkenazi Jews, typically emerging by the age of 60 and often not necessitating hospitalization.

Muscular Dystrophy and the Endocannabinoid System

The diverse forms of muscular dystrophy exhibit a progressive impairment of muscles in various regions of the body. While symptoms vary, most dystrophies are marked by muscle atrophy and spasms, frequently accompanied by persistent pain. Moreover, respiratory muscles may become affected, leading to breathing challenges and/or paralysis. Muscular dystrophy, a progressive muscle disorder, lacks a cure but is managed through symptom-focused approaches like corticosteroids, rehabilitation therapies, and pain management. Genetic testing aids in early detection, while emerging treatments like gene therapy show promise. There is a growing interest in exploring the therapeutic potential of Medical Cannabis for alleviating symptoms associated with dystrophy, which could significantly enhance patient care. This interest is primarily driven by three key factors:

- medical Cannabis has demonstrated effectiveness in managing muscular dysfunction, including conditions like muscular dystrophy;
- Cannabis-based treatments and their derivatives have shown promise in relieving chronic pain, offering relief to patients;
- the Endocannabinoid System (ECS) plays a role in regulating and developing skeletal muscles.

CB1 receptors are present in muscle tissue, together with other components of the ECS, such as CB2 and TRPV1 receptors and the enzyme FAAH.[8];[9] The ECS in the muscle system primarily regulates muscle energy supply by influencing glucose and insulin metabolism.[10];[11]
Moreover, ECS activity is altered during exercise and throughout the developmental stages of skeletal muscle.[12]

Muscular Dystrophy and Cannabinoids

Few scientific studies have investigated the role of Medical Cannabis and its derivatives in the treatment of muscular dystrophy.

A Study on Duchenne Dystrophy

A study on Duchenne dystrophy revealed altered expression patterns of the endocannabinoid 2-arachidonoyl glycerol (2-AG) in the muscles of patients and animals with Duchenne dystrophy compared to healthy controls. This correlated with increased CB1 receptor expression and satellite cell numbers.[13] A surplus of satellite cells appears to be harmful for individuals with Duchenne dystrophy.[14];[15] Treatment with rimonabant, a CB1 antagonist, reduced satellite cell proliferation and enhanced myotube formation in patient muscle fibers. Administering rimonabant to animals prevented loss of coordination and muscle strength in Duchenne dystrophy mice, attributed to improved muscle fiber health and reduced inflammation.

The Role of Cannabis Derivatives

Cannabidiol (CBD) and the varinic derivatives Cannabivarin (CBDV) and Tetrahydrocannabivarin (THCV) are receiving a lot of attention from the scientific community for their interesting properties.[17];[18] Their therapeutic potential in treating Duchenne dystrophy has been investigated.[16]

While CBD and CBDV showed promise in promoting myotube formation in human muscle cells, THCV did not. In animal models of Duchenne dystrophy, CBD and CBDV treatment led to improved locomotor activity, reduced inflammation, and increased autophagy. Although preliminary, these findings suggest a potential role for Medical Cannabis derivatives, particularly CBD and CBDV, in Duchenne dystrophy treatment, warranting further research.

Cannabis Use by Patients with Myotonic Dystrophy

A pilot survey conducted in Germany and the US in 2018 explored cannabis use in patients with myotonic dystrophy. Patients, aged 18 to 60, were anonymously surveyed about their interest in using Medical Cannabis, personal experiences, preferred administration routes, and perceived effectiveness for symptom relief. The majority expressed interest in trying cannabis products or participating in clinical trials. A significant percentage reported regular cannabis or cannabinoid use, noting subjective improvement in symptoms such as muscle pain, myotonia, and stiffness, with minimal side effects.[19]

Clinical Pilot Study

The Ludwig-Maximilians-University of Munich conducted a clinical study involving six patients with dystrophic and non-dystrophic myotonia to assess the use of cannabinoids for symptom relief.[20] Patients were administered THC and CBD oil in varying ratios and doses over a four-week period:

- THC:CBD = 1:10; 1.10 mg THC and 10.29 mg CBD, twice daily for the first 2 weeks;
- THC:CBD = 1:6; 3.31 mg THC and 20.58 mg CBD, 2 times daily for the next 2 weeks.

The results indicated a significant improvement in myotonia, particularly in the later weeks of treatment. Most patients also experienced relief from muscle pain and certain gastrointestinal symptoms. The only side effect reported by 4 out of 6 patients was increased constipation.

Muscular Dystrophy and Cannabis: Conclusions

Chronic pain in dystrophy patients is a common concern, with cannabis, particularly THC and CBD, showing efficacy in pain management and potentially reducing reliance on other painkillers, like opiates, with their

associated side effects and risks of addiction. The myorelaxant effect of cannabis is also sought after by patients to alleviate spasms.

Despite patient interest, scientific research on cannabis in dystrophies is limited. However, initial studies have shown promising results in reducing myotonia and myalgia. Additionally, research suggests that the Endocannabinoid System plays a role in muscle development and that cannabinoids, including divarinic derivatives like CBDV, could improve muscle function.

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3.3.3. CBD for Temporomandibular Pain

Myofascial Pain Syndrome

Myofascial pain syndrome is a painful pathology of muscular origin that is not easy to classify. This complex muscular disorder has been known by various names over the years, such as fibromyalgia, myositis, fibrositis, myalgia, and others. It can occur independently or alongside other conditions and is characterized by persistent, localized muscle pain, tightness, and sometimes neuralgia. A defining feature is the presence of trigger points, which are specific areas of tenderness or tightness within a muscle or its surrounding fascia (connective tissue). These points are often sensitive to pressure and can cause pain or discomfort locally or refer pain to other areas of the body when stimulated. Trigger points can develop due to various factors, including muscle overuse, injury, stress, poor posture, or underlying medical conditions.

Current therapeutic approaches for the management of myofascial pain involve acupuncture (acupuncture map points correspond with *trigger points* in a percentage of 71%), injections of analgesics and/or muscle relaxants, and deep tissue massage.

Temporomandibular Pain

Myofascial pain syndrome commonly affects the muscles involved in jaw movement, known as the masticatory muscles, especially in the temporomandibular region. When this occurs, it can lead to symptoms such as facial pain, neck pain, headaches, and ear pain. This condition is often referred to as temporomandibular pain or temporomandibular joint dysfunction (TMD).

Bruxism stands out as a primary risk factor for this distressing ailment. Stemming from heightened activity in the limbic system, it triggers intensified muscle contractions that persist even after cessation of the motor function. Essentially, it's akin to continued chewing without intent, with teeth incessantly grinding and touching, particularly during sleep but also while awake. Bruxism affects between 8 to 30% of the global population.

Natural and synthetic cannabis-derived compounds can block the excitability of trigeminal nociceptive neurons, resulting in the modulation of the intensity of TMD-related orofacial pain. The various bioactive compounds in cannabis, including phytocannabinoids, flavonoids, and terpenes, have been found to modulate pain signaling pathways through various mechanisms, including the reduction of the inflammatory response.[1]

A Study of Transdermal CBD Patches

A randomized, double-blind trial conducted by researchers from the University of Katowice in Poland investigated the myorelaxant effects of Cannabidiol (CBD) transdermal patches in temporomandibular pain.[2] In this

study, the experimental group received a transdermal patch containing 20% CBD ointment applied to the masseter muscle (the CBD oil used was *Charlotte's Web Hemp Extract Oil Formula Olive Oil 30*), while the control group received a placebo patch.

Results indicated a significant reduction in muscle activity and pain intensity in the experimental group compared to the control group. These findings confirm the muscle-relaxing effect of CBD and suggest its potential therapeutic use in temporomandibular pain management.

Conclusions

In 2022, a systematic review analyzed the efficacy of cannabinoid therapeutics in orofacial pain management. Of the five articles included, only one reported a significant effect on temporomandibular disorder pain relief—specifically, the study involving transdermal cannabidiol patches. Four articles reported no significant effects of cannabinoids for pain management across various orofacial pain conditions.[3] The use of transdermal patches for CBD delivery is worth highlighting, as CBD's relatively low polarity and lipophilic nature make it compatible with the lipid-rich environment of the skin, allowing for effective absorption when appropriately formulated. Although further research is needed in this field, CBD, as an alternative to THC, should be considered in masticatory muscle therapy in patients with temporomandibular pain.

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3.3.4. CBD Treatment for Low Back Pain

Low back pain is a pervasive and multifaceted condition that affects a substantial number of individuals worldwide. In 2020 alone, low back pain afflicted approximately 619 million people globally, a figure projected to escalate to 843 million cases by 2050. This upward trajectory is largely fueled by population expansion and aging demographics, underscoring the urgent need for effective management strategies.[1]

Low back pain spans a broad spectrum, comprising:[2]

- acute episodes lasting a short duration;
- chronic conditions persisting over extended periods.

Regardless of its temporal manifestation, low back pain can have profound implications for individuals' physical functioning, emotional well-being, and overall quality of life. It impedes mobility, disrupts daily activities, and can precipitate social isolation and psychological distress.

The most common causes of back pain are:[2]

- bad posture;
- repetitive strain injuries;
- improper lifting techniques;
- bad sleeping habits.

The etiology of low back pain is diverse, encompassing both specific and non-specific presentations. Specific low back pain may be ascribed to identifiable pathologies or structural abnormalities within the spinal cord, while non-specific low back pain lacks a discernible underlying cause in approximately 90% of cases.

Risk factors for low back pain are multifactorial, encompassing both modifiable and non-modifiable variables.

Notable contributors to non-specific low back pain are:

- sedentary lifestyles;

- smoking;
- obesity;
- occupational stress.

Specific low back pain may be attributable to:

- underlying diseases;
- tissue damage;
- referred pain from other organ systems.

While low back pain can manifest at any stage of life, its prevalence peaks between the ages of 50 and 55, transcending age groups and demographic categories, with women disproportionately affected compared to men. Signs and symptoms of LBP vary widely, encompassing a spectrum of sensations ranging from dull aches to sharp, radiating pain.[2]
The impact extends beyond physical discomfort, encompassing:

- disruptions in sleep;
- mood disturbances;
- functional limitations.

Acute episodes may resolve spontaneously for many individuals, but a subset will transition to chronic pain states, requiring comprehensive management strategies. Because conventional treatments often fall short in providing adequate relief for low back pain, cannabinoids, particularly cannabidiol (CBD), emerge as a potential intervention worthy of further exploration.

The Role of Cannabidiol in Treating Back Pain

CBD has garnered attention for its potential therapeutic effects, particularly in modulating pain and inflammation. Unlike its psychoactive counterpart, tetrahydrocannabinol (THC), CBD exerts its actions without induc-

ing intoxication, making it a viable option for individuals seeking relief from pain without unwanted side effects.

CBD interacts with the body's Endocannabinoid System to regulate various physiological processes, including pain perception and immune response. By modulating the activity of receptors and influencing neurotransmitter and endocannabinoid release, CBD may attenuate pain signals and mitigate inflammatory responses associated with low back pain.

Moreover, in the complex phenomenon of low back pain, pain perception involves various factors, including biological, psychological, and social elements. Unlike painkillers such as NSAIDs, CBD may impact multiple modalities, potentially reducing both pain and fear associated with low back pain.

The therapeutic potential of CBD in managing back pain extends beyond symptom relief to encompass broader benefits, such as:

- improved sleep quality;
- enhanced mood;
- reduced reliance on conventional analgesics.

CBD's mechanism of action, coupled with its favorable safety profile, positions it as a promising adjunctive therapy or standalone treatment for individuals with chronic low back pain.[1]

Scientific Studies on CBD for Back Pain

Research on the effectiveness of cannabinoids in acute low back pain is limited. The CANBACK study, a rigorously designed trial, compared 400 mg of CBD with a placebo in 100 participants with acute back pain.[4] After two hours, pain levels and Emergency Department (ER) stays were similar between the CBD and placebo groups. However, this study has limitations, including subjective pain assessment and lack of information on pre-ER medication use.

In a case report, a 40-year-old man with an L3 compression fracture experienced significant pain reduction after applying CBD cream topically (400 mg CBD per two ounces, where one ounce equals approximately 28 grams; thus 7.05 mg CBD/g). Despite unsuccessful conservative treatment, CBD cream alleviated his pain for about 10 hours.[5]

A cream containing 400 mg CBD per two ounces was effective and induced antinociceptive and anti-inflammatory effects in patients with low back pain.[6]

The effectiveness of CBD in treating chronic low back pain is also underresearched, with few randomized controlled trials available. Most studies evaluate cannabinoid preparations containing both CBD and THC, making it challenging to isolate CBD's specific effects. Moreover, the variability in preparation doses and the heterogeneity of low back pain conditions across studies pose challenges in assessing treatment effectiveness.[7]

Despite these limitations, CBD shows promise as a potential therapeutic option for chronic low back pain, with further high-quality research warranted to elucidate CBD's role in low back pain management and address the gaps in current knowledge.

Dosing and Delivery of Cannabidiol for Back Pain Relief

CBD is available in various formulations, including oils, capsules, topical creams, and edibles, allowing for tailored treatment approaches based on individual preferences and therapeutic goals. Topical CBD creams offer localized relief by targeting specific areas of discomfort, while oral formulations provide systemic effects for comprehensive pain management. The choice of administration route depends on factors such as the severity of symptoms, patient preferences, and the presence of comorbidities. For low back pain, the administration of CBD can vary depending on the product used and clinical experience. Previous studies have shown significant heterogeneity in CBD dosing.

A specific dosing regimen is not recommended due to the scarcity of evidence, but it appears that a dose of 0.1–12.5 mg/kg of CBD twice daily can be safely administered in adults.[7]

Studies suggest starting the therapy with the lowest dose showing clinically documented effects: 0.5-1 mg/kg/day and then adjusting the dosage according to the patients' needs.

Most studies on CBD for pain have focused on products containing different amounts of THC.

Cannabis composition can be categorized into 3 types:

- high THC;
- balanced THC : CBD;
- high CBD, low THC.

Studies have shown that high THC levels can negatively affect CBD efficacy.[7] For example, when THC levels are too high, CBD may have an antagonistic effect. However, the use of products containing only CBD has shown beneficial effects in chronic pain, possibly due to improvements in insomnia, anxiety, cognition, and/or mood.

Research on high-CBD products, such as Epidiolex® (99% CBD: 100 mg/ml), is limited regarding their efficacy in back pain. In summary, CBD administration for back pain should consider dosing, product composition, and individual clinical response.

Conclusions on Cannabidiol for Back Pain

CBD holds promise as a therapeutic option for managing low back pain, offering a holistic approach to symptom management and improved quality of life for affected individuals. By harnessing the synergistic effects of CBD on pain perception, inflammation, and associated comorbidities, healthcare providers can empower patients to explore alternative treatment modalities that align with their needs and preferences.

While CBD is generally well-tolerated, adverse effects such as fatigue, gastrointestinal disturbances, and changes in appetite may occur, necessitating careful monitoring and adjustment of treatment plans as needed.

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3.3.5. Cannabis Use in Sports Medicine

Cannabidiol as a Therapeutic Option for Athletes

The World Anti-Doping Agency (WADA) listed cannabis as a prohibited substance in all sports in 2004. The reasons for this are mainly motivated by the psychotropic effects of tetrahydrocannabinol (THC), which could affect athletes' performance. However, cannabis contains more than just THC. Cannabidiol (CBD), a key non-intoxicating component, is notable for its broad pharmacological activity.

In 2018, WADA removed Cannabidiol (CBD) from the list of prohibited substances in sport. This decision paved the way for the use of CBD among athletes, including both professional and amateur competitors.

Properties of Cannabidiol

CBD can be extracted directly from the cannabis plant or can be synthesized in a laboratory. Commercially, CBD can be found in different products such as oils, sprays, pills, tinctures, vaporizer liquid or balms. "Full spectrum" CBD products contain all the naturally occurring compounds found in the cannabis plant, including cannabinoids, terpenes, and flavonoids. This means that they may contain trace amounts of THC, but not enough to produce psychoactive effects. "Broad spectrum" CBD products also contain multiple cannabinoids and terpenes, but they undergo additional processing to remove all traces of THC, making them THC-free. The effect of CBD is dose-dependent, and intravenous injection, smoking or inhalation allow effective concentrations to be reached more quickly. Clearly, the latter is the recommended route outside study settings.
CBD has a low affinity for the cannabinoid receptors CB1 and CB2. It can enhance the action of endogenous cannabinoids, and reduce that of THC at the receptor site by acting as a negative allosteric modulator.
In addition to the classical cannabinoid receptors, CBD can bind to the serotonergic 5-HT1A receptors, the vanilloid receptors TRPV1 and the nuclear receptors PPARγ.

The Analgesic and Anti-inflammatory Effects of CBD

The analgesic and anti-inflammatory properties of cannabidiol (CBD) have been documented in the scientific literature since the 1980s.
CBD is capable of decreasing the activity of several markers of inflammation such as cytokines, prostaglandins E2 (PGE2), cyclooxygenase, nitric oxide, the production of oxygen-derived free radicals, and edema formation.

CBD also exerts promising analgesic effects, as demonstrated in several models of inflammatory and chronic pain, by regulating the production of pro-inflammatory mediators and interacting with targets involved in pain perception.

Potential Therapeutic Applications of CBD in Athletes

Athletes may find relief from pain, inflammation, and swelling linked to injuries through the use of CBD. Consequently, CBD could serve as a substitute for non-steroidal anti-inflammatory drugs, opioids, or corticosteroids. Although research on the utilization of CBD for managing sports injuries is limited, preliminary data indicates its potential efficacy in conditions such as osteoarthritis, delayed onset muscle soreness (DOMS), and "overuse injuries" linked to neuropathy, pain, and concussion.[1] Moreover, CBD has demonstrated the ability to alleviate allodynia (the sensation of pain triggered by a typically non-painful stimulus) and hyperalgesia (heightened sensitivity to pain), particularly showcasing efficacy in the reduction of chronic pain.

The Anxiolytic Effects of CBD

Effectively managing anxiety before, during, and after performance is crucial for athletes, as unresolved anxiety can impair performance, hinder recovery, and increase the risk of developing anxiety disorders.

In this scenario, CBD could be useful due to its anxiolytic properties, confirmed by numerous preclinical studies in various animal models of innate fear and behavioural anxiety.

In humans, CBD is able to reduce anxiety in various contexts. These effects have been correlated to the activation of 5-HT1A receptors and/or indirect enhancement of endocannabinoid transmission in brain areas involved in anxiety phenomena, such as the limbic system and paralimbic brain structures.

Furthermore, several studies indicate that CBD is able to facilitate the process of extinguishing fears. This means that it helps to forget unfavourable events. This property could be exploited for the recovery of athletes suffering from post-traumatic stress disorder (PTSD), which can occur after musculoskeletal injuries or concussions related to sports injuries.

The Neuroprotective Effects of CBD

Sports-related concussion represents a frequent injury among certain types of athletes and is categorized as a mild form of traumatic brain injury. Those affected may experience acute manifestations such as fatigue, dizziness, headaches, irritability, memory impairment, and difficulty concentrating. Often, these symptoms resolve spontaneously following a period of rest. Recently, studies in animals have shown that repeated treatment with CBD oil exerts beneficial effects on the behavioural dysfunctions, such as pain, aggression, and depressive behavior, which are commonly associated with traumatic brain injury.

These findings are significant as there are currently no effective therapies available for managing minor brain injuries, making the potential benefits of CBD treatment particularly noteworthy. Furthermore, repeated traumatic brain injuries, common in contact sports like boxing, heighten the risk of long-term neurological complications such as chronic traumatic encephalopathy (CTE). This neurodegenerative condition is marked by a progressive deterioration in memory and cognition, along with symptoms like depression, suicidal tendencies, aggression, and sometimes dementia reminiscent of Alzheimer's disease. Experimental data have shown that CBD is able to decrease neuroinflammation and oxidative stress related to CTE, although further studies, especially clinical, are needed to confirm this aspect.

CBD and Sleep Disorders

CBD can influence sleep in humans. This is not surprising, considering that the Endocannabinoid System is involved in regulating the sleep-wake cycle.

Various studies suggest that CBD may induce a biphasic effect, with low doses increasing wakefulness and higher doses inducing calming effects that facilitate sleep.

Although the mechanisms underlying these CBD properties have yet to be elucidated, these preliminary observations highlight CBD's role as a potential tool for sleep and drowsiness management in athletes.

In some sports, such as endurance races or motor marathons (for example: The 24 Hours of Le Mans), the ability to stay awake may be a determining factor. Conversely, sleep loss due to anxiety is common in athletes and has a negative impact on cognitive and physiological functions, resulting in reduced sports performance.

Current Limitations of CBD as a Therapeutic Agent

CBD could be useful for athletes due to its anti-inflammatory, analgesic, anxiolytic, neuroprotective properties and its influence on the sleep-wake cycle. Unfortunately, few data are available on the use of CBD in the context of athletic performance. Hence, while CBD holds promise for athletes, several factors should be considered before endorsing its use. There's limited research on CBD's effects in adult athletes and no studies have directly compared CBD with established drugs or therapies used by athletes. There's a possibility that CBD may be less effective or have more adverse effects than these conventional treatments, despite its generally safe profile in humans. Notably, common side effects reported in clinical trials include fatigue, diarrhea, and changes in appetite and body weight.

Additionally, dosage considerations are crucial. The desired effects, such as anxiolytic, neuroprotective, anti-inflammatory, and analgesic properties, seem to depend on the dosage administered. Future clinical research is needed to determine the optimal dosage required to achieve the intended therapeutic effects. Lastly, the regulation of CBD products available on the market is currently inadequate. Many products claim to

contain only CBD, but their purity and quantity may not be accurately reported, and the presence of THC may not be properly disclosed. This lack of oversight underscores the importance of thorough testing and regulation to ensure consumer safety and product efficacy. Indeed, a 2019 paper cautions against the use of over-the-counter CBD products, particularly those sourced from unreliable internet sources lacking quality control. Such products may contain elevated levels of other cannabinoids, like THC, with more than 2.5 mg/day found in over 30% of products on the German market. This raises concerns about potential positive doping tests among athletes.[2]

CBD in Sports: Conclusions

Reviewing the current scientific literature reveals that preclinical studies have consistently demonstrated CBD's anti-inflammatory, analgesic, anxiolytic, neuroprotective, and sleep-regulating properties. Consequently, CBD holds promise as a potential aid for athletes in managing injuries, anxiety, stress, and sleep disorders. However, the limited availability of clinical studies in this specific context, coupled with inadequate regulation and oversight of CBD products, necessitates caution when recommending this cannabinoid to athletes, at least until further research and regulatory measures are established.

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3.4. Cannabis and Cardiovascular Disorders

3.4.1. Cannabis in Cardiovascular Diseases

The Endocannabinoid System has a ubiquitous distribution throughout almost the entire human body and consequently regulates the function of many organs and systems. Apart from their known neurobehavioral and analgesic effects, cannabinoids exert a profound effect on immune, digestive and reproductive function and influence cell fate (including apoptosis), body temperature, bone formation and other aspects of human physiology.[2]

The cardiovascular system—blood, vessels and heart—is also influenced by the actions of the Endocannabinoid System. Cannabinoids play a significant role in regulating key cardiovascular parameters, including blood pressure, vasomotor control, cardiac contractility, vascular inflammation, and angiogenesis. Alterations in circulatory endocannabinoid levels and the expression of cannabinoid receptors within blood vessels, along with perturbations of cannabinoid signaling pathways, have been detected in several pathophysiological conditions including obesity, diabetes, advanced liver cirrhosis, cardiotoxicity, cardiovascular shock, atherosclerosis and hypertension.[3] Phytocannabinoids and their endogenous and synthetic analogues therefore exert complex cardiovascular effects, through both cannabinoid receptor-dependent and independent mechanisms.

Distribution of the Endocannabinoid System in the Cardiovascular System

CB1 receptors have been identified in various vascular regions, such as aorta and mesenteric artery, primarily within endothelial and muscle cells. This suggests involvement of the Endocannabinoid System in regulating vascular function. Activation of CB1 receptors—also via central mechanisms—typically induces vasodilation, leading to a hypotensive effect. However, in

some cases, a contractile response has been observed, highlighting the complex pharmacology of cannabinoids within the cardiovascular system.[4]
CB1 receptors are also found in the heart, particularly in cardiomyocytes. Stimulation of these receptors generally causes a negative inotropic effect, meaning it reduces the force of contraction of the heart muscle.[5]
CB2 receptors have been identified in the myocardium and at the vascular level, but their function is not yet well understood.[4] CB2 receptors are also expressed by immune cells in the cardiovascular system—particularly leukocytes and macrophages—and their activation reduces the release of inflammatory mediators such as cytokines and chemokines.[6] Interestingly, studies on abnormal cannabidiol (Abn-CBD) have led to the hypothesis of the existence of at least one unidentified cannabinoid receptor in the cardiovascular system. Abn-CBD, a synthetic regioisomer of cannabidiol (CBD), shares the same molecular structure but differs in the spatial arrangement of its atoms. Despite being inactive at the CB1 and CB2 receptors, Abn-CBD still exhibits blood pressure-lowering effects, even in animals lacking CB1 and CB2 receptors (knockout animals).[7]
Furthermore, the vasodilatory responses to anandamide observed in ex vivo experiments exhibit pharmacological characteristics that are inconsistent with activation of classical cannabinoid receptors.[9] Additionally, these effects of abnormal cannabidiol and anandamide are antagonised by a synthetic drug called O-1918, which is not active at the CB1 and CB2 receptors.[8]
Excluding TRPV1 receptors—which are also activated by anandamide and induce vasodilation through a distinct mechanism—a potential candidate for the so-called “third cannabinoid receptor” (or vascular receptor for anandamide) is GPR55, although its role remains highly debated.[9]
Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), and their synthesis and degradation systems are present at both the vascular and cardiac levels, where they exert various functions, mainly vasodilation and a decrease in vascular pressure and cardiac contractility.[10]

Analyzing studies in laboratory animals and in humans, the effects of stimulation of the Endocannabinoid System in the cardiovascular system, influenced by factors such as route of administration, duration, and dosage, can lead to various effects. These effects may involve CB1 receptor-mediated bradycardia or tachycardia, hypotension, and alterations in cardiac contractility. Additionally, these responses can be influenced by effects on the central nervous system, as well as direct impacts on the myocardium and vascular system.[11]

Despite this, the Endocannabinoid System appears to play a limited role in regulating cardiovascular parameters under normal physiological conditions. This is in line with the general function of the Endocannabinoid System, which is to maintain homeostasis, ensuring the body's balance.

When homeostasis is undisturbed, the Endocannabinoid System remains relatively inactive. However, in pathological conditions where homeostasis is disrupted, there is often an over-activation of the Endocannabinoid System. This can lead to both protective and harmful effects on the cardiovascular system, depending on the specific cardiovascular event and underlying conditions.

Therapeutic and Adverse Effects of Cannabinoids in Cardiovascular Conditions

Activation of the Endocannabinoid System, particularly through CB1 receptors, has been identified in instances of hypotension related to conditions such as hemorrhagic shock, septic shock, cardiac shock, and in heart failure induced by doxorubicin.[12];[13]

Increased Endocannabinoid System activity can be a cardiovascular risk factor in diseases such as metabolic syndrome or diabetes as it can cause plasma lipid alterations, abdominal obesity, hepatic steatosis and insulin and leptin resistance.[14];[15]

In case of hypertension, the activation of the Endocannabinoid System serves as a compensatory mechanism, moderating both elevated blood

pressure and increased cardiac contractility primarily through the activation of CB1 receptors.[16]

Activation of CB2 receptors in endothelial and inflammatory cells by endogenous or exogenous cannabinoids can limit the endothelial inflammatory response, chemotaxis (the recruitment of inflammation mediators to specific sites), the adhesion of inflammatory cells to the endothelium and the consequent release of various pro-inflammatory mediators, which are responsible for the initiation and progression of atherosclerotic phenomena and ischaemia-reperfusion damage.[17]

Thus, depending on the concomitant diseases, selective activation of CB1 or CB2 receptors or their inhibition may be able to provide beneficial therapeutic effects in various cardiovascular complications.

Hypertension

Hypotension is one of the principal physiological effects associated with activation of the Endocannabinoid System. As a result, since the 1970s, cannabis has attracted scientific interest as a potential therapeutic option for managing hypertension. However, the psychoactive effects of tetrahydrocannabinol (THC) have consistently restricted its application.

Despite this, recent studies in laboratory animals have revived the antihypertensive potential of cannabinoids, especially in light of the fact that the reduction in blood pressure primarily occurs in hypertensive animals, rather than those with normal blood pressure, highlighting the specificity of this effect.[18];[19] These studies suggest that the activation of the Endocannabinoid System acts as a compensatory mechanism in response to elevated pressure. This compensation seems to be primarily attributed to a decrease in cardiac contractility mediated by CB1 receptors, rather than a reduction in vascular resistance.

Additionally, this phenomenon has been corroborated by inhibiting the enzyme FAAH, which is accountable for the degradation of anandamide.[20] By preventing the degradation of endogenous anandamide, cardiac anan-

damide levels are elevated, resulting in a decrease in blood pressure and cardiac contractility specifically in hypertensive laboratory animals, but not in normotensive ones. Consequently, pharmacologically blocking the FAAH enzyme may present a promising therapeutic strategy for individuals with hypertension. Importantly, this approach avoids the central psychotropic effects induced by THC in cannabis use.[21];[22]

Atherosclerosis

Atherosclerosis is a pathological condition characterized by alterations in the arterial wall, leading to reduced elasticity due to the accumulation of various substances, including calcium, cholesterol, and fibrotic material. The initiation of the atherosclerotic process primarily involves pro-inflammatory cytokines such as TNF-alpha and bacterial endotoxins like lipopolysaccharide (LPS). These mediators, alongside factors like oxygen and nitric oxide radicals, synergistically promote the migration of smooth muscle cells and the deposition of extracellular matrix within the vascular bed. This process ultimately leads to the formation of atherosclerotic plaques.[23]
Reports on the efficacy of cannabinoids in this condition are mixed, with experiments reporting an increase in muscle cell migration and others a decrease, depending on the experimental conditions, the type of endocannabinoid or synthetic agonist and the type of cell used in the experiments.[24]
In a paper published in the journal *Nature* in 2005, a group of Swiss researchers demonstrated that oral administration of THC significantly attenuated the progression of atherosclerosis in laboratory animals by a mechanism mediated by CB2 receptors.[25] This was probably due to a decreased release of inflammatory mediators by immune cells in the vasculature. Stimulation of the Endocannabinoid System presents promising avenues for pharmacological development, particularly through the use of selective CB2 agonists, as opposed to THC.
For example, CB2-selective agonists like JWH133 and HU308 have demonstrated the ability to reduce the release of TNF-alpha and other pro-atherosclerotic factors in endothelial cells derived from the human aorta.[26]

Ischemic-Reperfusion Injury and Heart Attack

When a blood vessel is obstructed by a thrombus or an embolus, blood circulation is compromised or completely halted, leading to insufficient delivery of nutrients and oxygen to cells, resulting in ischemia. A transient ischemic attack may manifest as *angina pectoris*, characterized by chest pain and a feeling of constriction in the center of the chest, while a prolonged ischemic episode can culminate in a heart attack.

During these ischemic events and in the following infarction, endocannabinoid levels appear to decrease. The use of cannabinoid agonists can reduce the volume of the infarct area.[27]

If reperfusion is restored following ischemia, the situation can exacerbate, leading to reperfusion damage. Upon restoration of circulation, tissues previously affected by ischemia are identified as foreign by the innate immune system. This recognition triggers a potent inflammatory response, marked by the production of abundant oxygen radicals and cytokines, resulting in additional cellular damage.[28]

The role of the Endocannabinoid System in ischemic-reperfusion injury remains uncertain. Endocannabinoids are produced in excess during various forms of reperfusion injury—such as those associated with hemorrhagic shock and acute myocardial infarction—and, according to some studies, they may contribute to the decrease in cardiovascular function associated with these diseases.[29]

On the other hand, various researches show that endocannabinoids seem to play a protective role in myocardial ischaemia and reperfusion injury, as they contribute to the ischaemic preconditioning effect induced by LPS, heat stress or short periods of ischaemia.[30];[31]

Ischaemic preconditioning is the phenomenon whereby if a vessel is occluded for a short period before an ischaemic phenomenon, the subsequent reperfusion is less damaging.[32]

The probable bioprotective mechanism of cannabinoids in this condition seems to be due to their action on the CB2 receptor, which induces a

decrease in the inflammatory process and activation of endothelial cells due to ischaemia.[33] Although further confirmation is needed, controlling endocannabinoid stimulation by acting on CB2 may prove to be a useful therapeutic option.

Effects of Cannabis and Cannabinoids on Cardiovascular Parameters

The initial studies investigating the comprehensive effects of cannabis on cardiovascular parameters trace back to 1970. Even from these early investigations, it became evident that the cardiovascular effects induced by smoking cannabis are significantly influenced by the chemical composition of the plant, particularly the THC content, the inhaled dose, and the smoking method employed.[34] Early studies on cannabis showed a difference between acute and chronic use.

Acute cannabis smoking was seen to cause bronchodilation, an immediate increase in heart rate (tachycardia) that may last for more than 1 hour, and an increase in blood flow in the limbs (hypertension).[35];[36] These responses were not observed after the administration of propranolol, a beta-adrenergic blocker, indicating that the responses are due to an increase in adrenergic stimulation, thus of the sympathetic autonomic system.[37]

However, repeated use over days or weeks leads to the development of tolerance to the initial effects and smokers experience completely opposite effects such as bradycardia and hypotension.

The same applies to THC alone: while acute administration of THC generally causes an increase in blood pressure and heart rate, repeated administration of THC reduces blood pressure and heart rate, and here too the effects appear to be due to an action on the adrenergic system.[38];[39] Furthermore, early studies highlighted differences in the effects between THC and CBD, not only on heart rate but also on certain psychological reactions that indirectly impact cardiovascular parameters. Indeed, in healthy volunteers, an oral dose of 30 mg THC was found to increase heart rate and

blood pressure, whereas CBD (15-60 mg) produced no effect when administered alone. Interestingly, CBD significantly attenuated the effect of THC when the two drugs were administered together.[40]

CBD, in particular, exhibits a hypotensive action that could be leveraged for therapeutic purposes. Indeed, acute administration of CBD at high doses (600 mg) has been shown to reduce resting blood pressure as well as the increase in blood pressure induced by exercise and mental stress.[41]

Numerous beneficial effects of CBD have been noted in experimental models of various heart diseases (including myocardial infarction, cardiomyopathy, and myocarditis), stroke, neonatal hypoxic ischemic encephalopathy, sepsis-related encephalitis, cardiovascular complications of diabetes, and ischemia/reperfusion injuries of the liver and kidneys. In these pathological conditions, CBD has been observed to reduce organ damage and dysfunction, mitigate oxidative and nitrative stress, suppress inflammatory processes, and inhibit apoptosis, among other positive effects.[42]

Cannabis and Cardiovascular Health

While the effects of THC and CBD are relatively well-defined, establishing the precise impact of smoking cannabis on the cardiovascular system is challenging. In the absence of robust clinical studies, our understanding largely relies on individual case reports.

A comprehensive review of adverse events associated with recreational (non-medical) cannabis use was published in 2018 in *Nature Reviews Cardiology*.[43] According to the authors, "the last decade has seen an almost tenfold increase in the THC content of cannabis and increased availability of highly potent synthetic cannabinoids for recreational use. These changes have been accompanied by the emergence of serious adverse cardiovascular events, including:

- myocardial infarction;
- cardiomyopathy;

- arrhythmias;
- stroke;
- cardiac arrest."

However, it is important to consider that interpreting the data from these reports is complicated by several factors, as highlighted by the authors themselves and other researchers who have thoroughly examined these studies. These complexities arise from the simultaneous use of other substances such as nicotine and alcohol, as well as the absence of specific details regarding the type of cannabis consumed.

As highlighted by Professor Piano in a 2017 report by the US National Academies of Sciences, Engineering and Medicine concluded that "the available evidence is unclear on whether and how cannabis use is associated with myocardial infarction and stroke."[44]

Larger studies and systematic reviews have failed to provide clarity on the situation. For instance, when researchers examined the association between cannabis use and cardiovascular outcomes among the general USA population, they discovered that cannabis use is linked with adverse cardiovascular outcomes, with heavier use (more days per month) associated with higher odds of adverse outcomes.[44] On the contrary, when researchers investigated the major adverse cardiac and cerebrovascular events associated with cannabis use in hospitalized IBD patients in the USA, they did not find a statistically significant difference in major adverse cardiac and cerebrovascular events among hospitalized IBD patients with and without cannabis use.[45]

Cannabis and Cardiovascular Disease: Conclusions

Cannabinoids, through both central and local mechanisms, influence key cardiovascular parameters such as:

- heart rate;

- blood pressure;
- vascular and cardiac contractility;
- inflammation in cardiovascular districts.

The ability of the Endocannabinoid System to influence these cardiovascular parameters appears to be minimal under healthy conditions, whereas it is more pronounced under pathological conditions.

In the case of diseases or conditions in which the cardiovascular system is impaired, studies over the last few decades have shown that the Endocannabinoid System can play both a deleterious role, as in pathological states associated with excessive hypotension, and a compensatory protective role, as in certain forms of hypertension and inflammatory conditions that compromise cardiovascular health.

The use of drugs that act on the Endocannabinoid System, such as selective CB2 agonists in cases of myocardial infarction, atherosclerosis and ischaemia-reperfusion injury, or FAAH enzyme blockers in cases of hypertension, could prove to be a useful therapeutic strategy. However, our data are still preliminary and should be confirmed in further animal models and possibly in human clinical studies.

In any case, the use of cannabis—whether for medical or recreational use—should be discouraged or at least carefully screened in people with established heart disease, especially if smoking is used as a route of administration. In the case of heart disease, smoking cannabis increases the risk of chest pain, and various studies suggest that the risk of heart attack is higher in the hour after smoking cannabis than it normally would be.[46] This is due to the complex effects that cannabinoids have on the cardiovascular system, including raising the heart rate, dilating blood vessels and slowing the heart pump. For the same reason, intense physical exertion should be avoided immediately after smoking cannabis.

Thus, according to scientific research, smoking cannabis poses no significant threat to persons with minimal cardiovascular risk, but should be

avoided by anyone with a history of heart disease. This consideration is always paramount, particularly regarding the potential intrinsic damage to the cardiovascular system, and beyond, stemming from the irritants and carcinogens present in smoking, especially when combined with simultaneous tobacco combustion.

Finally, since the most serious cardiovascular problems have been found in recreational cannabis users and are usually related to intensive and prolonged use over time, patients receiving Medical Cannabis therapy should have no particular problems if they have no concomitant cardiovascular pathologies and should periodically monitor cardiac parameters, in case of the presence of alterations in the cardiovascular system.

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3.4.2. Cannabis and Hypertension in Elderly Patients

With the legislative openings towards Medical Cannabis in many parts of the world, elderly people have become the fastest growing group of Medical Cannabis users. The therapeutic indications for which cannabis is prescribed to the elderly primarily include:

- chronic pain;
- Parkinson's disease;
- Alzheimer's;
- chemotherapy-induced nausea and vomiting;
- Multiple Sclerosis.

Prescriptions for sleep and mood disorders are also becoming increasingly common. Despite the rise in prescriptions and patients, there is a notable lack of clinical studies investigating the effects of cannabis in older individuals as our bodies age, numerous physiological parameters undergo changes, impacting how we respond to various substances, including drugs.

Specifically, the cardiovascular system may operate less efficiently, particularly due to factors such as unhealthy lifestyle choices including sedentary behavior and poor dietary habits. Consequently, hypertension, characterized by elevated blood pressure, emerges as one of the primary challenges we face as we age. The World Health Organization estimates that approximately 1.13 billion are affected by hypertension, with the majority being older adults.

Cannabis and Hypertension: a Clinical Study

Various reports warn against the use of cannabis in elderly people, due to possible cardiovascular risks. This is mainly due to the action of tetrahydrocannabinol (THC) whose effects on cardiovascular parameters are not well established. To try to clarify the situation, a group of researchers monitored the cardiovascular parameters of elderly people undergoing cannabis therapy for 24 hours.

A total of 38 patients were enrolled in the study. Of these, four used cannabis by inhalation while all others used it in the form of an oil extract. Cannabis dosage was determined according to the reports of the participants. Every cigarette puff was calculated as containing 55.5 mg of active substances and each drop of oil as 0.05 ml. The average THC dosage was 21.1 mg and that of cannabidiol (CBD) 21.3 mg.

The main indications for which cannabis was prescribed were various types of chronic pain, mainly neuropathic (34.6% of the total). The results showed that chronic use of Medical Cannabis for 3 months was associ-

ated with a reduction in blood pressure, both diastolic and systolic, and a reduction in heart rate. The pressure *nadir* (the lowest value) was reached 3 hours after cannabis treatment. Electrocardiogram results showed no significant differences between the start and end of treatment, as did the analysis of blood and metabolic parameters.

Conclusions on Cannabis and Hypertension

The Endocannabinoid System is widely expressed throughout the body and influences various functions, such as cardiovascular functions. It is therefore not surprising that the use of Medical Cannabis or its derivatives have an effect on some of these parameters, such as blood pressure or heart rate. However, the effects of cannabis are not unique and depend greatly on the dose used and the type of product chosen.

According to studies, elderly patients with hypertension may benefit from a reduction in blood pressure when using cannabis for other therapeutic indications, such as chronic pain. However, pending a larger clinical study with fewer limitations, the use of Medical Cannabis in elderly hypertensive patients must always be carried out taking into account the risk/benefit ratio.

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3.4.3. Cannabidiol for Infant Ischemia

Perinatal Acute Ischemic Stroke

Acute ischemic arterial stroke is the most frequent acquired neurological disorder in newborns, affecting approximately 4 out of every 1,000 live births. The incidence is even higher in preterm infants, affecting around 60% of children and often resulting in permanent complications. About one third of affected infants develop unilateral cerebral palsy, which usually results in the loss of the use of one hand, with cognitive and learning deficits being also common.[1];[2]

The consequences of brain injury depend on the stage of brain maturation at the time of the insult. In preterm infants, lesions of the white matter are more common. This vulnerability is attributed to certain brain cell populations not being fully developed, rendering them more susceptible to glutamate toxicity and neuroinflammation. Conversely, in term infants, where white matter maturation is more advanced, neuronal degeneration in the grey matter is the predominant manifestation following hypoxic-ischemic insults.[3];[4]

Potential Therapeutic Use of Cannabinoids in Infants

Currently, therapeutic hypothermia—delivered as either head or whole-body cooling—remains the only established clinical intervention for infants with hypoxic-ischemic disease. However, hypothermia fails to prevent injury in all cases, and treatment does not consistently result in full functional recovery.[5]

Cannabinoids play a significant role in influencing various endogenous processes crucial for brain injury recovery. They are recognized for their ability to regulate the cell cycle and proliferation, survival, and differentiation of neural stem cells. This makes cannabinoids promising experimental drugs

for enhancing the body's natural repair mechanisms to neonatal ischemic insults.[6];[7]

Cannabinoids can modulate excitability and mitigate glutamate toxicity, characteristics that render Medical Cannabis beneficial in various diseases such as Amyotrophic Lateral Sclerosis or Multiple Sclerosis. Moreover, by activating CB2 receptors on immune cells, cannabinoids can regulate the intensity and duration of neuroinflammatory responses to pathological insults.

Lastly, cannabinoids have demonstrated the ability to decrease vascular reactivity, characterized by the increase in blood flow in response to ischemia. This is achieved primarily by reducing the adhesion of circulating leukocytes and preventing their infiltration into the inflamed brain. This mechanism holds significance for numerous disorders, ranging from ischemia to Multiple Sclerosis.[8]

In *in-vitro* experiments, the synthetic cannabinoid WIN- 55 inhibited the release of excitotoxic glutamate, the accumulation of TNFα and the induction of iNOS—key markers of inflammation—ultimately reduced cell death.[9]

In-vivo studies administering WIN-55 (1 mg/kg) immediately after the hypoxic-ischemic event showed a reduction of the extent of the lesion in adjacent areas of the brain.[10]

Experiments with CBD

CBD exhibits neuroprotective effects in neonatal animal models with brain damage resulting from acute hypoxic-ischemic events, as well as in adult mouse models. At a dosage of 1 mg/kg, CBD has been demonstrated to significantly reduce excitotoxic damage, oxidative stress, and inflammation for up to 7 days post-injury. These mechanisms play pivotal roles in generating permanent brain damage following arterial ischemic strokes.[11]

In a recent study on neonatal mice with severe stroke, CBD administered post-insult at a dosage of 5 mg/kg demonstrated significant benefits. CBD

reduced peri-stroke brain damage, restored neurobehavioral function in the short and long term, and prevented permanent functional disability. Despite not altering the stroke's extent, CBD's positive effects were evident as early as one week after the stroke, with no observed side effects. CBD restored lost mobility, improved neurobehavioral functions, and prevented further neuronal loss.[12]

Intravenous administration of CBD at a dosage of 0.1 mg/kg improved brain tissue oxygenation during the initial three hours post-ischemia-hypoxia and partially restored EEG amplitude from 1 to 6 hours in newborn piglets. Similar to rodent studies, CBD demonstrated long-term protective effects. Neurobehavioral analysis revealed that CBD-treated animals exhibited faster, and more significant functional recovery compared to those not receiving CBD.[13];[14]

Cannabidiol for Infants

The potential for cannabidiol (CBD) to emerge as a safe and effective treatment for neonatal hypoxia-ischemia is becoming increasingly tangible. This is supported by studies showcasing its beneficial effects on various neurophysiological parameters commonly utilized to monitor infants hospitalized for asphyxia. Taken together, these studies in animal models suggest that CBD could be an effective and safe drug in the acute and subacute phases of ischemic strokes and is the most suitable cannabinoid to be a candidate for clinical trials in infants with encephalopathy.

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3.5. Cannabis Therapy for Metabolic Disorders

3.5.1. Medical Cannabis in Diabetes Management

Diabetes manifests as hyperglycemia due to:

- Type 1 Diabetes: insufficient insulin production, resulting from autoimmune destruction of β-cells within the insulin-secreting islets of Langerhans in the pancreas.
- Type 2 Diabetes: insulin resistance, a condition of impaired cellular response to insulin, with obesity being a predominant risk factor for its onset.

While cannabis is primarily known for its main psychoactive component, THC, it also contains a wide array of compounds with diverse—and at times opposing—biological effects. In the context of diabetes management, current scientific research on medical cannabis is largely focused on two principal avenues. Let's explore each in detail.

Evidence Against the Use of Cannabis for Diabetes

Increased appetite

The use of cannabis, particularly its psychoactive component tetrahydrocannabinol (THC), and endogenous analogs like anandamide, which activate the central CB1 receptors, has been linked to increased appetite and subsequent weight gain in animal models.[1] This phenomenon underlies the therapeutic application of medical cannabis to stimulate appetite and caloric intake in conditions such as cachexia or during chemotherapy treatments. However, this appetite-stimulating effect poses a significant challenge for individuals attempting weight loss, especially for patients with Type 2 Diabetes, where obesity is a critical factor exacerbating insulin resistance.

Current scientific literature delineates that the appetite enhancement attributed to cannabis is predominantly associated with its acute rather than chronic administration.[2] This interaction between cannabis and the body's physiological mechanisms is evident in the stimulation of homeostatic hunger centers, which regulate energy balance, as well as the activation of hedonistic hunger centers, which enhance the pleasure associated with food consumption.

A subset of researchers suggests that the homeostatic function of the endocannabinoid system primarily modulates appetite and weight gain in individuals with below-normal body weight.[3] This hypothesis gains empirical support from investigations on cannabinoid antagonists, which, by counteracting THC's effects, produce anorectic outcomes.[4] Moreover, cannabis has been documented to reduce blood glucose levels, an action that can precipitate weakness and dizziness in naïve users employing excessively high doses, and potentially trigger hypoglycemic episodes in insulin-dependent patients. The reduction in blood glucose concentration, in turn, amplifies the appetite-inducing effects of endocannabinoids, further complicating the management of diabetes.

Endocannabinoid System Hyperactivation in Metabolic Syndrome and Obesity

Emerging scientific literature has delineated the critical role of the endocannabinoid system (ECS) in metabolic regulation, particularly highlighting the consequences of cannabinoid receptor 1 (CB1) hyperactivation in obesity and metabolic syndrome. Studies have consistently shown that CB1 receptor hyperactivation in peripheral tissues is a hallmark of obesity, closely associated with enhanced lipogenesis, hepatic steatosis (accumulation of triglycerides in the liver cells), and insulin resistance.[5];[6];[7] These processes are fundamental to the development of metabolic syndrome, a cluster of conditions increasing the risk of heart disease, stroke, and diabetes. CB1 stimulation is implicated in exacerbating inflammation linked

to metabolic diseases and obesity induction via poor dietary habits. This evidence underscores the therapeutic potential of inhibiting peripheral CB1 receptors to mitigate obesity and its associated metabolic disturbances.

The Cautionary Tale of Rimonabant

The selective CB1 receptor antagonist, SR141716 or Rimonabant, emerged as a promising therapeutic agent in the early 2000s, demonstrating significant efficacy in reducing body weight, appetite, and metabolic syndrome risk factors in high-risk obese patients.[8] The Rimonabant In Obesity/Overweight (RIO) clinical trials showcased its potential in inducing weight loss and improving metabolic markers.[9];[10]

However, the subsequent CRESCENDO trial, aimed at evaluating Rimonabant's efficacy in preventing cardiovascular events, revealed severe neuropsychiatric side effects due to the drug's central CB1 receptor blockade, leading to its market withdrawal by the FDA in 2007.[11]

This outcome emphasized the critical need for selective targeting of peripheral CB1 receptors to avoid central nervous system-related adverse effects, marking a pivotal moment in the development of ECS-targeting therapies.[12];[13]

Cannabidiol (CBD) and Peripheral ECS Modulation

The intricate relationship between ECS hyperactivation and metabolic syndrome underscores the system's potential as a therapeutic target for obesity and its comorbidities. While the initial enthusiasm for CB1 receptor antagonists was tempered by significant safety concerns, the ongoing investigation into compounds like CBD revitalizes interest in peripheral ECS modulation as a viable strategy. Continued research is essential to fully understand the ECS' role in metabolic health and to develop targeted interventions that safely and effectively address the global obesity epidemic.[14]

The Evidence Supporting Cannabinoid Use in Diabetes

Lower Incidence of Diabetes and Healthier Body Weight

Epidemiological studies have provided compelling evidence that cannabis users exhibit a lower risk of developing diabetes compared to non-users. Notably, despite the association of chronic cannabis use with increased caloric intake, findings indicate that body mass index (BMI) remains unaffected or is even reduced among cannabis users.[15];[16] This paradox may be attributed to the actions of cannabinoids other than THC, which do not interact with CB1 receptors and might play an unrecognized role in metabolic regulation.

A landmark study conducted by researchers at the University of California, Los Angeles, involving 10,896 American adults, found that current or former cannabis users had a lower prevalence of obesity. This observation held true even after adjusting for various social and demographic variables.[17] The study concluded, "Our analysis...shows that participants who use cannabis have a lower prevalence of Diabetes Mellitus and a lower likelihood of developing this condition than participants who do not use it."[18] Further corroborating this, studies from the US have linked cannabis use with favorable metabolic markers, including a lower body mass index, smaller waist circumferences, and higher levels of HDL cholesterol.[19];[20];[21] These findings challenge the traditional view associating cannabis with increased appetite and caloric intake, suggesting that the effects on appetite may predominantly result from occasional rather than chronic use.

Physiological and Metabolic Effects of Cannabinoids

Cannabis influences a broad spectrum of physiological pathways affecting glycaemia and insulinemia, notably altering the secretion of appetite-regulating hormones such as ghrelin. It also modulates the activity of adiponectin, a hormone that plays a key role in regulating blood sugar levels and body weight, thus offering protection against diabetes despite its appetite-stimulating effects.[22]

Researchers at Michigan State University analyzed eight studies and found that the risk of contracting diabetes in cannabis users was 30 per cent lower than in non-users.[23]

Lower Insulin and Circulating Glucose

Clinical investigations have examined the effect of cannabis consumption on insulin sensitivity and glucose metabolism. Notably, studies conducted at Harvard Medical School and Beth Israel Deaconess Medical Center found that cannabis users had significantly lower fasting insulin levels and reduced insulin resistance compared to non-users among a large adult population.[24]

These effects appear most pronounced during periods of recent cannabis use.

Cannabis and Pancreatic Health

Preclinical studies on obese rat models have demonstrated that administration of Medical Cannabis extracts can reduce body weight and increase pancreatic weight, suggesting a protective effect on pancreatic β-cells, crucial for insulin production.[25] While THC has shown potential anti-obesity effects, its psychoactive properties limit its clinical application.[26];[27] In contrast, CBD, known for its non-psychoactive properties, has been shown to exert beneficial effects on pancreatic health and insulin regulation, particularly in type 1 diabetes models[28] CBD's protective effects are induced by qualitative modifications of the pancreatic islets (Langerhans islets), inhibiting specialised beta cells destruction, preventing future degeneration of insulin-releasing cells.[29]

Endocannabinoid System Downregulation and Cannabinoid Therapeutics in Obesity and Diabetes

Recent research indicates that individuals with obesity exhibit a diminished functionality of CB2 receptors. Compounds like tetrahydrocannabivarin

(THCV) that can activate these receptors might counteract obesity-related inflammatory effects, thereby offering protection against diabetes.[30]

In rodent models, activation of endogenous CB2 receptors by 2-arachidonoylglycerol (2-AG) is notably reduced in states of diabetes, suggesting a mechanistic link between CB2 receptor dysfunction and metabolic syndrome.[31]

This observation was echoed in a study involving 501 obese children in Italy, revealing compromised CB2 receptor functionality. Those administered selective CB2 agonists experienced a reversal of obesity-induced inflammatory states.[32]

Preventive Potential of Cannabinoids

A pivotal study in 2006 demonstrated that daily administrations of 5 mg/kg CBD markedly lowered the occurrence of hereditary diabetes in a mouse model. While 86% of the control group developed diabetes, only 30% of the CBD-treated mice did, indicating not just a lower incidence but also a delayed disease onset, corroborated by subsequent studies.[33];[34];[35]

Additionally, in a high-fat diet-induced Type 2 diabetes mouse model, control subjects developed diabetes by week 17, whereas the majority of CBD-treated mice remained diabetes-free till week 2.[36];[37]

Therapeutic Efficacy of Tetrahydrocannabivarin (THCV)

THCV, a minor cannabinoid known for its unique pharmacological properties, acts as a CB1 receptor antagonist and a CB2 receptor agonist.[38] This dual function plays a significant role in metabolic regulation, potentially reducing appetite via CB1 blockade while mitigating inflammation and oxidative stress through CB2 activation. Even at low doses, THCV exhibited 'hypophagic' properties, reducing both food intake and body weight in animal models.[39] A 2013 study highlighted THCV's metabolic benefits, including diminished glucose intolerance and improved insulin sensitivity, suggesting its utility in treating metabolic syndrome and Type 2 diabetes,

either alone or in combination with existing therapies.[40] A subsequent trial involving diabetic patients further supported THCV's role in enhancing glycaemic control.[41]

Application of Tetrahydrocannabinolic Acid (THCA) in the Management of Diabetes

In 2020, research explored the effects of Tetrahydrocannabinol Acid (THCA), the non-psychoactive precursor to THC. This study revealed that THCA significantly curtailed obesity-induced fat mass and body weight gain in animal models, improved glucose tolerance, insulin resistance, and effectively prevented hepatic steatosis and adipogenesis.[42] THCA was identified as a partial, selective modulator of PPARγ receptors, displaying lesser adipogenic activity compared to full agonists like rosiglitazone, pointing towards its potential in diabetes treatment.[43];[44] Since THCA is constitutively present in the plant and is only subsequently transformed into THC by the action of heat, it could be hypothesized that raw cannabis may also be effective in treating diabetes.

Cannabinoids in the Management of Diabetes Symptoms and Complications

Cannabinoids have been shown to modulate energy metabolism and influence the progression of diabetes, offering symptomatic relief for various complications associated with the condition. Diabetes can lead to severe macrovascular and microvascular complications, including atherosclerosis, which heightens the risk of heart attack and peripheral arterial disease. Microvascular complications typically manifest as nephropathy, retinopathy, and peripheral neuropathy, significantly impacting patients' quality of life and contributing to major health issues such as kidney failure, lower limb amputations, and blindness in adults.

Cardiomyopathy and Cardiovascular Dysfunction

Cannabinoid system activation has been identified as a protective mechanism against pro-inflammatory cascades, such as ROS-MAPK, which are implicated in the cardiovascular dysfunctions arising from diabetes.[45];[46] A pivotal study demonstrated that CBD administration mitigated symptoms of diabetic cardiomyopathy in a type 1 diabetes mouse model. The researchers underscored CBD's potential for treating diabetic complications, supported by its favorable safety and tolerability profile in humans.[47]

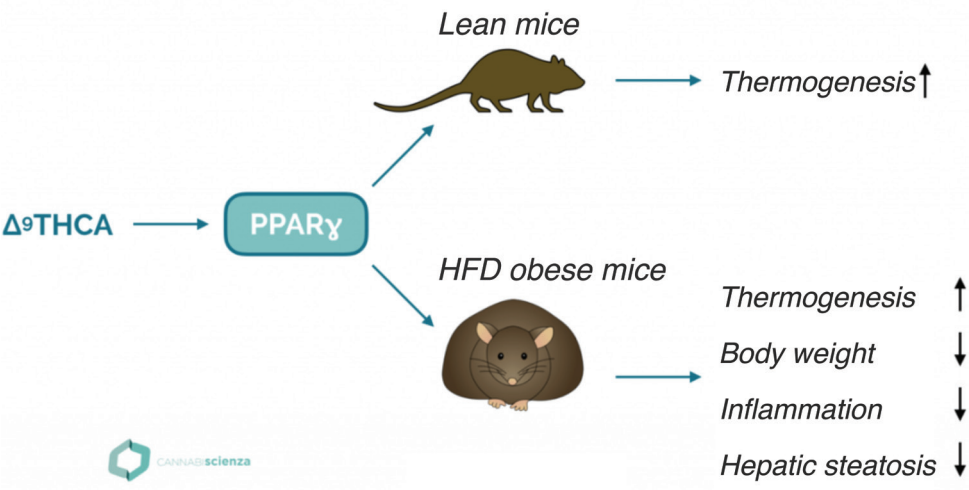

Image 19. Effects of THCA on Lean and high-fat diet (HFD) obese mice.

Blindness Prevention

Diabetic retinopathy, a leading cause of adult blindness, has been shown to be ameliorated by CBD treatment. A study in the *American Journal of Pathology* highlighted that rats subjected to CBD treatment for 1 to 4 weeks exhibited significant protection against diabetic retinopathy.[48]

Subsequent research confirmed CBD's ability to reduce oxidative stress, prevent retinal cell death, and inhibit vascular hyperpermeability in models of this condition.[49];[50] CBD's neuroprotective and anti-inflammatory actions in retinal microglial cells, possibly through the inhibition of adenosine reuptake, further elucidate its therapeutic potential.[51];[52]

Alleviation of Nephropathy

Advanced diabetic nephropathy, a severe kidney-related complication, has shown improvement with CBD intervention, suggesting that non-psychotropic CB2 activators like THCV and β-Caryophyllene may offer similar benefits. These substances, recognized for their therapeutic effects, underscore the broader potential of cannabinoids in managing diabetes-induced renal issues.[53]

Cannabis and Diabetes: Conclusions

The interplay between cannabis usage and diabetes management reveals a landscape punctuated by promising epidemiological insights and emerging clinical evidence. The neutral to positive impact of cannabis on diabetes, as suggested by epidemiological data, alongside clinical studies demonstrating the efficacy of specific cannabinoids in modulating blood glucose levels and alleviating diabetes-related symptoms, positions cannabis as a potential adjunct in diabetes care.

Key cannabinoids such as CBD, THCV, and THCA, along with agents that block peripheral CB1 receptors or activate CB2 receptors, and possibly agonists of GPR55 and GPR119 receptors, represent the forefront of pre-clinical research. These compounds are heralded for their therapeutic promise, underscoring a burgeoning interest in harnessing their mechanisms for diabetes management. The imperative for more extensive and rigorous studies remains paramount to substantiate these early findings and to elucidate the comprehensive role of cannabinoids in diabetes therapy.

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3.5.2. Cannabis and Obesity: the Role of THCA

Tetrahydrocannabinolic acid (THCA) is a precursor cannabinoid found in the raw cannabis plant. Unlike its decarboxylated counterpart, THC, THCA does not produce psychoactive effects, making it an intriguing subject for scientific investigation, particularly in the context of obesity and metabolic diseases. Recent research has illuminated THCA's potential in combating obesity-related conditions, highlighting its multifaceted role in reducing body weight and fat mass, alongside mitigating inflammation and liver steatosis—a common feature of metabolic syndromes.[1]

The Acidic Cannabinoids

The exploration of cannabis extracts and cannabinoids has unveiled their therapeutic potential across a spectrum of medical conditions. Despite the promising benefits of tetrahydrocannabinol (THC), its psychotropic effects often present a barrier to its therapeutic application. This limitation has shifted research focus toward non-psychotropic cannabinoids, which do not induce the psychoactive effects associated with THC.

Cannabinoids in the cannabis plant are predominantly synthesized and stored as acidic precursors. These acid cannabinoids undergo decarboxylation, transforming into their neutral, active forms upon exposure to heat. Tetrahydrocannabinolic acid (THCA), one of the major acidic cannabinoids, serves as the precursor to THC but exhibits distinct properties that set it apart from its psychoactive counterpart.

THCA's lack of psychotropic effects expands its appeal for medical use, offering the therapeutic benefits of cannabinoids without the associated high. Unlike THC, which primarily interacts with cannabinoid receptors, THCA shows a preference for binding to peroxisome proliferator-activated receptor gamma (PPARγ). These receptors are crucial in managing metabolic disorders, playing a pivotal role in regulating lipid and glucose metabolism. By targeting PPARγ receptors, acidic cannabinoids like THCA offer a promising avenue for addressing metabolic disorders, highlighting a significant area of interest in the ongoing study of cannabis-based therapies.

The Role of Thermogenesis in Obesity Management

Amid the ongoing search for effective obesity treatments, the spotlight has increasingly focused on novel pharmacological targets that indirectly influence body weight, such as thermogenesis. Thermogenesis, the process of heat production within the body, emerges as a critical metabolic pathway with substantial implications for energy homeostasis and fat reduction.

Understanding Thermogenesis

Thermogenesis involves the generation of heat through biochemical reactions, primarily occurring in adipose (fat) and muscle tissues. This process accounts for approximately 90% of the energy produced by the body's metabolism, underscoring its pivotal role in maintaining body temperature and overall energy balance.

Body weight regulation hinges on the equilibrium between calorie intake and energy expenditure, with thermogenesis playing a vital role in burning calories and thus facilitating weight control.

Adipose Tissue and Its Dual Role

The body harbors two distinct types of adipose tissue, each serving unique functions in energy management:

- *White Adipose Tissue (WAT)*: Specialized in energy storage, WAT accumulates fat during periods of caloric surplus.
- *Brown Adipose Tissue (BAT)*: The primary site of heat production, BAT's thermogenic activity is crucial for burning calories and regulating body temperature.

Central to the function of brown adipose tissue (BAT) is uncoupling protein 1 (UCP1), also known as thermogenin—a mitochondrial protein that drives the thermogenic process. UCP1 uncouples oxidative phosphorylation, allowing energy to be dissipated as heat, which constitutes a key mechanism for regulating body temperature and energy expenditure.

Browning of White Adipose Tissue

A noteworthy aspect of adipose tissue dynamics is the potential for WAT to transform into BAT-like tissue through a process known as "browning." This transformation is partially mediated by peroxisome proliferator-activated receptor gamma (PPARγ) receptors. The resulting "brite" or "beige" adipocytes exhibit enhanced thermogenic capacity, contributing to reduced body fat mass.

Stimulating PPARγ receptors to promote browning represents a promising strategy for enhancing thermogenesis and, by extension, managing body weight and metabolic disorders such as diabetes. This approach underscores the complex interplay between adipose tissue types and their collective impact on the body's metabolic health, offering a glimpse into the potential of targeting thermogenesis as a pathway for obesity and diabetes management.

The THCA Study

A recent study explored the therapeutic potential of THCA, focusing on its role as a partial agonist of PPARγ receptors, in contrast to full agonists like rosiglitazone (RGZ) which, despite their antidiabetic efficacy, come

with adverse effects such as weight gain, edema, and osteoporosis.[1] *In-vitro* experiments demonstrated that THCA induces less fat production and enhances bone tissue repair more effectively than RGZ, suggesting a lower risk of RGZ's side effects. Additionally, molecular docking and transcriptomics studies identified THCA as a partial PPARγ agonist, potentially offering a safer profile for diabetes treatment.

Experiments on mice, both on normal and high-fat diets, showed that THCA stimulates thermogenesis, decreases fat mass, improves glucose intolerance and insulin resistance, and prevents hepatic steatosis and inflammation. THCA also promotes the browning of white adipose tissue, increasing thermogenin expression, which is crucial for burning fat and improving metabolic health. These findings highlight THCA's potential as a promising therapeutic agent for managing diabetes and obesity with reduced side effects.

Therapeutic Effects of THCA on Metabolic Disorders

THCA stands out as a promising compound for improving metabolic disorders, addressing the significant challenge posed by obesity in society—a leading risk factor for mortality from various diseases, including diabetes. Traditional treatments like glitazones (e.g., RGZ), despite their efficacy as full PPARγ agonists in diabetes management, have seen diminished use due to adverse effects such as bone loss, obesity, and fluid retention. The search for new drugs has thus pivoted towards finding compounds with partial agonist activity on PPARγ to mitigate these side effects.

As a partial PPARγ agonist, THCA exhibits a lower propensity to induce fat production compared to glitazones and possesses beneficial effects on bone density. Additionally, THCA has been shown to reduce fat mass and potentially ameliorate the metabolic and inflammatory issues linked to diet-induced obesity. This differentiates THCA from other cannabinoids like THC, which are known for their estrogenic and lipogenic effects, likely

due to THCA's distinct mechanism of action that does not involve the classic cannabinoid receptors.

Highlighting THCA's potential, research suggests its value in activating thermogenesis without the undesirable side effects associated with other treatments. THCA and non-decarboxylated cannabis extracts are considered promising options for managing obesity and metabolic diseases, offering a novel approach to tackling these prevalent health issues.

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3.6. Dermatological Diseases and the Endocannabinoid System

The Skin as More Than a Protective Barrier

The skin serves as the body's largest organ and a comprehensive barrier against external threats, fulfilling a role that extends beyond mere protection to include neuroendocrine and immunological functions.[1] It synthesizes hormones, regulates body temperature, and senses environmental stimuli, efficiently communicating these to the nervous and immune systems for a coordinated response.[2];[3] The skin's ability to produce antimicrobial agents and regulate immune responses through cytokines and chemokines showcases its critical role in both physical and mental health, and indicates its potential systemic health implications.[4] Central to its complex functionality is the Cutaneous Endocannabinoid System (CECS), which exemplifies the skin's adaptability and its significant impact on overall health.

The Skin and the Endocannabinoid System

The Endocannabinoid System (ECS), a critical regulator of homeostasis within the human body, is naturally found within the skin. This presence aligns with the historical application of Cannabis Sativa L. for topical purposes, a practice dating back to ancient civilizations across China, Egypt, and the Arab world during the Middle Ages. These societies utilized cannabis preparations for treating wounds, ulcers, skin diseases, and even in mummification processes, as evidenced by numerous archaeological findings. Cannabis-based tinctures and ointments were commonplace in pharmacies well into the early 20th century until regulatory restrictions curtailed their medicinal use. Previously supported primarily by anecdotal evidence, the contemporary understanding reveals that the ECS is not only present in the skin but also plays a pivotal role in maintaining its health and functionality. This modern recognition underscores the therapeutic potential of cannabis-derived topical treatments, bridging ancient practices with current scientific insights.

The Endocannabinoid System in Dermatology

The Endocannabinoid System (ECS) comprises various components within the dermal layer, extending beyond neuronal endings. This includes endocannabinoids such as Anandamide and 2-arachidonoylglycerol (2-AG), receptors (CB1, CB2, and TRPV1 etc), and enzymes involved in the endocannabinoids' biosynthesis and degradation processes (FAAH, MAGL, etc.).

Localisation

The presence of ECS components is confirmed in a diverse array of skin cells: epidermal keratinocytes, melanocytes, mast cells, fibroblasts, sebocytes, sweat glands, and specific hair follicle types.[6]

Functions

In the dermatological context, the ECS regulates numerous physiological processes. These include cell growth, proliferation, apoptosis, inflammatory and immune responses, sensory stimuli transmission to the central nervous system, and the synthesis of lipids and epidermal components.[7]

Application of Medical Cannabis in Dermatology

Current evidence on the utilization of cannabinoids for dermatological conditions suggests a wide range of potential therapeutic applications. Nevertheless, it is essential to acknowledge that the majority of this data are derived from pre-clinical studies, with a notable scarcity of randomized, controlled clinical trials within this domain.

Acne Vulgaris

Acne vulgaris, often misconceived as a mere hallmark of adolescence, is in fact an inflammatory disease, sometimes chronic, primarily resulting from the inflammation of sebaceous glands. This inflammation leads to an overproduction and alteration of sebum composition, culminating in the formation of pimples and associated itching.[9] The etiology of acne encompasses genetic predisposition, hormonal imbalances, and bacterial infections. To date, no acne remedy, synthetic or natural, has been conclusively validated by scientific evidence. However, emerging data on the Endocannabinoid System (ECS) offer promising directions. Anandamide and 2-arachidonoylglycerol (2-AG) presence in sebaceous glands, along with the expression of CB2 receptors—whose activation is linked to increased sebum production—suggests that CB2 receptor inhibitors might be beneficial in acne management.[10]

Moreover, TRPV1 receptors have been implicated in sebum production control. A 2014 in vitro study demonstrated that cannabidiol (CBD) could inhibit sebum production and sebaceous gland proliferation by acting on TRPV1

receptors.[11] Beyond CBD, other phytocannabinoids like tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), and cannabichromene (CBC) have shown efficacy in reducing sebum production and local inflammation.[12]
The therapeutic potential extends beyond isolated cannabinoids. A 2015 clinical study highlighted the efficacy of a cannabis seed oil extract-based cream, which, when applied twice daily, significantly reduced sebum production and erythema without adverse effects.[13] This evidence underscores the complexity and therapeutic promise of cannabis-based interventions in acne vulgaris treatment, marking a compelling area for further clinical exploration.[13]

Eczema/Dermatitis

Dermatitis—or more appropriately eczema (a term of Greek origin meaning 'boiling')—is an inflammatory, non-infectious dermal reaction that causes a skin rash characterized by itching, erythema, the presence of blisters and/or the formation of scabs.
The most common types of eczema (synonymous with dermatitis) are:

- contact dermatitis;
- asteatotic eczema;
- atopic eczema.

Together, they affect about 3.5% of the world's population and are mainly due to genetic or environmental factors.
Research indicates the involvement of CB2 receptors in contact dermatitis, triggered by exposure to irritants or allergens. Both CB2 agonists and antagonists have been observed to exacerbate inflammation, whereas inverse agonists, applied systemically or topically, have demonstrated efficacy in reducing inflammation.[14]
Asteatotic eczema, prevalent in older adults, features itchy, dry, rough, and flaky skin. A randomized, double-blind trial involving 60 patients showed that an emollient cream containing cannabinoid-like substances, N-pal-

mitoylethanolamine (PEA) and N-acetylethanolamine, effectively improved skin hydration, dryness, and itching.[15]

Atopic dermatitis, marked by sudden skin inflammation, dryness, itching, erythema, and blister formation, lacks a known etiology but is believed to result from a mix of hereditary, stress, and environmental factors. PEA has emerged as a potent treatment by inhibiting FAAH enzyme action, thus enhancing Anandamide availability. Anandamide, acting on TRPV1 receptors on keratinocytes, offers anti-itching benefits. Synthetic FAAH inhibitors and topical Anandamide applications have also shown efficacy.[16];[17];[18] PEA's direct anti-itching effect, mediated through CB2 receptor action, has been encapsulated in the Mymix® lamellar matrix cream, demonstrating decreased itching, inflammation, and increased remission rates in atopic dermatitis.[19] This finding is supported by a prospective observational study in a cohort of 2456 patients, where PEA-based cream not only alleviated symptoms but also reduced the need for cortisone-based treatments.[20] Furthermore, CB1 receptor engagement has been implicated in atopic dermatitis management, with THC-based preparations showing effectiveness in treatment protocols.[21]

Psoriasis

Cannabinoids have emerged as promising agents in psoriasis treatment, attributed to multiple mechanisms: anti-proliferative effects on keratinocytes, inhibition of immune cells (macrophages, lymphocytes) and inflammatory cytokine release, and angiogenesis reduction.[22] The CB2 receptors, predominantly located on immune cells, are central to these mechanisms. Additionally, CB1 and PPARγ receptors, the latter influenced by PEA, are significant in psoriasis pathology. Pre-clinical studies have validated the efficacy of phytocannabinoids or their analogues acting on these receptors in ameliorating psoriasis symptoms.[23] Given the association of psoriasis with stress and the significant role of pain in the condition, the central effects of THC or its analogues, particularly at low doses, could also be

beneficial. However, the absence of clinical trials on these treatments underscores the need for further investigation to establish their efficacy and safety in psoriasis management.

Itching

Defining itching presents a unique challenge in dermatology, with ongoing debates regarding its classification as a sensory experience. Cannabinoids hold significant promise in dermatological applications, particularly for itching relief. The involvement of CB1 and CB2 receptors, along with TRPV1, in mediating itching sensation highlights the potential therapeutic role of cannabinoids.[24] Capsaicin, known for its "spicy" effect in chili peppers, exemplifies an effective anti-itch remedy by desensitizing TRPV1, thereby reducing itch propagation.[25] Clinical practice has long recognized capsaicin-based topical treatments for various itch types, including postherpetic neuralgia and aquagenic itch.[26] Furthermore, emollient creams containing PEA have demonstrated efficacy in alleviating itching associated with diverse pathological conditions.[27] Dronabinol, a synthetic analogue of THC, has also shown potential in managing cholestatic pruritus, as supported by various individual clinical reports.[28] These findings underscore the therapeutic potential of cannabinoids and related compounds in addressing itching, highlighting the need for further research to fully understand and exploit these mechanisms for itch relief.

Systemic Sclerosis

Systemic sclerosis is an autoimmune disorder characterized by connective tissue cell dysfunction, leading to augmented extracellular matrix protein deposition, small vessel vasculopathy causing tissue hypoxia, and an immune response that produces pro-inflammatory cytokines and autoantibodies. This disease manifests as a progressive skin thickening due to excessive collagen accumulation, which can be either confined to the skin (cutaneous systemic sclerosis) or involve internal organs (diffuse

systemic sclerosis). Emerging evidence suggests the utility of ECS modulation in systemic sclerosis. In animal studies, JWH-133, a selective CB2 receptor agonist, demonstrated a capacity to significantly ameliorate the disease's clinical progression by reducing the immune response.[29] Additionally, the cannabinoid agonist WIN55,212-2 has been shown to decrease extracellular matrix deposition and address various abnormalities in sclerodermal fibroblasts, such as resistance to apoptosis and the pathological differentiation of these cells into myofibroblasts.[30] These findings point towards the potential therapeutic benefits of ECS modulation in systemic sclerosis, highlighting a promising avenue for future research and treatment strategies.

Skin Tumours

Skin cancer, a prevalent form of cancer, primarily arises in areas exposed to ultraviolet radiation, with incidence rates particularly high among individuals frequently exposed to the sun for leisure or occupational purposes. Those with lower levels of skin melanin pigmentation face the highest risk. Recent data show a continuous increase in skin cancer cases, including melanoma, the most aggressive type.

Both CB1 and CB2 cannabinoid receptors are found in melanoma and non-melanoma skin tumors, as well as benign skin lesions. The role of CB2 is believed to be more significant than that of CB1 in leveraging the therapeutic effects of cannabinoids on these cells.[31] Activation of these cannabinoid receptors disrupts endothelial cell migration, inhibits growth, reduces vascularization, and promotes apoptosis in tumorigenic epidermal cells.[32] Additionally, CB2 receptor agonists diminish the expression of endothelial growth factor (VEGF) and other pro-angiogenic factors, thereby curtailing melanoma progression and its metastatic potential.[33]

A notable study in 2015 by British researchers highlighted that Sativex®, a cannabis-derived pharmaceutical, could reduce the viability, proliferation, and growth of melanoma cells more effectively than temozolomide, the

standard chemotherapy drug for melanoma. This was achieved through enhanced autophagy and apoptosis, suggesting a potent application of cannabinoids in skin cancer treatment strategies.[34]

Cannabis and Dermatological Diseases: Concluding Insights

Dermatological conditions, while often not perceived as severely as other diseases by a significant portion of the population, represent a widespread health concern. It is noteworthy that approximately 35% of primary care patients report acute or chronic skin diseases. Within the myriad of research areas for the ECS, dermatological applications stand out as one of the most promising yet nascent fields. The scarcity of research in this domain means that the majority of skin diseases, particularly inflammatory ones, are frequently addressed with over-the-counter products, whose effectiveness remains largely unsubstantiated. The endocannabinoid system (ECS) holds significant potential for addressing this gap, as supported by preclinical evidence demonstrating the efficacy of cannabis extracts, PEA, CBD, and THC analogues across a range of dermatological conditions. Topical preparations of these substances also tend to exhibit fewer side effects, presenting a safer alternative for skin disease management.
Patients suffering from serious conditions such as psoriasis, systemic sclerosis, and skin cancer might find relief in ECS-modulating agents. However, the current scarcity of clinical studies markedly restricts their application.

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3.6.1. Case Studies: Cannabinoids in Dermatology

In this section, we explore a collection of dermatological case studies highlighting the application of CBD-infused topical treatments. These cases are introduced by Dr. Marcello Albanesi, an allergist and immunologist who founded the Marcello Albanesi Allergy and Immunology Unit in Bari, Italy. After extensive research into the properties of cannabis-derived products, Dr. Albanesi began incorporating them into the treatment regimens for various skin conditions in his practice. He is joined by Dr. Concetta De Chirico, who has co-contributed to the detailed descriptions of these clinical scenarios.

Eczematous Dermatoses

This case involves a 76-year-old woman diagnosed with eczematous dermatitis of the neck, face and upper limbs, previously treated with prednisone 25 mg, 1 tablet per day, orally.

Cannabinoid therapy

The previous therapy has been replaced with:

- Dermohemp barrier cream with Cannabidiol (CBD) 0.5%, 1 application per day;
- Clobetasol ointment 0.05%, 1 application daily.

After 36 days of single daily application, there was a switch to 2 applications per day of both products. After 21 days of therapy, Dr. Albanesi reports a marked improvement in the eczematous lesions on the neck, face and upper limbs, with no observed side effects.

Desquamative Dermatitis

The second case study is that of a 49-year-old woman diagnosed with desquamative dermatitis of the hands.
The woman was previously being treated with clobetasol ointment 0.05%, 1 application per day.

Cannabinoid therapy

To the previous therapy, Dr Albanesi added:

- Dermohemp barrier cream with CBD 0.5%, 1 application per day.

After one month of therapy, the barrier cream was replaced with a galenic preparation of Occluvan (base cream) + CBD 1%.
Dr. Albanesi reports that, although the therapy is still ongoing, a partial improvement of symptoms (not observed with the previous therapy) is noted.
Below is a summary table of the 2 case studies.

Table 39.

	Patient 1	Patient 2
Age and gender:	76-years-old, female.	49-years-old, female.
In therapy since:	1 month.	3 months.
Diagnosis:	Eczematous dermatitis (neck, face, upper limbs).	Desquamative dermatitis of the hands.
Possible therapy prior to the use of Medical Cannabis or cannabinoids:	Prednisone 25 mg cpr, 1 daily.	Clobetasol ointment 0.05%, 1 application daily.
Current therapy:	- Dermohemp barrier cream with CBD 0.5%, 1 application per day; - Clobetasol ointment 0.05%, 1 application daily.	Dermohemp barrier cream with CBD 0.5%, 1 application per day; Clobetasol ointment 0.05%, 1 application daily.
Initial dosage:	1 application per day.	1 application per day.
Possible dosage corrections:	After 36 days - switched to 2 applications per day.	After one month, the barrier cream was replaced with Occluvan (basic cream) + CBD 1%.

	Patient 1	Patient 2
Duration of treatment with cannabis or cannabinoids (at the time of the interview):	21 days.	1 month (initial therapy) + 1 month (modified therapy).
Results obtained with the introduction of Medical Cannabis or cannabinoids in therapy (follow-up):	Clear improvement in eczematous lesions.	Partial improvement of symptoms, therapy still in progress.
Any reported side effects:	None	None

Summary of the treatment of dermatitis with Medical Cannabis, as reported by Dr. Albanesi.

Autoimmune Urticaria and Eczematous Dermatitis

This case study details the clinical profile and therapeutic approach for a 28-year-old male diagnosed with autoimmune urticaria and eczematous dermatitis affecting the upper and lower limbs, diagnosed at 27. Prior to the introduction of cannabinoid therapy, the patient was treated with Tacrolimus specifically for eczematous dermatitis of the hands.

The therapeutic strategy shifted to include a barrier cream containing 1% Cannabidiol, applied once daily. In conjunction with this, the patient was prescribed Fexofenadine 180 mg daily and Clobetasol ointment 0.05%, also applied daily for the first 14 days. This approach emphasizes the integration of cannabinoid with conventional therapies to manage skin inflammation effectively.

Dosage Adjustments and Therapy Progress

After 45 days, the antihistaminic therapy was discontinued, and the patient transitioned to using Ceramol 311 with 1% CBD along with a CBD-containing cleansing cream for daily skin washing and cleansing. This adjustment is indicative of the therapy's adaptability based on the patient's progressing condition.

Treatment Duration, Outcomes and Side Effects

Duration of the therapy was 2 months. The patient showed significant improvement after one month of treatment.

In this case, a topical application of CBD in conjunction with other therapeutic agents showed efficacy in managing a complex dermatological condition effectively.

No side effects were reported during the treatment course, highlighting the tolerability and safety of the therapeutic regimen employed.

Treatment of Eyelid Dermatitis

This case analysis presents the treatment methodology for a 76-year-old female diagnosed with eyelid dermatitis at 75. The management of her condition prior to introducing cannabinoid involved the use of the antihistamine Cetirizine for allergic symptoms related to dermatitis.

Introduction of Cannabinoid-Based Treatment

The treatment regimen was augmented to include a barrier cream with 1% Cannabidiol, applied daily. This was complemented by the application of Clobetasol ointment 0.05%, once daily for a week, and a daily dose of Fexofenadine 120 mg. The cannabinoid application aimed to leverage its anti-inflammatory properties to mitigate symptoms directly at the affected site.

Modifications During Treatment

One month into the treatment, the initial antihistamine (Fexofenadine) was switched to Cyproheptadine, suggesting a refinement in the management strategy to better address the patient's symptoms or potential side effects from the initial medication.

Duration and Outcomes of Treatment

After 2 months of treatment, there was a noted improvement within the first month of treatment, progressing to complete resolution of symptoms after two months. This rapid and effective resolution highlights the efficacy of the combined therapeutic approach, particularly the integration of Cannabidiol in treating dermatological inflammation.

Safety and Tolerability

The treatment exhibited excellent tolerability, with no adverse effects reported, underscoring the safety of CBD as a component of dermatological therapy regimes.

Table of summary for the previous studies.

Table 40.

	Patient	**Patient**
Age & Gender:	28-years-old, male.	76-years-old, female.
Diagnosis:	Autoimmune urticaria of upper and lower limbs. Eczematous dermatitis.	Eyelid dermatitis.
Age of diagnosis:	27	75
Previous therapy before the use of medical cannabis or cannabinoids:	Tacrolimus for eczematous dermatitis of the hands.	Cetirizine
Current therapy (whether it has been added to the previous therapy or replaced it, details of prescribed medical cannabis or cannabinoids, strains, THC:CBD ratio, starting dosage, etc.):	- Barrier cream containing Cannabidiol 1%, 1 application per day; - Fexofenadine 180 mg 1 tablet per day; - Clobetasol ointment 0.05% 1 application per day for 14 days.	- Barrier cream containing Cannabidiol 1%, 1 application per day; - Cobetasol ointment 0.05% 1 application /day for 7 days; - Fexofenadine 120 mg 1 tablet per day.
Route of administration:	Topical	Topical
Any dosage adjustments during therapy:	- After 45 days, discontinuation of antihistaminic therapy; - Ceramol 311+ 1% CBD + CBD containing cleansing crème for skin washing/ cleansing.	After 1 month, Fexofenadine was replaced with Ciproeptadine.

	Patient	Patient
Length of treatment (length of time patient has been in therapy with cannabis/cannabinoids):	2 months.	2 months.
Follow-up (results obtained with the use of medical cannabis/cannabinoids; description of the ongoing progress or changes observed in the patient's condition after the initiation of therapy):	Improvement after 1 month.	Improvement after 1 month, resolution after 2 months.
Any reported side effects (type, severity, management):	None	None
Additional Considerations:	None	None

Summary of the treatment of dermatitis with Medical Cannabis, as reported by Dr. Albanesi.

Alopecia Areata Management

This case review explores the therapeutic strategy for a 34-year-old female diagnosed with alopecia areata at 33. Notably, no prior treatments were administered before the initiation of a cannabinoid-enhanced therapy.

Cannabinoid-Enhanced Therapeutic Strategy

The chosen treatment approach for managing this autoimmune hair loss condition involved the topical application of Clobetasol ointment 0.05% mixed with 1% Cannabidiol (CBD). Additionally, a Clobetasol-containing shampoo was used, applying these treatments directly to the affected areas. This regimen aimed to utilize the anti-inflammatory properties of both Clobetasol and CBD to mitigate the autoimmune reactions characteristic of alopecia areata.

Treatment Implementation and Duration

The route of administration was, obviously topical, ensuring targeted action and minimized systemic exposure.

The duration of treatment was 3 months, within which the treatment was maintained without adjustments, indicating an initial effective response without the need for dosage modification.

Outcomes, Effectiveness and Safety

Complete resolution of the alopecia areata symptoms was achieved after three months of consistent treatment.

There were no side effects reported throughout the treatment course.

This case underscores the potential of integrating CBD with traditional steroid treatments to enhance therapeutic outcomes in dermatological conditions such as alopecia areata. The absence of prior treatments provided a clear indication of the direct effects of the cannabinoid-infused regimen, contributing valuable insights into the management of autoimmune-induced alopecia.

Adolescent Atopic Dermatitis Treatment

This case study outlines the treatment protocol for a 15-year-old female diagnosed with atopic dermatitis at 13. The patient had not received any previous treatments before the initiation of a cannabinoid-enhanced therapy regimen.

Treatment Strategy and Implementation

The therapeutic approach for this case involved a topical regimen that included:

- daily application of a barrier cream containing 1% CBD aimed at reducing skin inflammation and soothing the affected areas;
- Clobetasol Ointment 0.05%, applied once daily for a duration of 7 days to aggressively manage flare-ups and reduce symptomatic severity;

- Ebastine, an antihistamine, 10 mg once daily for 10 days, to control the histamine-mediated allergic responses commonly seen in atopic dermatitis.

The combination of cannabidiol with traditional therapeutic agents like corticosteroids and antihistamines was designed to address both the inflammation and the allergic components of atopic dermatitis.

Administration and Duration of Treatment

The total duration of cannabinoid therapy spanned 3 months, with clinical assessments noting improvements and adjustments to the treatment regimen based on the patient's response.

Clinical Outcomes and Follow-up

The treatment strategy resulted in noticeable improvement within one month, with complete resolution of the dermatitis symptoms after two months of consistent treatment.

Throughout the treatment period, no side effects were reported, highlighting the safety and tolerability of the treatment regimen, especially the use of CBD in pediatric dermatology.

This case reflects the potential effectiveness of integrating CBD into treatment plans for atopic dermatitis, even in adolescents.

Table 41.

	Patient	**Patient**
Age & Gender:	34-years-old, female.	15-years-old, female.
Diagnosis:	Alopecia areata.	Atopic dermatitis.
Age of diagnosis:	33	13
Previous therapy before the use of medical cannabis or cannabinoids:	None	None

	Patient	Patient
Current therapy (whether it has been added to the previous therapy or replaced it, details of prescribed medical cannabis or cannabinoids, strains, THC:CBD ratio, starting dosage, etc.):	- Clobetasol ointment 0.05% + CBD 1%; - Clobetasol-containing shampoo.	- Barrier cream containing Cannabidiol 1%, 1 application per day; - Clobetasol ointment 0.05% 1 application per day for 7 days. - Ebastine 10 mg 1 tablet per day for 10 days.
Route of administration:	Topical	Topical
Any dosage adjustments during therapy:		
Length of treatment (how long has been in therapy with cannabis/cannabinoids):	3 months.	3 months.
Follow-up (results obtained with the use of medical cannabis/cannabinods):	Resolution after 3 months.	Improvement after 1 month, resolution after 2 months.
Any reported side effects (type, severity, management):	None	None
Additional Considerations	None	None

Summary of the treatment of alopecia and dermatitis with Medical Cannabis, as reported by Dr. Albanesi.

3.7. Cannabis Treatment for Inflammatory Bowel Disease (IBD)

Pathophysiology of Autoimmune Intestinal Diseases

Although chronic inflammatory bowel diseases (IBD) have been recognized for decades, their precise causes remain idiopathic, meaning they are of unknown origin.[1] Current hypotheses regarding their pathogenesis suggest that the chronic inflammation arises from a combination of factors. Environmental influences (such as pollution, diet, smoking, etc.) in individuals with genetic susceptibility may provoke an abnormal immune response against the normal constituents of the intestinal microbiota. These con-

stituents ought to be treated as self by the immune system—recognized as part of the body and not targeted for attack.[2]

Key Differences Between Forms of IBD

IBD is commonly diagnosed in individuals between the ages of twenty and thirty. The two main forms of inflammatory bowel disease—Crohn's disease and ulcerative colitis—are distinguished by the specific regions of the gastrointestinal (GI) tract they affect:[3]

- Crohn's disease can impact any section of the gastrointestinal tract, but it most frequently affects the ileocecal area (the lower right side of the abdomen);
- ulcerative colitis, on the other hand, is confined to the rectum and/or colon area.

The general symptoms of IBD are overlapping and mainly involve:

- diarrhea;
- abdominal pain;
- weakness;
- fatigue;
- weight loss.

However, whereas diarrhea and abdominal pain are the most frequent initial symptoms in Crohn's disease, ulcerative rectocolitis, on the other hand, usually presents with bloody diarrhea (containing bright red blood and mucus), accompanied by a feeling of incomplete evacuation (tenesmus) and, in some cases, anemia.[3]

The Societal and Healthcare Burden of IBD

Inflammatory Bowel Disease (IBD) significantly impacts national health services financially. It is estimated that between 2.5 and 3 million people in

Europe suffer from IBD, with direct healthcare costs amounting to EUR 4.6 to 5.6 billion per year.[4] In addition to these direct costs, there are so-called indirect costs, which are personally incurred by the patient. IBD considerably affects sufferers' lives, leading to loss of control over bowel functions, feelings of being unclean and odorous, diminished work capacity, and challenges in social and sexual life, accompanied by anxiety and depression. Among the most debilitating issues is chronic fatigue, akin to that experienced by cancer patients, which severely impacts patients' social and work lives, despite ongoing research efforts to find effective treatments.[4]

Current Treatments

Current treatments for Crohn's disease and ulcerative colitis primarily include the chronic use of anti-inflammatory medications, such as glucocorticosteroids and mesalazine. Immunosuppressants like azathioprine are preferred for maintaining remission despite their unproven long-term effectiveness. Sulfasalazine and its derivative, 5-aminosalicylic acid (5-ASA), are beneficial during the acute phase of mild-to-moderate disease and for preventing relapses. The introduction of biological therapies, including anti-TNFα monoclonal antibodies (infliximab and adalimumab) and vedolizumab, has shown promise in maintaining remission in relapsing IBD. However, the potential for severe side effects (such as the risk of bone marrow destruction, hepatitis, pancreatitis, and lymphoproliferative disorders from immunosuppressants, and increased infection risk from biological therapies), along with the high treatment costs, underscore the need for exploring new treatment alternatives.[5] Targeting the Endocannabinoid System (ECS) might offer a significant breakthrough in treating Inflammatory Bowel Disease (IBD).

The Endocannabinoid System as a Potential Therapeutic Target in IBD

The ECS is extensively distributed throughout the gastrointestinal (GI) tract, playing a crucial role in maintaining GI homeostasis. The CB1 and CB2 receptors, endocannabinoids such as anandamide, N-acylethanolamine (NAE), and 2-arachidonoylglycerol (2-AG), their biosynthetic enzymes (NAPE-PLD and DAGL), along with their degradation enzymes—FAAH, NAAA, and MAGL are distributed in the GI tract. Additionally, cannabinoid-like compounds, including PEA and OEA, contribute to a wide range of functions from regulating eating behaviors and gastroprotection to influencing the composition of the microbiota.[6]

The Endocannabinoid System (ECS) holds several functions that could be leveraged in the treatment of Inflammatory Bowel Disease (IBD). These include the modulation of intestinal motility, control of visceral hypersensitivity, reduction of inflammation, and regulation of intestinal permeability. Each of these aspects plays a critical role in the pathology of IBD and presents potential therapeutic targets for managing the disease.

Intestinal Motility

In the context of IBD, a significant challenge is managing symptoms like frequent diarrhea, which is linked to increased intestinal motility due to chronic inflammation of the intestinal wall. Targeting intestinal motility represents a strategic approach to alleviating such symptoms.

Under normal conditions, cannabinoids and endocannabinoids lead to a reduction in intestinal motility, predominantly through the activation of the CB1 receptor.[7];[8] In the setting of chronic inflammation, characteristic of IBD, a decrease in motility can also be mediated by activating the CB2 receptor.[9] This condition, common in IBD, results in an elevated number of cannabinoid receptors, notably CB2, suggesting that reduced doses of cannabinoids could efficiently lower intestinal motility.[10]

Another beneficial effect in IBD treatment involves reducing the intestinal secretion of electrolytes and bile acids, as their excessive secretion, along with decreased water absorption, contributes to diarrhea. By activating CB1 receptors in the intestine, a decrease in these secretions can be achieved.[11]

Intestinal Inflammation

The inflammation of the intestinal wall, characteristic of IBD, can be effectively managed by targeting the ECS. In this context, CB2 receptors, primarily found on immune cells like macrophages and lymphocytes, play a significant role, alongside CB1 receptors and other non-typical cannabinoid receptors such as TRPV, PPAR, GPR55, and A2A.[12];[13] The activation of these receptors by endocannabinoids, as well as natural and synthetic cannabinoids, leads to a reduction in circulating inflammatory cells, primarily through a decrease in the release of pro-inflammatory cytokines and an overall reduction in 'immune tone,' resulting in diminished inflammation.[14];[15]

Increased intestinal permeability is a critical factor in IBD's pathogenesis, as it allows the passage of bacterial products and other antigens through the intestinal wall, leading to inflammation and tissue damage. This increase in permeability is largely due to damage to the intestinal epithelium—the cells lining the intestinal wall. Reducing intestinal permeability is a vital strategy in IBD management. Activating the CB1 receptor has been shown to promote repair of the intestinal epithelium following injury and reduce intestinal permeability, although this area requires further research for more conclusive data.[16];[17]

Moreover, the reduction of intestinal wall inflammation through the activation of cannabinoid receptors also indirectly contributes to the improvement of intestinal permeability.[18]

Nausea and Pain

Nausea and chronic pain significantly detract from the quality of life for patients with IBD. Cannabinoids present a promising avenue for relief, particularly in managing visceral pain—a type of pain emanating from the thoracic and abdominal internal organs, known for its diffuse and hard-to-localize nature. The efficacy of cannabinoids in this area is supported by numerous studies, highlighting the role of both CB1 and CB2 receptors. Activation of these receptors can diminish the sensation of visceral pain by influencing both the central and peripheral nervous systems.[19]

Additionally, the effectiveness of cannabinoids and their derivatives in combating nausea, especially when related to pathological conditions or chemotherapy, has been well-documented. This relief is primarily achieved through the activation of central CB2 receptors.[20];[21]

An important aspect to consider is the interplay between the ECS and the gut microbiota. Alterations in the normal composition of the microbiota are believed to be a trigger for IBD. Modulating the ECS can change the gut microbiota's composition and, conversely, using probiotic bacteria can influence the activity of the ECS. This interaction not only has the potential for analgesic effects but may also improve mood.[22];[23]

Studies on Cannabis in IBD

The ECS emerges as a compelling therapeutic target for IBD, primarily because of its direct role in regulating GI tract homeostasis. This aligns with longstanding anecdotal evidence suggesting that cannabis use can alleviate IBD symptoms. A growing body of research, encompassing both human and animal studies, has progressively supported this hypothesis.

Preclinical Research

Preclinical research has significantly contributed to our understanding of the ECS's involvement in IBD. The initial study highlighting this relationship

dates back to 2004, using CB1 receptor knock-out mice. Researchers observed an increased susceptibility to the development of chronic colitis in these mice. While there are no exact animal models for ulcerative colitis or Crohn's disease, chronic colitis closely replicates the pathological conditions of IBD.[24] Subsequent research demonstrated that mice lacking the CB2 receptor were also more prone to the development of colitis.[25] Additionally, the expression levels of both receptors were reported to increase in animals with chronic colitis, though findings across studies show some variation.[26];[27];[28]

Further animal experiments have corroborated that utilizing drugs targeting primarily the CB2 receptor, as well as CB1 or both, can ameliorate the clinical manifestations of colitis. This includes reducing chronic diarrhea, signs of intestinal inflammation and tissue damage, and weight loss, which are hallmark symptoms of IBD.

These studies collectively underscore the protective role of cannabinoid receptor activation against IBD.[29]

Clinical Research

The transition to clinical research marked a pivotal step in understanding the ECS's role in IBD in humans. Initially, researchers focused on identifying single nucleotide polymorphisms (SNPs, mutations of single genes within the ECS) to determine their impact on IBD, acknowledging heredity as a potential trigger for these diseases. Polymorphisms identified in various ECS components (such as receptors and degradation enzymes) generally correlated with a worsening of the clinical presentation.[30] Although these alterations were observed in a limited number of patients and thus couldn't be directly linked to IBD development, they reinforce the ECS's significant, though not exclusive, role in the emergence of IBD symptoms.

Biopsy samples from patients with Ulcerative Colitis and Crohn's disease showed altered levels of endocannabinoids, including Anandamide and PEA, compared to healthy individuals.[31];[32] PEA, in particular, has been

noted for its effectiveness in inhibiting the infiltration of pro-inflammatory cells into the colonic mucosa and reducing the expression and release of pro-inflammatory markers characteristic of ulcerative colitis, both in laboratory animals and human biopsy samples.[33]

Furthermore, in ulcerative colitis, variations in endocannabinoid levels, receptor expression, and degradation pathways have been found to correlate with clinical scores—reflecting both the degree of inflammation and the disease stage, whether acute or in remission.[34]

Medical Cannabis and IBD

A study conducted in 2012 explored the impact of cannabis treatment on quality of life, weight, and clinical score in a small cohort of IBD patients over a three-month period. The participants were provided with cannabis cigarettes, instructed to smoke them whenever they experienced pain, with a limit of 50 grams of cannabis per month and a maximum of three inhalations at a time to minimize central side effects. Post-treatment observations included a notable weight gain in all patients—a positive outcome for IBD sufferers—along with improvements in the disease activity index, general health perception, and daily function.[35]

Further research involved clinical studies on IBD patients using various THC doses and administration methods. These studies consistently reported improvements in patients' quality of life.[36];[37] Moreover, a 2014 article highlighted the prevalent use of cannabis among IBD patients, with numerous studies indicating a correlation between this practice and a reduction in symptoms, particularly abdominal pain and nausea, as well as an enhanced overall quality of life.[38]

It is important to note, however, that despite the observed symptom relief and quality of life improvement in these studies, the use of phytocannabinoids or synthetic cannabinoids did not achieve the primary endpoint of IBD remission.[39] Nonetheless, synthesizing information from clinical trials

and reports from patients who independently chose cannabis for IBD relief provides general insights into its use in IBD contexts.

Dosage Indications

Most patients seem to respond to 1 gram of cannabis per day, though it is recommended to begin treatment with a lower dose (less than 1 gram/day), especially for those not accustomed to cannabis. Generally, IBD patients show a preference for high tetrahydrocannabinol (THC) content, primarily for pain management, and opt to use it at night to reduce side effects.

Modulating the Endocannabinoid System in the Treatment of IBD

The collective insights from human and animal studies have highlighted an upregulation of ECS components and its protective role in IBD, paving the way for various therapeutic strategies aimed at modulating ECS activity. The employment of non-selective agonists, such as the endocannabinoid anandamide and the phytocannabinoid THC, has shown to be beneficial in reducing inflammation in laboratory animals with chronic colitis. This is also true for the use of the CB1-selective agonist AEA and cannabidiol (CBD).[40];[41];[42] Given the potential central effects triggered by CB1 activation, subsequent research has focused on mainly CB2-selective agonists to minimize side effects. These studies in animals with chronic colitis have been promising, indicating that CB2 agonists can significantly mitigate colitis-associated inflammation across different disease stages.[43];[44] An alternative therapeutic approach involves inhibiting the degradation systems of endocannabinoids to enhance ECS tone. For instance, obstructing the FAAH enzyme to elevate anandamide levels has proven effective in alleviating inflammation induced by colitis in lab animals.[45];[46];[47] A similar outcome was achieved by inhibiting the MAGL enzyme, responsible for the degradation of 2-arachidonoylglycerol.[48]

IBD: Conclusions

Results from both human studies and animal models of IBD have highlighted the Endocannabinoid System (ECS) as a crucial pharmacological target in managing Inflammatory Bowel Disease (IBD). This attention is drawn to the ECS's pivotal role in maintaining gastrointestinal (GI) tract homeostasis. The prevailing view within the scientific community, supported by experimental data, posits that enhancing endocannabinoid signaling could offer protection against IBD.

Stimulation of the ECS, particularly at the peripheral level, has shown potential in reducing symptoms such as abdominal pain and nausea, improving the quality of life for many IBD patients. Despite this, the transition from animal models to human trials reveals a more complicated scenario. The absence of direct experimental models of IBD and limited clinical data from a small patient cohort complicates the interpretation.

Additional Considerations:

- Effective dosages and administration routes for cannabis-based treatments in IBD vary widely among individuals. Starting with low doses and gradually increasing based on tolerance and effect is a common approach, although specific dosage guidelines require further research for standardization.
- The long-term impact of cannabis use in IBD patients remains an area needing more clarity. While some evidence suggests benefits in symptom management and quality of life, potential risks, including tolerance and dependency, necessitate a careful evaluation over extended periods.
- Cannabis may interact with conventional IBD treatments, such as immunosuppressants and biologics, either by enhancing their effects or contributing to increased side effects. Comprehensive studies to understand these interactions are essential to ensure safe co-administration.

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3.7.1. Case Study: Crohn's Disease

Dr. Privitera's case involves a 35-year-old woman with Crohn's disease who initiated Medical Cannabis therapy in July 2018. Prior to this, her treatment regimen included:

- Mesalazine;
- Infliximab.

Despite being on a treatment regimen that included an anti-inflammatory (Mesalazine) and a monoclonal antibody (Infliximab), the patient experienced significant symptoms before starting Medical Cannabis therapy in July 2018. Her condition was characterized by:

- mucoid diarrhea, with as many as 15 discharges per day, indicating severe gastrointestinal distress and inflammation;
- moderate abdominal pain, with peaks in intensity lasting several weeks, ranging from 4 to 8 on the Visual Analogue Scale (VAS). This level of pain suggests significant discomfort that likely impacted her quality of life;
- frequent episodes of fever and general malaise, signs that her body was in a state of inflammation and possibly fighting off infections, which can be common in Crohn's disease due to complications or the effects of the disease on the immune system.

The prescribed Medical Cannabis included two specific strains, each prepared differently to achieve the desired therapeutic effect:

- Cannabis Flos Bedica: this variety, characterized by a THC content of 14% and CBD content of less than 1%, was extracted into 200 mL of ethyl alcohol. The extract was then encapsulated into 100 gastro-resistant (delayed-release) capsules, allowing for controlled release and absorption in the intestines, where it could exert localized effects without being destroyed by stomach acid. The initial dosage was set at 3 mg, taken twice daily, totaling 6 mg/day.
- Cannabis Flos Bediol: With a THC to CBD ratio of 6.3% to 8%, this variety was also extracted into 200 mL of ethyl alcohol and then diluted in 150 mL of MCT (medium-chain triglyceride) oil, a carrier oil that aids in the absorption of cannabinoids. The starting dosage for Bediol extract was 1.7 mg/day, divided into two intakes.

Following the initiation of Medical Cannabis therapy, the patient experienced significant improvements in her Crohn's disease symptoms. Within two months, there was a noticeable enhancement in both the frequency and quality of bowel movements. This positive trend continued, leading to the normalization of bowel habits seven months after starting treatment.

The patient reported a decrease in abdominal pain. While pain before bowel movements persisted, it became much more manageable and was considered acceptable by the patient.

The frequency of fever episodes, indicative of inflammatory activity, diminished.

Despite contracting COVID-19 after receiving the anti-COVID vaccines, the patient's clinical course was comparable to that of a healthy individual, suggesting no adverse impact of her underlying condition or the cannabis treatment on her ability to combat the virus.

Importantly, the patient has not experienced any flare-ups of her Crohn's disease since commencing the cannabis therapy.

After four years of continuous treatment, the patient reported experiencing no significant side effects, demonstrating good tolerance to the cannabis compounds utilized in her therapy. This treatment did not interfere with her work activities and played a significant role in enhancing her overall quality of life.

Dr. Privitera highlighted the importance of the 'delayed release' formulation, which was specifically requested to maximize the efficacy of the treatment. This approach was informed by the understanding of the crucial role cannabinoid receptors play within the gastrointestinal tract. Despite the low doses administered, the clinical impact was substantial—attributed to the direct action of THC on the intestinal mucosa and its absorption into the enteric nervous and muscular tissues.

This case underscores the potential benefits of medical cannabis in managing conditions like Crohn's disease, especially when conventional treatments may not suffice. The careful consideration of the formulation and

the targeted delivery of cannabinoids can lead to meaningful improvements in patient outcomes without compromising their daily functions or causing detrimental side effects. This personalized and cautious approach to medical cannabis underscores the necessity of thorough clinical evaluation and customization of treatment plans to individual patient needs, leveraging the therapeutic potential of cannabinoids in a safe and effective manner. Below is a summary table of the treatment.

Table 42.

	Patient
Age and gender:	35-years old, female.
In therapy since:	4 years.
Diagnosis:	Crohn's disease.
Possible therapy prior to the use of Medical Cannabis or cannabinoids:	Mesalazine; Infiximab.
Current therapy (type of Medical Cannabis or cannabinoids prescribed):	- Cannabis Flos Bedica (THC 14% : CBD <1%), 5 g extracts in 200 mL ethyl alcohol; subsequent distribution in 100 gastro-resistant (delayed- release) capsules. - Cannabis Flos Bediol (THC 6.3% : CBD8%), 5 g extracts in 200 mL ethyl alcohol; subsequent dilution in 150 mL MCT oil.
Initial dosage:	- Bedica extract: 3 mg/meal x 2 intakes/day = 6 mg. - Bediol extract: 1.7 mg/day, 2 intakes/day.
Possible dosage corrections:	No dosage and/or formulation changes were necessary.
Duration of treatment with cannabis or cannabinoids (at the time of the interview):	4 years.
Results obtained with the introduction of Medical Cannabis or cannabinoids in therapy (follow-up):	Two months after starting treatment, the patient reported a marked improvement in frequency and quality of bowel; The improvement in symptoms persisted, leading to normalization of bowel function within seven months from the start of treatment. Observed results: - reduction of abdominal pain (pain remains before going to the toilet, but absolutely acceptable to the patient); - reduction in febrile episodes; - no flare-ups since the start of therapy.

	Patient
Any reported side effects:	None. Reported good tolerance to both compounds. The therapy did not affect work activity and contributed significantly to the improvement of the patient's quality of life.
Other considerations:	In this particular case, a 'delayed release' formulation was requested from the pharmacist.

Summary of the treatment of Crohn's disease with Medical Cannabis, as reported by Dr. Privitera.

3.8. Neuropsychiatric Applications of CBD

Cannabidiol (CBD) has garnered significant interest for its therapeutic potential across a spectrum of neuropsychiatric conditions. Its actions on the brain arise from its influence on endocannabinoid tone, serotoninergic and opioid transmission, as well as neurogenesis.[1]

CBD's anxiolytic, antipsychotic, anti-inflammatory, analgesic, antiepileptic, antiemetic, and anticancer properties make it a subject of extensive study. Distinctly different from tetrahydrocannabinol (THC), CBD does not primarily target the classic CB1 and CB2 receptors in the endocannabinoid system.[2] This distinct mechanism of action, combined with its lack of narcotic effects, positions CBD as a potentially versatile and manageable molecule in therapeutic applications.

CBD's broad therapeutic potential is particularly promising in the context of anxiety disorders, schizophrenia, inflammation-related conditions, pain management, epilepsy, and nausea, among other conditions.

CBD and Its Effects on the Brain

How is CBD able to induce anxiolytic, antipsychotic and antidepressant effects?

The Modulation of the Emotional Response to Fear

A study from 2009 demonstrated CBD's potential in modulating the brain's response to fear, highlighting its anxiolytic effects.[3] In the research, 15 healthy participants were exposed to images of frightening faces, and their reactions were observed under the influence of CBD (600 mg) or THC. The results showed that CBD could attenuate responses to fearful stimuli, particularly in the anterior and posterior cingulate and the amygdala, regions known for emotion modulation. Additionally, CBD influenced skin conductance responses, indicating a dampened reaction to fear. These findings suggest that CBD's action on neurons in limbic and paralimbic areas contributes to its capacity to lessen neuronal arousal and, consequently, reduce subjective anxiety in fearful situations.[3]

CBD was able to attenuate responses to fearful stimuli in two brain areas that modulate our emotions, namely in the anterior and posterior cingulate and in the amygdala, and, in addition, it was able to modulate skin conductance responses to fearful stimuli, which also indicates an attenuated response. From these data, it became clear that CBD's effects on the activation of neurons in limbic and paralimbic regions may contribute to its ability to reduce neuronal arousal and, consequently, subjective anxiety from fearful situations.

Further studies reinforced these observations, indicating that CBD's anxiolytic effects might involve altering prefrontal-subcortical connectivity, particularly through the stimulation of the amygdala and the anterior cingulate cortex area.[4] Interestingly, CBD also attenuated the level of blood oxygenation in the amygdala of healthy subjects exposed to different levels of anxiety. This seems relevant not only for generalized anxiety, but

may offer a rationale for the psychiatric management of patients who have experienced traumatic events. Indeed, the amygdala is overactive in patients with post- traumatic stress disorder (PTSD) and its degree of activation may correlate with the severity of PTSD symptoms.[5]

Modulation of the FAAH Enzyme: Anxiolytic, Antidepressant and Pro-social Effects of CBD

CBD's interaction with CB1 and CB2 receptors was found to be too weak to fully account for its pharmacological impact. Instead, nearly two decades of research have pointed to CBD's role in inhibiting FAAH, the enzyme responsible for breaking down Anandamide (AEA), a principal endocannabinoid.[6] By hindering FAAH's action, CBD effectively boosts AEA levels, enhancing endocannabinoid tone without directly activating or inhibiting receptors. This indirect mode of action prolongs AEA's beneficial effects on the ECS.[7]

This increased endocannabinoid tone is crucial. Conditions such as PTSD and fibromyalgia, characterized by a deficient endocannabinoid tone, suggest a potential predisposition to various psychopathologies when this tone is lacking.[8];[9] Despite some conflicting evidence regarding CBD's interaction with FAAH, further research emphasizes the therapeutic potential of FAAH inhibition for enhancing mood, aiding trauma recovery, and reducing pain perception.[10];[11];[12];[13]

An intriguing case involves a Scottish woman with a genetic mutation affecting FAAH function, leading to elevated blood levels of endocannabinoids and a life relatively free of pain and characterized by quick healing and an overall good mood, despite potential physical ailments.[14] This case and similar effects observed with CBD underscore the significant role FAAH inhibition may play in managing pain and improving endocannabinoid tone.[15]

Other Mechanisms of CBD Action: from Serotonergic Interaction and Neurogenesis to Action on Opioid Receptors

While inhibition of the FAAH enzyme is a key mechanism by which CBD operates, it's far from the only way CBD exerts its effects. Research has highlighted CBD's interaction with serotonergic 5-HT1A receptors, attributing to its antidepressant and pro-social impacts.[16];[17] Furthermore, CBD's role in enhancing neurogenesis in the hippocampus, vital for memory and learning, points to its potential benefits for individuals with PTSD by aiding in the processing of traumatic memories.[18];[19]

CBD also interacts with opioid receptors as a negative allosteric modulator, reducing opioid action and potentially aiding in managing opioid tolerance.[20] This modulation extends to CB1 receptors, possibly mitigating the psychotropic effects of THC when both are used concurrently.[21] Additionally, CBD's actions include PPAR-γ receptor agonism, GPR12 receptor reverse agonism, and GPR55 antagonism, illustrating its diverse pharmacological profile beyond the ECS.[22] These mechanisms underline CBD's multifaceted therapeutic potential, offering insights into its use in various neuropsychiatric and cognitive conditions.[22]

Clinical Applications in Neuropsychiatry

CBD's effects on the ECS, serotoninergic and opioid pathways, and its ability to promote neurogenesis, suggest its potential in treating several neuropsychiatric disorders. Here's a brief overview of conditions where CBD's effects are being explored:

- *CBD for Schizophrenia*: Research indicates CBD might induce antipsychotic effects, potentially with fewer side effects than traditional medications.
- *CBD for Anxiety*: Studies have shown CBD could reduce symptoms across various anxiety disorders, such as generalized anxiety and social anxiety, likely due to its interaction with serotonin receptors.

- *CBD for PTSD*: CBD's impact on the endocannabinoid system and neurogenesis could help manage PTSD symptoms, including anxiety and sleep disturbances.
- *CBD for Parkinson's Disease*: Initial studies suggest CBD may have protective effects on the nervous system and could improve life quality by addressing symptoms like sleep issues and psychosis.

Although promising, further detailed clinical trials are necessary to fully establish CBD's effectiveness and safety in these disorders. The existing data, however, indicate that CBD could emerge as an important treatment option in neuropsychiatry.

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3.8.1. Cannabis and CBD for Post-Traumatic Stress Disorder (PTSD)

The Mediterranean Sea, along with historical contexts such as childhood trauma in regions long ravaged by war—such as Palestine—and among war veterans in America, is increasingly recognized as a source of significant psychological distress, contributing to the rising incidence of Post-Traumatic Stress Disorder (PTSD) among its crossers and nearby residents. Cannabis and cannabidiol (CBD) offer a promising avenue for addressing the symptoms of PTSD. CBD, with its therapeutic potential in neuropsychiatric conditions, including anxiety and PTSD, could serve as a pivotal tool in managing the condition's multifaceted challenges. Its mechanisms—ranging from modulating endocannabinoid tone to influencing serotonergic pathways and promoting neurogenesis—highlight its potential to alleviate the hallmark symptoms of PTSD, such as re-experiencing traumatic events, heightened anxiety, and disturbances in sleep. By harnessing CBD's non-psychoactive properties, Europe, alongside other regions, could integrate this plant-based therapy into broader strategies aimed at mitigating the psychological aftermath of trauma.

This approach not only aligns with the growing acceptance of cannabis-based medicines for various health conditions but also emphasizes the importance of exploring holistic and accessible treatments for mental health challenges, particularly those as pervasive and debilitating as PTSD.

What is Post-Traumatic Stress Disorder (PTSD)?

PTSD is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, rape, or other violent personal assault. PTSD is characterized by the individual's struggle to recover from the shock and horror of these events, often reliving the trauma through

flashbacks and nightmares. Emotional numbness and sleep disturbances are common, as are feelings of isolation, irritability, and guilt.

The disorder is more frequently associated with "human-caused" traumas such as wars, traffic accidents, and harassment than with natural disasters. This distinction highlights the profound impact of interpersonal violence and the traumas experienced during migration, including the violence encountered during flight, dehumanizing conditions in detention centers, and the traumatic experiences of witnessing or being subject to sexual violence.

The experiences of migrants often encompass these types of "human" traumas, underscoring the acute need for awareness, understanding, and treatment options for PTSD within this population. The psychological toll of such experiences cannot be understated, with the prolonged and complex trauma significantly influencing the prevalence and expression of PTSD among survivors.

Not only a Problem for Migrants but also for Rescuers and Hosts

PTSD impacts not only migrants who have survived traumatic events but also extends to rescuers and hosts, affecting the broader social fabric surrounding these incidents. For example, Dr. Anna Crepet, associated with *Médecins Sans Frontières*, equated the emotional toll of aiding migrants on the Italian coast to working in war zones, highlighting the profound psychological impact on those involved in rescue and aid operations. Statistics reveal a varied risk of PTSD across different groups involved in or exposed to traumatic situations: approximately 30-40% of direct victims, 10-20% of rescue workers and personnel in rehabilitation and rescue centers, and 5-10% of the general population who interact with traumatized individuals might experience PTSD symptoms. These figures, however, only provide a general idea, with actual prevalence rates differing based on specific demographic and situational factors.[1]

These percentages are a simplification, with several studies showing that the prevalence of PTSD can be substantially higher or lower depending on particular observation groups. Women, in particular, have been identified as having a higher prevalence of PTSD, a fact underscored by reports of widespread sexual assault among female migrants. This vulnerability is exacerbated by the lack of adequate social support structures in host countries, placing both migrants and their rescuers at increased risk of developing PTSD.[2] This is regardless of the fact that, as Dr Anna Crepet says: "practically all women who survive the journey from their homes in Africa or the Middle East have been raped, often arriving several months pregnant." The issue of PTSD among migrants and those assisting them is compounded by political and social neglect in Europe, potentially contributing to a cycle of fear, violence, and mistrust. While concrete statistics on PTSD induced by migration challenges are elusive, the need for action to address this psychiatric condition is clear, underscoring the importance of comprehensive support systems for all affected parties.

Symptoms of PTSD

PTSD is characterized by a range of symptoms that can be grouped into three main categories:[3]

- Intrusion Symptoms: This includes hyper-amnesia or the persistent and unwanted recollection of the traumatic event. Individuals may relive the experience through flashbacks, nightmares, or distressing thoughts triggered by reminders of the trauma, such as certain smells or sounds.
- Hyperarousal Symptoms: This category encompasses hyper-excitation, such as being easily startled or shocked, experiencing irritability, having difficulty sleeping, and showing exaggerated startle responses. It also includes an abnormal level of fear or anxiety when assessing potential threats.

- Avoidance Symptoms: This involves a deliberate effort to avoid thoughts, feelings, conversations, places, people, and activities that might bring back memories of the trauma. This evasive behavior is a protective mechanism to avoid re-traumatization.

How Cannabis can Help

Research indicates that Medical Cannabis may alleviate PTSD symptoms by reducing tension.[4] War veterans in the USA have intensively used cannabis for self-administration to relieve PTSD symptoms, supported by anecdotal evidence.[5] A 2009 study found that 72% of PTSD patients experienced significant relief from flashbacks and reduced nightmare frequency with Nabilone (THC) treatment.[6] A 2012 systematic review confirmed cannabis's benefits in reducing symptom severity and improving sleep and mood.[7] Studies show the regulation of cannabinoid receptors, particularly CB1 activation, is key in eliminating fear-related memories, suggesting THC-containing cannabinoid preparations could be beneficial.[8];[9];[10];[11] However, while low doses of THC reduce anxiety, high doses or use in stressful conditions can increase it.[12];[13] This is why it is suggested to use the entire cannabis phytocomplex, which contains CBD, that does not activate CB1 receptors and is considered for its anxiolytic and antipsychotic properties, possibly acting through serotonergic receptors.[14];[15]

Conclusion

Considering the profound impact of PTSD on individuals and society—including the medico-social costs and challenges in re-employment for those affected—it's essential to explore all potential therapeutic avenues. Medical Cannabis, alongside psychotherapy, is proposed as a valuable tool for supporting both migrants and rescuers coping with PTSD. This approach emphasizes the importance of comprehensive care strategies that

address the complex needs of those experiencing post-traumatic stress, aiming to facilitate recovery and integration into daily life.

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3.8.2. Rationale for the Use of CBD for Autism and two Case Studies from Brazil

Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) encompasses a range of neurological developmental conditions that typically manifest early in life and often coincide with general cognitive impairments.[1]
The symptoms of ASD are diverse and include:[2]

- persistent deficits in communication and social interaction;
- restricted and repetitive patterns of behavior, interests, and activities, including stereotyped or repetitive motor movements;
- often (but not always) intellectual disability.

These disorders cannot be attributable to global developmental delay or brain malformations. ASD is approximately four times more prevalent in males than in females and is associated with comorbidities, such as:

- insomnia;
- anxiety;
- depression;
- epilepsy;
- gastrointestinal dysfunction;
- attention deficit hyperactivity disorder (ADHD).

According to a 2022 study, the prevalence of autism diagnosis is approximately 100 per 10,000 children, compared to around 62 per 10,000 in 2012.[3] The rise in autism prevalence is undoubtedly influenced by enhanced surveillance and expanded diagnostic criteria. Previously underrepresented regions, like Africa and the Middle East, have improved their capacity to assess autism prevalence, contributing to the upward trend in reported cases. Additionally, environmental factors, such as air pollution, which is

increasingly pervasive even in regions like Africa, may play a role in the rising incidence of autism among children.

Autism and Pollution

Recent studies suggest that both genetic and environmental factors could contribute to ASD.[4] However, the extent to which environmental factors have influenced the recent surge in ASD cases remains unclear. Conflicting data in the literature regarding the role of environmental factors can be attributed to methodological challenges, including the selection of pollutants for analysis and their quantification. Moreover, it is crucial to determine whether a critical window of exposure exists that is particularly associated with the onset of ASD in children.

Numerous studies have investigated the correlation between autism and various air pollutants, with a focus on substances such as:

- ozone (ground-level);
- lead;
- particulate matter (PM);
- carbon monoxide (CO);
- nitrogen dioxide (NO2);
- sulphur dioxide (SO2).

European studies have reported no association between maternal exposure to air pollution and ASD in children.[5];[6] In contrast, several studies in the United States and other countries have reported associations. A systematic literature review and meta-analysis conducted in 2020 revealed evidence supporting an association between autism prevalence and maternal exposure to PM 2.5 (particulate matter less than 2.5 μm in diameter), weak evidence for NO2 and limited evidence for PM 10 and ozone.[7] Another study indicated that for every 5 μg/m3 increase in PM 2.5, there was an elevated risk of ASD in infants. This risk was observed to increase

during pre-conception (by 17%), pregnancy (by 5-16%), and the postnatal period (by 11-16%).[8]

In addition to air pollutants, particularly PM 2.5, heavy metals like lead and methyl mercury have also been implicated in the development of ASD. Research suggests that exposure to these metals may contribute to ASD, although there is limited information available regarding the role of cadmium.[9] One possible explanation for this association is the reduced ability of children with ASD to excrete toxic metals, leading to their accumulation in the body.[10]

Therapeutic Approaches for Autism Spectrum Disorder

There are several treatment modalities available, often utilized in combination. These include:[11]

- behavioral and developmental interventions;
- educational interventions;
- social-relational interventions;
- pharmacological interventions;
- psychological interventions;
- complementary and alternative therapies (e.g., special diets, art therapy, mindfulness).

While pharmacological treatments do not cure ASD, they aim to manage specific symptoms. Some medications target hyperactivity, self-injurious behavior, or attention-related issues, while others address comorbid conditions like anxiety, depression, epilepsy, and gastrointestinal problems, which are particularly challenging in ASD management.[11]

In recent years, CBD has gained attention as a potential treatment for ASD, with many doctors in various countries incorporating it into their therapeutic strategies.

CBD for ASD Management

CBD is believed to be potentially useful in ASD due to its interaction with the endocannabinoid system and its influence on various neurotransmitter systems.[12] CBD exhibits neuroprotective properties, which may be relevant in autism where there can be alterations in brain development and function. Moreover, some research suggests that neuro-inflammation may play a role in the pathophysiology of ASD. CBD has anti-inflammatory properties and can modulate the immune response, which may contribute to reducing inflammation in the brain and alleviating associated symptoms. While seizures are not a core symptom of autism, they occur at a higher rate in individuals with ASD compared to the general population. CBD has been approved as a treatment for certain types of epilepsy, and its anticonvulsant properties may benefit individuals with autism who experience seizures as a comorbid condition.

CBD may help alleviate symptoms of anxiety and stress commonly experienced by individuals with ASD and may also help manage challenging behaviors associated with autism, such as aggression, agitation, and irritability. Its calming effects can potentially reduce disruptive behaviors and improve overall mood stability. Moreover, many individuals with ASD experience sleep disturbances and CBD has been reported to improve sleep quality.

Regarding side effects, compared to traditional pharmacological interventions, CBD is generally well-tolerated and has a favorable side effect profile. This makes it a potentially attractive option for individuals with ASD who may be sensitive to the side effects of conventional medications.

The Experience of a Prescribing Clinician

Dr. Mauro Cardoso Lins is a Brazilian physician with extensive experience in treating patients with ASD and ADHD, particularly children and adolescents. Interviewed by Cannabiscientia, Dr. Lins tells us that his experience

with CBD to treat mild-to-moderate to severe cases of autism is, so far, exciting.

According to his experience and data collected, CBD is effective in improving many aspects of behavior, especially in early and mild-moderate cases, but also in more severe ones.

The observed improvements include:

- decreased aggression (probably the most important result);
- increased attention span;
- enhanced communication and sociability;
- improved task completion.

Product used, Posology, Routes of Administration, and Duration of Treatment

Dr. Lins employs pure isolated and broad-spectrum pharmaceutical-grade CBD oil. He adheres to the principle of "start low and go slow" when determining dosage.

For children, the starting dose ranges from 15 to 25 mg per day, administered 2 or 3 times daily depending on the individual case. The dosage is then gradually increased until the desired therapeutic effect is achieved, with minimal side effects. Regular follow-up evaluations are conducted every 2 to 3 months to assess progress and adjust the dosage if necessary. Dr. Lins recommends monitoring liver enzymes through blood tests at the outset of treatment and every 6 months thereafter. Additionally, evaluating food allergies and gastrointestinal issues can provide valuable insights for managing certain cases.

For administration, Dr. Lins suggests sublingual delivery on an empty stomach whenever feasible. Alternatively, CBD can be incorporated into food after a meal to mask its taste, depending on the patient's level of aggressiveness and compliance.

Two Case Studies from Brazil

Dr. Lins presents the cases of two children with ASD treated with CBD.

Table 43.

	Patient 1	Patient 2
Age and gender:	11 years old, male	6 years old, male
In therapy since:	2018	2020
Diagnosis:	ASD with mild intellectual disability. Oppositional and hyperactive behaviour. Anxiety. Aggressive behaviour towards the mother. Difficulty handling frustration, tendency to destroy objects. Non-significant MRI and EEG studies. No gastrointestinal problems.	ASD. Very limited vocabulary. Severe sensory processing disorder. Gastrointestinal problems (improve with a gluten and casein-free diet), currently not on a diet. Severe behavioural problems. Aggressive and self- injurious behaviour. Hyperactivity. Normal MRI and normal EEG (2021) - Epileptic seizure in February 2022.
Possible therapy prior to the use of Medical Cannabis or cannabinoids:	- Risperidone - Fluoxetine - Valproic acid - Methylphenidate - Carbamazepine.	- Risperidone - Aripiprazole (induces worsening of behaviour).
Current therapy (type of Medical Cannabis or cannabinoids prescribed):	- Aripiprazole 10 mg - Clonidine 0.15 mg + melatonin 10 mg (both for sleep disorders) - Pure CBD, 75 mg twice a day.	- Valproic acid - Pure CBD, 25 mg twice a day.
Duration of treatment with cannabis or cannabinoids (at the time of the interview):	3 months.	1 month.
Results obtained with the introduction of Medical Cannabis or cannabinoids in therapy (follow-up):	Impressive changes in oppositional behaviour. Ability to sit and talk to the doctor, not present before CBD therapy. No defiant or oppositional behaviour. Behavioural changes perceived by therapist, family and teachers.	Reduced hyperactivity. Increased attention to activities. Reduction in aggressive behaviour, especially towards the mother.

Summary of the treatment of ASD with Medical Cannabis, as reported by Dr. Lins.

Major Challenges in the Treatment of ASD

According to Dr. Lins, the management of GI disorders is one of the biggest challenges in treating patients with ASD. Compared to their peers, children and adolescents with ASD tend to have more GI problems, such as:[12]

- abdominal pain;
- constipation;
- diarrhoea;
- gastritis;
- enterocolitis;
- oesophagitis;
- food allergies;
- dysbiosis.

These GI symptoms suggest a potential link between GI dysfunction and the severity of ASD symptoms, with some studies proposing that ASD may be influenced by abnormalities in the gut-brain axis.[12] CBD, with its anti-inflammatory and immunomodulatory properties, could be beneficial in managing these ASD-related GI symptoms. Dr. Lins notes improvements in GI function in children with ASD treated with CBD.

Moreover, Dr. Lins addresses the challenge of insomnia in children with ADHD, noting that while CBD can improve behavior, it may also exacerbate insomnia. To mitigate this, adjusting the timing of CBD administration is recommended.[12] This careful consideration of CBD's application highlights its potential utility in managing complex symptoms associated with ASD and ADHD, emphasizing the need for tailored treatment approaches.

Conclusions

ASD's complexity, with its multifactorial origins including genetic, environmental, and psychological components, presents challenges in treatment, which traditionally focuses on behavioral improvement and social integration. The limited pharmacological options, primarily due to side effects, target comorbidities rather than the core symptoms of ASD. The emergence of Medical Cannabis, particularly CBD-based treatments, as a therapeutic option has shown promise in numerous cases. This is supported by the experiences of several physicians, including Dr. Lins, and open-label clinical trials.[13] The positive outcomes observed by clinicians like Dr. Lins, who aim to improve patient living conditions through innovative treatments, highlight the importance of further exploration and funding in this area.

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3.8.3. Case Studies: CBD for Autism Spectrum Disorders

Dr. Mauro Lins has been exploring the use of cannabinoids in the treatment of children with autism spectrum disorder (ASD), showcasing three case studies that illustrate the potential benefits of this approach. All the children treated had normal EEG and MRI evaluations.

These case studies underscore the potential of CBD as a supplementary treatment in managing ASD symptoms. Dr. Lins's careful, patient-specific dosage adjustments exemplify the approach needed in cannabinoid therapy, highlighting both the transformative impact on patient quality of life and the critical need for continued research and personalized treatment strategies in ASD management.

Case Study 1: Breaking Barriers with CBD

The first case involves a 7-year-old boy with a high level of ASD support needs. Before trying CBD, he was on:

- antipsychotics including periciazine and aripiprazole, which were discontinued due to ineffectiveness and adverse effects, respectively;
- valproic acid for mood stabilization.

Transitioning to a broad-spectrum, THC-free CBD therapy, the child began with:

- 0.5 mg/kg/day, eventually reaching 1.5 mg/kg/day.

This adjustment led to noteworthy behavioral improvements over six months:

- reduced hyperactivity;
- cessation of stereotypies;
- enhanced attention span, enabling him to engage with toys and television, marking significant progress.

No side effects were observed. Interestingly, due to import issues in Brazil, the product became unavailable, leading to an interruption in treatment. During this period, stereotyped behaviors reappeared, accompanied by significant irritability and agitation. These symptoms resolved following the reintroduction of CBD.

Case Study 2: Managing Outbursts and Enhancing Sociability

The second case study describes an 8-year-old girl, also with a high level of ASD support needs, who struggled with severe temper outbursts and aggressive behavior. Her prior regimen included:

- risperidone.

Dr. Lins supplemented risperidone with CBD to manage the escalation in behavioral issues. The starting dose of CBD was:

- 0.5 mg/kg/day of CBD.

Her treatment dose was gradually increased on a monthly basis to 4.0 mg/kg/day. This integration saw a reduction in the severity and frequency of her temper outbursts, alongside gains in attention span, vocabulary, and social interaction skills, without any adverse effects.

Case Study 3: Addressing Behavioral Rigidity and Aggressiveness

The third case focuses on an 8-year-old boy with moderate level of ASD support needs, exhibiting severe behavioral challenges including aggressiveness and defiance. Prior to CBD, his treatments included:

- melatonin;
- risperidone (discontinued due to negative side effects).

CBD was added to the previous therapy at a 0.5 mg/kg/day. CBD was gradually increased to 1.0 mg/kg/day on a weekly basis. This regimen resulted in:

- remarkable behavioral flexibility;
- cessation of aggressiveness;
- academic improvement.

The only side effect reported was an increased appetite, which the family considered beneficial.
The following table describes the case studies:

Table 44.

	Patient 1	Patient 2	Patient 3
Age & Gender	7 years old - male.	8 years old - female.	8 years old - male.
Diagnosis	Autism Spectrum Disorder (support level 3).	Autism Spectrum Disorder (support level 3).	Autism Spectrum Disorder (support level 2).
Age at time of diagnosis:	4 years old.	2 years old.	3 years old.
Previous therapy before the use of medical cannabis or cannabinoids:	Antipsychotics 1. periciazine (discontinued, no response) 2. Aripiprazole (discontinued, worsening of behavioral symptoms + food compulsion). 3. Valproic acid (as mood stabilizer).	Antipsychotics 1. Risperidone.	Melatonin. Risperidone was initiated and discontinued due to severe daytime drowsiness and irritability.

	Patient 1	Patient 2	Patient 3
Current therapy:	Valproic acid. Broad spectrum CBD ("THC free") Starting dose 0.5 mg / kg/day. Current dose 1.5 mg/kg/day CBD added to valproic acid.	Risperidone Broad spectrum CBD ("THC free") Starting dose 0.5 mg/ kg/day. Current dose 4.0 mg/kg/day CBD added to risperidone.	Melatonin Broad spectrum CBD ("THC free") Starting dose 0.5 mg / kg/day. Current dose 1.0 mg/kg/day.
Route of administration:	Per os (oral).	Per os (oral).	Per os (oral).
Any dosage adjustments during therapy:	Gradual increase at follow-up, approx. 5 mg per month.	Gradual increase on monthly basis.	Gradual increase on weekly basis.
Length of treatment:	Six months.	Seven months.	One month.
Follow-up:	Hyperactive behavior decreased significantly. Stereotypies (vocal and motor) ceased. Important increase in attention span. Patient can now play with toys and watch TV, tasks he had never engaged in before.	CBD was added due to severe temper outbursts and aggressive behavior that developed gradually over time. Temper outbursts remained severe in intensity but decreased substantially in frequency. Attention span and vocabulary increased. Sensory issues and hyperactive behavior are less intense. Better social interactions and eye contact.	CBD was added due to severe behavioral rigidity, aggressiveness towards adults and children, self-injurious behavior, defiant behavior and sleep disorder. After CBD was introduced, behavior was more flexible, school performance was better, aggressiveness ceased.
Any reported side effects (type, severity, management):	None	None	Increase in appetite (regarded as positive effect by family).
Additional Considerations	Due to import issues, the product was unavailable, and treatment was interrupted. Stereotyped behavior returned with great irritability and agitation. They ceased upon reintroduction of CBD. Patient has normal EEG and MRI evaluations. No history of seizures.	Patient has normal EEG and MRI evaluations. No history of seizures.	Patient had a normal MRI evaluation. No history of seizures.

Summary of the treatment of ASD with Medical Cannabis, as reported by Dr. Lins.

3.8.4. Hands-on Experience: CBD in Attention Deficit Hyperactivity Disorder (ADHD)

This discussion explores the potential benefits of cannabidiol (CBD) in managing symptoms of attention deficit hyperactivity disorder (ADHD), drawing from a mother's account of using CBD and other cannabinoid treatments for her child.

Introduction

R., a second-grade student, works on his homework alongside his mother, who notes the challenges in maintaining his focus both at home and in school. The preliminary diagnosis suggests a combination of behavioral and emotional disorders, marked by significant hyperactivity or fatigue, stereotypies, and a potential for Asperger's syndrome, although a definitive diagnosis has yet to be established.

In the search for effective treatments, an increasing number of families are exploring CBD as an alternative to conventional medications for managing symptoms of autism and attention disorders. R. is among those children who have embarked on CBD therapy, witnessing notable improvements in his condition. This shift towards CBD underscores the ongoing exploration of alternative treatments within the realm of pediatric behavioral and emotional disorders.

R. is one of the children who is following these therapies and is experiencing significant improvements in the condition thanks to CBD.

CBD and ADHD: Dosages and Forms of Administration

Experimenting with Different Dosages and Forms of Administration

Adjusting the dosage and method of CBD administration for therapeutic purposes, particularly in children, often requires patience and experimen-

tation. The European Commission has clarified that CBD is not classified as a 'narcotic drug' under UN Conventions, highlighting its safety profile and the absence of narcotic effects. This distinction is crucial for its use in children or adults sensitive to THC's psychoactive properties.

For children like R., the journey to finding the most effective way to administer CBD involved navigating personal preferences and responses to various forms of the substance. The concentrated oil's strong taste, a common issue among younger patients, led R.'s family to explore alternative methods. Chewing gum infused with CBD emerged as a favored option due to its ease of use, though initial trials indicated that even this method required dosage adjustments to avoid drowsiness during activities like homework.

R.'s mother's innovative approach, including creating sesame oil extractions from food-grade hemp, underscores the importance of customization in CBD therapy. Through trial and reflection, such as reducing the gum's portion to match R.'s needs, caregivers can find a balance that maximizes CBD's benefits while minimizing any undesired effects. This process highlights the adaptability required in integrating CBD into therapeutic regimens, especially for managing conditions in pediatric patients.

CBD and ADHD: Symptom Reduction and Management

CBD reduced Symptoms of Attention Deficit Disorders

The implementation of CBD in R.'s regimen brought noticeable improvements in managing his attention deficit disorders. During the administration of CBD products, there was a significant uptick in his alertness, coupled with a reduction in episodes of hyperactivity and excessive fatigue. R.'s mother observed enhanced focus and concentration when using CBD gum and found that extracts made from food-grade hemp also yielded positive outcomes.

The initial trials with CBD marked a clear shift in R.'s behavior, making him more attentive and less prone to hyperactivity. His mother's testimony

underscores her belief in CBD's efficacy for a range of pediatric conditions, particularly those related to attention deficit disorders. Armed with these promising results and the support of a knowledgeable pediatrician, R.'s family is prepared to continue exploring CBD as a therapeutic avenue, confident in its potential benefits and ready to navigate the associated psychological and financial considerations. This experience illustrates the broader possibilities that CBD presents for children facing similar challenges, highlighting the importance of individualized treatment plans and professional guidance in optimizing therapeutic outcomes.

Medical Cannabis and Studies on ADHD

The narrative of R. and his mother aligns with a broader interest in exploring the therapeutic potential of Cannabidiol (CBD) for attention deficit hyperactivity disorder (ADHD). A 2019 observational study in Brazil focused on 15 pediatric patients with ADHD symptoms and reported significant improvements following treatment with high CBD concentration capsules, with a THC:CBD ratio of 1:75.[1]

This outcome reinforces the notion that CBD can enhance sleep quality, reduce hyperactivity, and subsequently improve mood and general health, thereby augmenting the effectiveness of psycho-pedagogical interventions. Over time, such interventions may further bolster the social, cognitive, and behavioral gains made through cannabinoid treatment.

The doses used in the study were standardized and individually established by a titration process in a range based on previously reported doses of CBD for the treatment of refractory epilepsy associated with regressive autism.[2];[3]

The average initial dose of CBD was:

- 2.90 mg/kg/day varying according to the severity of the individual case at the start of treatment;

- minimum: 2.30 mg/kg/day;
- maximum: 3.60 mg/kg/day.

Dosage adjustment was carried out intensively during the first 30 days and to a lesser extent during the following 150 days. The average dose of CBD administered was:

- 4.55 mg/kg/day;
- minimum of 3.75 mg/kg/day;
- maximum of 6.45 mg/kg/day.

The average THC dose over the same period was:

- 0.06 mg/kg/day;
- minimum of 0.05 mg/kg/day;
- maximum of 0.09 mg/kg/day.

The administration schedule was two daily doses, one in the morning and one in the evening. A recent systematic review expressed moderate evidence for CBD and CBD-containing compounds such as Nabiximol® to alleviate symptoms of disorders such as schizophrenia, social anxiety disorder, autism spectrum disorder (ASD) and ADHD. The same review indicates weaker evidence for insomnia, anxiety, bipolar disorder, post-traumatic stress disorder and Tourette's syndrome.[4]

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3.8.5. Case Studies: Autism and ADHD

A Clinical Case from Spain

Dr. Mery Peña, medical director at the Kalapa Clinic in Spain, presents the case of an 11-year-old boy diagnosed with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), with genetic alterations of possible clinical relevance on chromosome 2 (MYT1L gene), and 2 other variants with possible clinical relevance. The child has been treated with cannabinoids for three years. Before being treated with cannabinoids, the child was undergoing treatment with:

- Guanfacine, 2 mg per day;
- Risperidone, 1 ml every 8 hours;
- Clorazepate, 10 mg, to control agitation or insomnia.

To this therapy, Dr. Peña added:

- CBD oil at 10% (extracted in supercritical CO2, 5 mg per drop), 3 times daily (19.8 mg/day).

Subsequently, the therapy was corrected in this way:

- first, increase in CBD dose;
- then, reduction in the dose of risperidone;
- furthermore, the addition of THC;
- finally, the addition of CBG.

The child's current treatment is the following:

- CBD oil 10% (extracted using supercritical CO2), 7 drops, 3 times daily, (5 mg per drop; 105 mg/day; 2.3 mg/kg/day for 46 kilos);

- THC 4% + THCA 3% oil (decarboxylated + acidic forms of THC, respectively), 1 drop in the morning and afternoon + 2 drops in the evening (5.3 mg THC + 4 mg THCA per day);
- 10% CBG oil (extracted using supercritical CO2), 2 drops in the morning, afternoon, and evening (4 mg per drop, 24 mg CBG per day).

After three years of treatment, Dr. Peña tells us that the child's mother, psychiatrist, teachers and caregivers make a positive assessment of the ongoing therapy, reporting that the child has significantly improved as a result of using cannabinoids, although the child still displays a lot of agitation and disinhibition on some days. In addition, the dosage of risperidone was reduced to a quarter (0.25 mL, 3 times a day), also reducing its side effects.

Below is a summary table of the treatment carried out.

Table 45.

	Patient
Age and sex:	11-year-old, male
In therapy since:	3 years
Diagnosis:	Autism + ADHD. Genetic alterations of possible clinical relevance on chromosome 2 (MYT1L gene), and 2 other variants with possible clinical relevance.
Eventual past medications:	Guanfacine 2 mg per day; Risperidone 1 ml every 8 hours; Clorazepate 10 mg, to control agitation or insomnia.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	CBD 10% oil (supercritical CO2 extraction), 7/7/7, (5 mg per drop; 105 mg/day; 2.3 mg/kg/day for 46 kilos). THC 4% + THCA 3% oil (Decarboxylated + Acidic forms of THC), 1/1/2, (5.3 mg THC + 4 mg THCA per day). CBG 10% oil (supercritical CO2 extraction), 2/2/2, (4 mg per drop; 24 mg CBG per day).
Starting dosage:	CBD oil 19.8 mg/day.
Possible corrections in dosage:	Increasing doses of CBD, then reducing dosage of risperidone, then introducing THC, the last intervention in the cannabinoid treatment is introducing CBG.

	Patient
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	3 years.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Mother, psychiatrist, teachers and caregivers make a positive balance. Still very hard days with loads of agitation and disinhibition, but is significantly better with cannabinoids. The dosage of risperidone has been reduced to a quarter (0.25mL, 3 times a day).

Summary of the treatment of Autism and ADHD with Medical Cannabis, as reported by Dr. Peña.

A Clinical Case from Malta

Dr. Jean Claude Scicluna is a medical doctor and neuroscientist from Malta. Aside from his various research projects, within academia and industry, he founded what was initially the Malta Cannabis Clinic, which has now evolved into a digital clinic as plantmedicineclinics.com.

Dr. Scicluna presents the clinical case of an 8-year-old boy diagnosed with ASD, with communication and behavioral problems. The diagnosis occurred when the child was four years old and he has been on risperidone therapy ever since.

Dr. Scicluna replaced risperidone with:

- CBD at 10% in hemp oil;
- melatonin in the evening in case of insomnia problems.

The initial CBD dosage was:

- 0.25 mL 2 times per day;
- increased to 0.5 mL 2 times per day after 2 weeks.

At the time of the interview, the child had been on CBD therapy for more than a month.

Dr. Scicluna explains the results of the therapy, quoting the words of the child's mother: "We came to the clinic with our son, stopped the risperidone a few days before coming to the clinic and then started him on CBD to help alleviate his confusion and frustration."

After 2 weeks of treatment, "we are giving him 0.25 mL morning and evening (later increased to 0.5 mL) and we have noticed very positive changes: he is calmer but still energetic, he seeks us out more and is happy to try to communicate in his own way. For the first time in his life, he asked for water. He has never asked for anything, he usually shows it to us, we say the word and he repeats it, but this time he specifically asked for it. We are very happy with these small changes, but at the same time with these big steps. As for the side effects, we have noticed that he eats a little less (which is an advantage in his case) and that he sleeps very late, but when he shows no sign of falling asleep, from 11am to midnight I give him 2 ml of melatonin."

Below is a summary table of the treatment carried out.

Table 46.

	Patient
Age and sex:	8-year-old, male.
In therapy since:	Diagnosed aged 4.
Diagnosis:	Autism Spectrum Disorder with communication/ behavioural problems.
Eventual past medications:	Risperidone.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	CBD 10% in hemp seed oil.
Starting dosage:	0.25 ml, twice a day.
Possible corrections in dosage:	0.5 ml, twice a day, after 2 weeks.
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	1 month.

Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	The mother: "We came to the clinic with our son, we had stopped risperidone a few days before the clinic and started him on CBD to help ease his confusion and frustration." After 2 weeks: "We are giving him 0.25 ml morning/ evening and have noticed some very good changes! He is calm but still energetic, he is seeking us more and is happy to try and communicate in his own ways. He asked for water for the very first time in his life. He never asked for anything, he shows us and we say the word and he repeats it, but this time he asked specifically for it. We are very happy with the little changes, yet such big steps. As for any side effects, we noticed that he is eating a bit less (which is a plus in his case), and also, he is sleeping really late, but when he's really not showing any signs of sleep by 11 - midnight, I give him 2 ml melatonin."

Summary of the treatment of ASD with Medical Cannabis, as reported by Dr. Scicluna.

3.9. Cannabis for Glaucoma

Glaucoma represents a significant challenge in ophthalmology, being a major cause of irreversible blindness globally. The disease primarily affects the optic nerve, and its progression is closely linked to increased intraocular pressure (IOP), among other factors. While there are various pharmacological treatments available to manage IOP, finding effective and patient-friendly options remains a priority. The exploration of cannabis and cannabinoid-based medications for glaucoma treatment traces back to the 1970s. This period marked the beginning of what could be considered the modern era of Medical Cannabis research, spurred by the need to address glaucoma among other conditions. Research during those years unveiled the potential of cannabinoids to lower intraocular pressure, offering a novel approach to glaucoma management.

Glaucoma

Glaucoma, deriving from the Greek words “gláukōma” and “glaukós,” meaning ‘glaucous, cerulean, celestial,’ describes a group of eye diseases characterized by increased IOP. This condition is historically noted for causing the affected eye to appear opaque blue to grey. The link between elevated IOP and glaucoma was first documented in 1622 by English physician Richard Banister, highlighting the condition’s long standing recognition in medical history.

The aqueous humor is central to understanding glaucoma’s pathophysiology. This fluid nourishes the eye and maintains its shape, circulating between the lens and the cornea. When drainage pathways are blocked, fluid accumulates, leading to increased pressure akin to water building up behind a dam. This pressure is believed to harm the optic nerve by impeding nutrient flow, potentially leading to blindness.

Glaucoma is primarily categorized into two types:[1]

- *Open-angle glaucoma*, the more common form, progresses gradually without symptoms, stemming from slow alterations in aqueous humor outflow.
- *Angle-closure glaucoma* presents suddenly and is less common, marked by acute and severe outflow obstruction. Symptoms can include intense eye pain, redness, corneal edema, nausea, vomiting, and blurred vision.

Glaucoma stands as the second leading cause of blindness globally, trailing only behind cataracts, impacting over 60 million individuals. The condition primarily manifests as open-angle glaucoma, a gradual yet relentless assault on the retinal cells and optic nerve, culminating in the narrowing of the visual field and eventual vision loss. Its insidious nature, often progressing without symptoms, underscores the vital need for regular eye examinations, particularly post-40, to detect and mitigate its silent progression.

The precise origins of glaucoma remain elusive to researchers, who have pinpointed only risk factors, not direct causes. Among these, increased intraocular pressure (IOP) is notable, alongside age and ethnicity, with a higher prevalence observed in individuals of African descent and particularly in Caribbean populations. The focus of most current treatments is on managing this modifiable risk factor, aiming to lower IOP to prevent or slow the disease's progression.

The emphasis on early detection and the management of risk factors like IOP highlights the complex challenge glaucoma presents to both individuals and healthcare professionals. As research continues, understanding and treating this subtle disease remains a priority in preserving vision and quality of life for millions worldwide.

Treatment Strategies for Glaucoma

The primary strategy for treating glaucoma involves pharmacological interventions, typically administered through eye drops aimed at reducing IOP.[2] This pressure reduction is crucial for preventing damage to the optic nerve, which can lead to vision loss. The medications target various pathways involved in the circulation of aqueous humor within the eye, particularly focusing on enhancing outflow or reducing the production of this fluid.

Key classes of medications include:

- Pilocarpine: a cholinergic agonist that facilitates fluid passage by contracting muscles controlling the trabecular meshwork. While effective, it can constrict the pupil and potentially narrow the visual field;
- beta-blockers (e.g., timolol): reduce fluid production but are contraindicated in patients with asthma or certain heart conditions due to their systemic side effects;

- alpha-2 agonists (e.g., apraclonidine, brimonidine) and carbonic anhydrase inhibitors (e.g., acetazolamide): both classes decrease fluid production but come with their own set of side effects;
- prostaglandin F2A analogues (e.g., latanoprost, unoprostone): relatively safe drugs that improve the outflow of aqueous humor from the eye.

When medication is insufficient in managing IOP, surgical options are considered. Techniques vary from laser surgery to enhance the drainage pathway, to more invasive procedures such as creating a new drainage canal or inserting drainage tubes. Though effective, surgeries are reserved for cases where medical treatment fails or is inadequate due to the potential for rare but serious complications.
This comprehensive approach highlights the multifaceted nature of glaucoma treatment, underscoring the importance of tailored interventions to manage this complex condition effectively.

Cannabis and Glaucoma: a History of Activism

The history of cannabis in the treatment of glaucoma and its role in the medical cannabis movement is intertwined with activism and legal milestones. The story begins in 1971 with early reports recognizing cannabis's potential to lower IOP. This discovery set the stage for cannabis to gain recognition, not just as a recreational substance, but as a medical aid with tangible benefits for those suffering from this eye condition.
The turning point in this narrative was the experience of Robert C. Randall, who, in 1974, discovered the beneficial effects of cannabis on his glaucoma symptoms. After being arrested for growing cannabis, Randall's legal battle and subsequent acquittal in 1976, under the argument that he was using cannabis out of medical necessity, marked a pivotal moment in the fight for medical cannabis legalization. This case underscored the therapeutic potential of cannabis and propelled Randall into activism.

His advocacy led to significant developments, including the initiation of the Marijuana Research Project at the University of Mississippi, the first state-run medical cannabis cultivation program in the U.S., which legally provided cannabis to patients, including Randall, until 1992. His efforts didn't stop there: Randall co-founded the Alliance for Cannabis Therapeutics and was instrumental in a 1987 lawsuit that resulted in a DEA (the US anti-drug agency) judge's acknowledgment of cannabis's safety profile for therapeutic use.

Robert C. Randall's legacy extends beyond his death in 2001, symbolizing the profound impact of patient advocacy on medical cannabis research and policy reform. His story highlights the intersection of medical necessity, legal challenges, and the relentless pursuit of access to treatment options for debilitating conditions like glaucoma.

The Efficacy of Cannabis and Cannabinoids in Glaucoma

Cannabis and cannabinoids hold promise in treating glaucoma primarily through two mechanisms:

1. *Lowering IOP*: The interaction with the CB1 receptor, notably present in the eye's anterior structures like the trabecular meshwork and Schlemm's canal, among others, helps reduce IOP. This effect is also supported by cannabinoids' role in modulating prostanoid synthesis via the cyclooxygenase (COX) pathway. The widespread distribution of CB1 receptors across various ocular tissues indicates that cannabinoids might lower IOP by affecting both the production and outflow of aqueous humor.
2. *Neuroprotection*: Studies have shown cannabinoids can protect retinal ganglion cells from damage, a crucial factor in preventing glaucoma-related vision loss. This neuroprotective effect stems from three primary actions: inhibiting the release of glutamate, endothelin-1, and nitric oxide—substances that can contribute to nerve damage in glaucoma.

Cannabinoids that are useful in the Treatment of Glaucoma

Clinical research has demonstrated the efficacy of certain cannabinoids in both reducing IOP and potentially slowing the progression of glaucoma. Among the various cannabinoids, tetrahydrocannabinol (THC) stands out for its effectiveness when administered orally, intravenously, or through inhalation. However, direct application to the eye as eye drops has proven less effective due to THC's fat-soluble nature, which challenges its solubility in the aqueous environment of the eye. Innovations such as cyclodextrin-based formulations are being explored to enhance THC's solubility and efficacy in eye treatments.

Both natural and synthetic cannabinoids, including inhaled cannabis and THC, have been shown to significantly lower IOP in glaucoma patients and even in individuals with normal IOP. This effect typically persists for about three to four hours. Despite these promising results, the practical use of THC is sometimes limited by its short duration of action and potential side effects.

Cannabidiol (CBD), while able to modestly reduce IOP, has been observed to induce some ocular toxicity. In contrast, Cannabigerol (CBG) emerges as a promising alternative, capable of reducing IOP without significant toxicity.[3] Additionally, Palmitoylethanolamine (PEA), particularly when administered orally, not only reduces IOP but also significantly decreases intraocular vasodilation, all without adverse side effects.[4]

Tailored Therapy for the Patient: Considerations of a Prescriber

"Despite the large number of manuscripts on the use of cannabinoids in glaucoma, the overall scientific evidence on this topic remains controversial. In addition to the lack of randomized controlled trials, we must also point out that the majority of the manuscripts cited dates back in the 1970s and early 1980s. This may represent a further limitation because manu-

scripts from that period often present problems with data dissemination, statistical analysis, population homogeneity and safety assessment. For these reasons, the scientific evidence on this topic remains limited." These are the conclusions of a systematic literature review published in 2020.[5]

Dr. Lorenzo Calvi, Anaesthesiologist, Ethnopharmacologist, Visiting Professor at the University of Milan, does not seem to agree with these conclusions.

Dr. Calvi's experience treating 150-160 glaucoma patients with cannabinoids reveals remarkable success, with notable improvements observed in the vast majority of cases. Highlighting the effectiveness of therapy, Dr. Calvi emphasizes the minimal dosage required to achieve these results, significantly enhancing patient compliance by avoiding the psychoactive side effects commonly associated with cannabis use. This success underscores the necessity of tailoring treatments to individual patient needs, an approach Dr. Calvi refers to as the "summa of therapeutic reasoning," where therapy is intricately adapted to the dynamics of each patient's daily life and the evolution of their condition.

The customization of therapy involves a nuanced understanding and application of available cannabinoid tools, guided by the clinician's expertise. Dr. Calvi advocates for preserving the natural synergy between cannabinoids and terpenes found in the cannabis plant, achieving clinical efficacy at low dosages while ensuring safety.

Dr. Calvi's insights extend beyond glaucoma, suggesting the potential applicability of cannabis and cannabinoid therapies across a range of conditions. His personal observations of patient progress have challenged preconceptions about cannabis, highlighting its therapeutic potential. He calls for increased education among medical professionals on the benefits and low risks of cannabinoid use, suggesting that a deeper understanding could transform patient care.

The collaborative relationship between doctor, patient, and pharmacist—referred to as the "galenic triangle"—is crucial in cannabinoid therapy, en-

suring a cohesive and effective treatment plan. Dr. Calvi stresses the importance of continuous dialogue and coordination among these parties to maximize therapeutic outcomes, advocating for a communal effort that is rewarded with the success of the treatment.

Cannabis and Glaucoma: Conclusions

"The hypotensive effect in glaucoma resistant to conventional therapies" is one of the main indications for the use of cannabis and cannabinoids.
The utilization of cannabis and cannabinoids for treating glaucoma, particularly in cases resistant to conventional therapies, is underscored by significant research alongside countless anecdotal patient experiences. These sources collectively highlight the ability of cannabinoids to lower IOP and manage the progression of glaucoma effectively. However, challenges remain in their application, primarily due to cannabinoids' high lipophilicity, which complicates formulation into eye drops, and the central side effects associated with THC. Moreover, the relatively short duration of their action further restricts their widespread use.
Despite these obstacles, medical cannabis and cannabinoids continue to be regarded as a viable alternative in glaucoma treatment. This perspective is largely reinforced through clinical practice, as illustrated by Dr. Lorenzo Calvi's experiences, emphasizing the importance of customizing therapy to meet the unique needs of each patient. Tailoring treatment in this manner acknowledges the individual complexities of glaucoma and the patient's specific condition, ensuring that the therapeutic benefits of cannabinoids can be maximized while minimizing potential drawbacks.

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3.10. Cannabis-Based Mouthwashes

Burning mouth syndrome is a chronic and often distressing disorder that is frequently associated with the development of anxiety and depression. A pilot study from the University of Turin, Italy, shows how *Cannabis Sativa* oil can be effective in combating this disorder.

Burning Mouth Syndrome

Burning mouth syndrome (BMS) is an aggravating condition characterized by a persistent sensation of burning in the mouth, absent any clear medical or dental causes. Despite the normal appearance of the oral mucosa, individuals with BMS experience ongoing discomfort and a burning sensation reminiscent of the pain felt from consuming a scalding beverage. This chronic disorder can endure for months, significantly impacting sufferers' quality of life.

The "International Classification of Orofacial Pain," introduced in 2020, defines BMS as a daily recurring intraoral burning sensation or dysesthesia lasting more than two hours a day for over three months, without any clinically evident causal lesions.[1]

The syndrome often presents pain of an intensity comparable to a toothache but is distinguished by its burning nature. Symptoms predominantly manifest during the day, subside at night, and do not usually disrupt sleep. Accompanying symptoms may include dry mouth (xerostomia) and an altered ability to taste (dysgeusia)—a condition similar to that experienced by some patients with Covid-19.

The impact of BMS extends beyond physical discomfort, often contributing to the development of mood disorders like anxiety and depression due to the persistent pain, altered taste, and other unpleasant sensations such as bad breath. Consequently, psychotherapeutic support is commonly recommended for affected individuals. Currently understood as primarily a chronic neuropathic pain condition with an often-elusive cause, treatment for BMS focuses on symptom management, with no definitive cure available. Therapeutic options that may offer relief include the use of benzodiazepines or alpha-lipoic acid, alongside psychotherapeutic interventions, aiming to improve patients' quality of life despite the persistent nature of the syndrome.

A Study with Cannabis Oil

Research has uncovered that patients with burning mouth syndrome exhibit changes in cannabinoid receptors CB1, CB2, and TRPV1 within the oral mucosa.[2] Recognizing the effectiveness of Cannabis in various neuropathic conditions, a pilot study was initiated to explore its potential in alleviating the symptoms of burning mouth syndrome.[3] This preliminary investigation involved 17 participants, primarily women and the elderly, who had been experiencing symptoms for at least 12 months.

Patients were treated with cannabis oil from the Bediol variety, containing 6.3% THC and 8% CBD. As there is no indication in the literature on the dosage for this syndrome, the patients received increasing doses of cannabis oil:

- 5 drops for the first 5 days;
- 10 drops for the next 5 days;
- 15 drops for another 5 days;
- finally, 20 drops for 13 days.

During the 4-week study period, patients took the oil twice a day. The study aimed to evaluate pain intensity changes, with secondary assessments on anxiety, depression levels, and side effects, through patient questionnaires.

Cannabis 'extinguishes' the Burning Mouth

The pilot study focusing on the use of Cannabis Sativa L. oil for treating burning mouth syndrome yielded promising outcomes, with all participants experiencing a significant reduction in oral symptoms and pain, improvements which lasted for up to 24 weeks post-treatment. Furthermore, notable enhancements in anxiety and depression levels were observed, without the emergence of significant side effects. These results are particularly encouraging given the lack of reliable, long-term treatment options for this syndrome that do not carry substantial risks, such as the addiction potential seen with clonazepam, a commonly considered effective treatment.

The study's authors express optimism regarding these findings, emphasizing the need for further research through larger clinical trials to validate Cannabis Sativa L. oil as a safe and effective treatment for burning mouth syndrome. This initial research highlights the potential of cannabis oil in not only alleviating symptoms but also in improving the overall quality of life for those afflicted by this challenging condition.

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3.11. Medical Cannabis in Palliative Care

Professor Donald I. Abrams, from the Department of Hematology-Oncology at the University of San Francisco, USA, discusses the rationale for prescribing cannabis to cancer patients in his publication entitled *Should Oncologists Recommend Cannabis?*.[1]

Cannabis and Cancer Therapy: the Story

The historical and therapeutic relationship between cannabis and cancer therapy stretches back millennia, with its potential uses in oncology hinted at through archaeological and historical evidence. For instance, the discovery of a 2,700-year-old mummified young woman in Siberia, who appeared to have metastatic breast cancer and was found with cannabis, suggests ancient uses of the plant for potentially managing cancer symptoms or effects.

Despite the global wave of prohibition that stifled cannabis research and treatment in the 20th century, significant advancements have been made in recent decades. The development of delta-9-tetrahydrocannabinol

(THC) as a drug in 1986 marked a turning point, initially approved to treat nausea and vomiting from chemotherapy, with its indications later expanded to include anorexia associated with AIDS wasting syndrome and chemotherapy. This progression underscores the logical assumption that cannabis, the botanical source of THC, harbors similar therapeutic benefits.

The endocannabinoid system, comprising cannabinoid receptors and endogenous cannabinoids (endocannabinoids), is believed to have evolved to modulate our responses to painful stimuli. Phytocannabinoids from the cannabis plant interact with this system, with clinical evidence strongly supporting their analgesic effects among other benefits. This foundational understanding prompts further exploration of cannabis's role in cancer therapy, from symptom management to potentially broader therapeutic applications.

Practical Advice for the Use of Cannabis in Oncology

In oncology, the antitumor properties of cannabinoids like THC and CBD have shown promise in vitro and animal studies, yet human clinical evidence remains limited. However, this shouldn't deter the utilization of cannabis in cancer treatment. Cannabis may be a valuable addition to palliative care, for multiple therapeutic benefits, including:

- alleviating nausea;
- enhancing appetite;
- managing pain;
- improving mood;
- promoting better sleep.

Concerns around the inhalation of cannabis as a drug delivery method are noted, especially given modern medical standards. However, adverse effects from cannabis inhalation are relatively rare, and a variety of alter-

native delivery methods are available. These include ingestible forms of cannabis, which can be accessed through pharmacies or dispensaries, offering safer and potentially more acceptable options for both patients and healthcare providers in managing cancer-related symptoms.

Conclusions

Given the evolving landscape of Medical Cannabis research and its reported benefits, incorporating cannabis into palliative care represents a promising frontier for enhancing patient well-being. The potential of cannabis to address a spectrum of symptoms commonly encountered in palliative care—such as pain, nausea, loss of appetite, mood disorders, and sleep disturbances—underscores its value as a multifaceted therapeutic option. However, the application of cannabis in this context requires a thoughtful, evidence-based approach. Healthcare providers, particularly those in oncology and palliative care, should stay informed of the latest research and regulatory guidelines to offer well-founded recommendations.

To optimize patient outcomes, a push for enhanced education and training on the medical applications of cannabis is essential. Such initiatives should aim to equip healthcare professionals with the knowledge to navigate the complexities of cannabis pharmacology, administration methods, and potential interactions with existing treatments.

In conclusion, the strategic integration of cannabis into palliative care, supported by ongoing research, patient-centered care strategies, and comprehensive healthcare professional education, has the potential to significantly improve the quality of life for patients facing serious illnesses.

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3.11.1. Efficacy and Tolerability of Sativex® in Glioblastoma Patients

Various studies analyzed the efficacy and safety of Sativex®, a nasal spray containing cannabinoids (THC and CBD in a 1:1 ratio), in patients with glioblastoma, one of the brain tumors with the highest mortality rate.

Brain Tumours: Glioblastoma Multiforme

Glioblastoma multiforme (GBM) stands as one of the most aggressive and prevalent brain tumors, arising from glial cells, particularly astrocytes. This type of cancer typically manifests in the cerebral hemispheres and is less common in the brainstem and spinal cord. It mainly affects adults, with an average onset age of 53, and is relatively rare in individuals younger than 15. Globally, glioblastoma occurs at a rate of approximately 4-5 cases per 100,000 people annually, though some studies suggest a higher incidence. The underlying causes of glioblastoma remain largely speculative, with ongoing research exploring the role of neuronal stem cells that can differentiate into various brain cells, including those that might develop into tumors. These neoplastic stem cells have shown resistance to conventional treatments like chemotherapy and radiotherapy, contributing to the disease's high mortality rate. Exposure to ionizing radiation is the only well-established risk factor, with other potential factors including environmental and occupational exposures, though conclusive evidence is lacking. Treatment options for glioblastoma are limited and primarily focus on extending patient survival rather than cure. Surgical removal of the tumor, where feasible, is the preferred initial treatment, often followed by radiotherapy and chemotherapy with temozolomide, particularly benefiting patients with specific genetic mutations in the MGMT gene. Despite these interventions, the prognosis remains poor, with only a modest extension in life expectancy and a high likelihood of tumor recurrence within three years post-diagnosis.

Cannabis, Glioblastoma and Brain Tumours

The therapeutic application of Medical Cannabis and cannabinoids in the field of oncology, particularly for symptom management such as nausea, vomiting, appetite stimulation, chronic pain, and psychological disorders, is increasingly recognized. Beyond symptom management, research has extended into the anti-tumor efficacy of cannabinoids like tetrahydrocannabinol (THC), its synthetic analogue Nabilone, and cannabidiol (CBD), demonstrating promising results in in vitro and animal model studies, though human data remains less conclusive. Cannabigerol (CBG) has also emerged as a compound of interest for its anti-tumor properties in cell line studies.[1]

Notably, glioblastoma cells express cannabinoid receptors CB1 and CB2, with an increase in CB2 expression correlated with tumor progression. This observation points to the endocannabinoid system's potential role in glioblastoma, supporting the hypothesis that cannabinoids may inhibit the tumorigenesis of neoplastic stem cells in the brain.[2] Studies suggest that THC and CBD can reduce tumor progression in glioma models, primarily through apoptosis induction and the inhibition of cell proliferation and vascularization.[3]

Combining cannabinoids with temozolomide has shown enhanced outcomes in animal studies, including in temozolomide-resistant models. A clinical trial conducted in 2006 indicated that intracranial THC injection could reduce glioblastoma proliferation in a subset of patients, marking an early step towards understanding cannabinoids' potential in treating glioblastoma and possibly other brain tumors.[2]

Cannabis and Glioblastoma: the Use of Sativex® and Temozolomide

A clinical trial explored the combination of Sativex®, a cannabis-based medicine containing THC and CBD, with temozolomide, a chemotherapy

drug, for glioblastoma treatment. Conducted by GW Pharmaceuticals alongside British and German researchers, the study aimed to assess the safety, tolerability, and potential impact on tumor progression and patient survival.[4]

Patients diagnosed with glioblastoma were treated with high doses of temozolomide followed by Sativex®, adjusting the dosage based on tolerability. The study was structured in two parts: an initial open-label phase to familiarize both investigators and patients with the treatment, and a subsequent randomized, double-blind phase comparing Sativex® plus temozolomide against a placebo plus temozolomide.

Findings from the trial indicated a significant survival advantage at one year for patients treated with Sativex®, with a two-year survival rate of 50% compared to 22% for the placebo group. Additionally, a majority of the Sativex® group exceeded their expected survival based on the European Organisation for Research and Treatment of Cancer (EORTC) prognostic kit, without Sativex® affecting the pharmacokinetics of temozolomide.

Recent clinical trials and studies further support the exploration of Sativex® in conjunction with temozolomide for treating recurrent GBM.[5] Moreover, a still ongoing (in 2024) randomized phase II trial (ARISTOCRAT) aims to assess the preliminary efficacy of Sativex® in patients with recurrent GBM, focusing on the combination's potential to improve outcomes. These recent studies underscore the ongoing interest and investigation into cannabinoids' role in cancer treatment, particularly glioblastoma.

Cannabis and Glioblastoma: A Potential Therapy

Pre-clinical studies have highlighted the potential anti-tumor effects of Medical Cannabis, THC, CBD, and CBG on glioblastoma, an aggressive brain tumor. However, translating these findings to human treatments poses significant challenges. Studies focusing on the tolerability and safety of Sativex® in glioblastoma patients found it to be generally tolerable, with

customizable dosages and manageable side effects like fatigue, dizziness, headache, and vomiting. Despite this, some patients treated with Sativex® experienced severe side effects, including infections and gastroenteritis.

Research also explored glioblastoma progression at six months and one-year survival rates, revealing no significant changes in tumor progression but an improved one-year survival rate with Sativex® treatment compared to previous studies. However, due to the small participant number, these results should be approached with caution, as they lack the statistical power to be generalizable.

Considering the dire prognosis of glioblastoma, where surgical resection offers no guarantee against recurrence and the mortality rate remains high, even the modest improvements in survival rates observed with Sativex® and temozolomide treatment are encouraging. This underscores the need for more extensive clinical trials with larger patient populations to thoroughly evaluate the efficacy and safety of cannabis-based therapies in glioblastoma treatment.

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3.11.2. Case Study: Breast Cancer and Related Comorbidities

Dr. Janosch Kratz shared the case of a woman with breast cancer who was being treated with Medical Cannabis. The woman, aged 64, presents:

- breast cancer;
- bone metastases;
- intraspinal abscess;
- post-operative paraplegia after hemorrhage.

The patient is naive to cannabis and presents the following symptoms:

- pain;
- spasticity;
- insomnia;
- tiredness;
- lack of appetite and weight loss.

Before cannabinoid treatment, the woman was treated with:

- Oxycodone/Naloxone 10mg/5mg, 3 times daily (1 - 1 - 0 - 1);
- Baclofen 10 mg, 3 times daily (½ - ½ - 0 - 1);
- Pregabalin, Mirtazapine, Zopiclone at night;
- Novaminesulfone (as needed), 20-40 drops.

Before starting Medical Cannabis therapy, the woman was experiencing:

- intense pain rated at 8 out of 10 on the Visual Analog Scale (VAS);
- the need for rescue medication more than 15 times a month;
- frequent awakenings leading to approximately four hours of sleep per night;
- a high level of suffering;
- social withdrawal;
- depressive mood;
- a severely restricted quality of life.

The woman started treatment with Medical Cannabis to try to control:

- pain;
- spasticity;
- insomnia;
- loss of appetite and weight loss.

To address her symptoms, which included pain, spasticity, insomnia, and loss of appetite leading to weight loss, Dr. Kratz recommended starting treatment with a CBD-dominant cannabis preparation for its better tolerance profile. The chosen method of administration was oral, utilizing an oil extract with a THC to CBD ratio of 5:20. This means that each milliliter (mL) of the extract contained 5 mg of THC and 20 mg of CBD. The initial treatment plan called for administering this extract three times daily was:

Table 47.

Breakfast	Lunch	Dinner	Days of treatment
0	0	0,5 ml	3 days
0	0	1	3 days
0	0,5	1	3 days
0,5	1	1	3 days
1	1	1,5 ml	3 days

Initial treatment plan for breast cancer with Medical Cannabis, as reported by Dr. Kratz

After an initial 2 weeks period, the patient showed:

- good tolerability to the treatment;
- enhanced sleep quality and a calmer, more motivated demeanor;
- inadequate pain control (VAS 6-7/10);
- frequent use of emergency medication (5x in 14 days);
- no improvement in spasticity and appetite.

Given these outcomes, the treatment plan was adjusted to include a THC-dominant extract, complementing the initial CBD-rich therapy.

An extract with a THC:CBD ratio of 25:0 (0.1 mL corresponding to 2.5 mg THC) was then used, to be added to the previous treatment as follows:

- 0-0.1 mL (3 days);
- 0-0.2 mL (3 days);
- 0.1 mL-0-0.2 mL.

This adjustment improved the pain scale. Side effects worsened in the first few days of treatment and then stabilized. After 2 months of therapy, improvements were observed:

- pain levels decreased to a VAS rating of 4-5 out of 10;
- need for rescue medication reduced significantly;
- patient experienced weight gain, suggesting an improvement in appetite;
- sleep quality continued to improve, contributing to an enhanced overall quality of life;
- despite some initial side effects such as dizziness and memory challenges, these stabilized over time;
- notably, there was a positive shift towards social reintegration.

Below is a summary of the treatment.

Table 48.

	Patient
Age and sex:	64-years-old, female.
In therapy since:	August 2022.
Diagnosis:	Breast cancer, osseous metastases, intraspinal abscess, postoperative paraplegia after bleeding. Clinical status: - Pain intensity VAS 8/10; - Rescue medication > 15 days/month; - 2-3 awakenings/night (approx. 4 h sleep/night); - high level of suffering; - social withdrawal.

	Patient
Eventual past medications:	Oxycodone/Naloxone 10mg/5mg, 3 times daily (1-1-0-1) Baclofen 10 mg, 3 times daily (½-½-0-1) Pregabalin, Mirtazapine, Zopiclone at night Novaminesulfone (as needed/as needed), 20-40 drops.
Current medications (type of Medical Cannabis or cannabinoids prescribed):	Extract (oil) with THC:CBD ratio, 5:20 (1 mL corresponding to 5 mg THC, 20 mg CBD); Extract (oil) with THC:CBD ratio, 25:0 (0.1 mL corresponding to 2.5 mg THC).
Starting dosage:	First 2 weeks: THC:CBD, 5:20, 3 times daily, according to the schedule.
Possible corrections in dosage:	After the first 2 weeks, THC:CBD extract, 25:0, 3 times daily was added to the therapy as follows: 0-0.1 mL (3 days). 0-0.2 mL (3 days). 0.1 mL-0-0.2 mL.
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	2 months.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Improvement in Pain intensity VAS 4-5/10. Metamizole as rescue medication for 5 days/month. Significant improvement in sleep quality. Weight gain of 2 kg. Significant improvement in quality of life despite existing pain symptoms. Gradual social reintegration.
Reported adverse effects:	Overall good tolerability of the preparations: Dizziness, sleepiness, slight difficulty of finding words and affection of memory in the first week after THC increase (all reversible).
Other consideration:	Cannabis naive patient.

Summary of the treatment of breast cancer with Medical Cannabis, as reported by Dr. Kratz.

3.11.3. Case Study: Esophageal Cancer

In the field of oncology and palliative care, Medical Cannabis can be useful in decreasing the use of drugs with heavy side effects, such as opioids. In the management of a 53-year-old man with advanced esophageal adenocarcinoma, Dr. Privitera embarked on a transition from traditional opioid therapy to Medical Cannabis, motivated by the adverse effects associated with opioid use. Before this therapeutic shift, the patient had explored all conventional treatments and was engaged in the so-called “Di Bella

protocol," which incorporates a mix of hormones, chemotherapy agents, and vitamins tailored to individual patient needs, alongside opioids for pain management.

Dr. Privitera gradually replaced opioid therapy with Medical Cannabis, using:

- Extract of Cannabis Flos Bedica (THC 14% : CBD <1%), 1 g + 2 g of pure CBD in 200 mL alcohol; subsequent dilution with muco-adhesive gel (400 ml);
- Extract of Cannabis Flos Bedica, 5 g extracts in 200 mL of ethyl alcohol; subsequent dilution in 10 mL of MCT oil.
- Cannabis Flos Bedrocan (THC 22% : CBD <1%), inflorescences for vaporisation.

The initial dosage was:

- Bedica + CBD in mucoadhesive gel: 10 mL, 30 minutes before main meals (corresponding to 50 mg CBD/administration = 150 mg/day);
- Bedica extract: 5 drops in the evening = 10 mg/ intake;
- Bedrocan for inhalation: 3.3 mg/ intake x 4 times daily = 13.2 mg/ day.

The regimen prescribed aimed at leveraging the therapeutic potential of cannabinoids to manage pain, spasticity, insomnia, and issues related to inappetence and weight loss, with initial dosages designed to optimize efficacy while monitoring for tolerability.

Before the treatment with Medical Cannabis:

- in view of the cardial location and the degree of local infiltration, the patient reported unmanageable, continuous hiccups with exacerbations after meals;
- patient reported severe abdominal pain, predominantly at the epigastric site, but radiating throughout the abdomen (site of peritoneal carcinosis);
- presented severe anorexia and nausea;
- insomnia (due to both pain and hiccups).

After starting cannabinoid treatment, the caregiver reported a marked improvement in:

- hiccups after taking the mucoadhesive gel;
- appetite;
- pain symptoms (VAS score of 8 to 3);
- sleep quality;
- opioid intake (only as needed).

The patient reported no particular side effects during therapy.
Dr. Privitera specifically requested a formulation of the compound 'Bedica + CBD' in mucoadhesive gel.
The pathophysiological hypothesis was that the direct action of CBD in the mucosa of the esophagogastric joint and in the parietal layers could exert a regulatory effect on the nerve activity of the phrenic nerve (infiltrated by the neoplasm). This choice was based on data indicating the central role of cannabinoid receptors in the gastrointestinal tract.
Below is a summary of the treatment carried out:

Table 49.

	Patient
Age and gender:	53-years-old, bad.
In therapy since:	November 2019 - May 2020 (exitus).
Diagnosis:	K oesophagus (poorly differentiated adenocarcinoma).
Possible therapy prior to the use of Medical Cannabis or cannabinoids:	Patient already undergoing all traditional treatment schemes. Undergoing treatment with 'Di Bella protocol.' Opioids for analgesic therapy (with related side effects).
Current therapy (type of Medical Cannabis or cannabinoids prescribed):	- Extract of: Cannabis Flos Bedica (THC 14% : CBD <1%) 1000 mg + 2000 mg pure CBD in 200 mL alcohol; subsequent dilution with muco-adhesive gel (400 ml); - Cannabis Flos Bedica (THC 14% : CBD <1%), 5 g extracts in 200 mL ethyl alcohol; subsequent dilution in 10 mL MCT oil. - Cannabis Flos Bedrocan (THC 22% : CBD <1%), inflorescences for vapourisation.

	Patient
Initial dosage:	- Bedica + CBD in mucoadhesive gel: 10 mL, 30 minutes before main meals (corresponding to 50 mg CBD/administration = 150 mg/day); - Bedica extract: 5 drops in the evening = 10 mg/ intake; - Bedrocan for inhalation: 3.3 mg/ intake x 4 times daily = 13.2 mg/day.
Possible dosage corrections:	No dosage and/or formulation changes were necessary.
Duration of treatment with cannabis or cannabinoids (at the time of the interview):	5 months (patient deceased in May 2020).
Results obtained with the introduction of Medical Cannabis or cannabinoids in therapy (follow-up):	After the start of treatment: - the caregiver reports a marked improvement in hiccups after taking the mucus gel; - Improved appetite reported; - Reported improvement in pain symptoms (VAS 8 to 3) - Reported improvement in night rest.
Any reported side effects:	None. Reported good tolerance to all prescribed cannabinoid medications.

Summary of the treatment of esophageal cancer with Medical Cannabis, as reported by Dr. Privitera.

3.12. Cannabis in the Treatment of Migraine

Migraine is a prevalent type of headache characterized by medium to severe pain, often described as sharp or throbbing and usually localized on one side of the head.[1] This condition can lead to significant discomfort, with symptoms such as nausea, vomiting, and heightened sensitivity to light and sound, pushing sufferers to seek relief in quiet, darkened spaces. Statistically, migraine is more common among women, with a reported threefold increased likelihood of experiencing migraines compared to men. Despite this gender disparity, about 12% of the general population has experienced a migraine attack at some point. Typically, the onset of

migraine occurs during adolescence, with fluctuations in the intensity and frequency of attacks through adult life, often seeing a reduction after the age of 50.[2]

Pathophysiology of Migraine

The underlying causes of migraines involve a complex interplay of factors, where genetic predisposition, external stimuli, certain health conditions, and hormonal changes are all significant contributors.[3];[4] While triggers such as specific foods and drinks, stress, sleep disturbances, changes in climate, and certain medications are well-documented, they do not fully explain the pathophysiology of migraine.[5]

Research has illuminated the role of altered neural transmission mechanisms in migraines, particularly pointing to hyperactivation within the trigeminal-vascular system. This hyperactivation leads to the release of neuropeptides that cause inflammation in the cranial blood vessels and meninges. These processes result in the vessels dilating and produce the characteristic severe pain associated with migraine attacks.[6];[7]

Treatment and Care of Migraine

Managing migraines involves first attempting to identify and mitigate any potential triggers, such as dietary factors or environmental changes. When lifestyle adjustments prove insufficient or impractical, especially in cases where migraines disrupt daily life, seeking medical advice for pharmacological intervention is crucial.[8];[9]

Acute migraine treatments aim to alleviate pain and associated symptoms during an attack and might include:

- NSAIDs like paracetamol, aspirin, and ibuprofen for mild to moderate pain.

- triptans, which target pain propagation mechanisms by counteracting blood vessel dilation in the brain.
- ergotamine derivatives for severe or treatment-resistant migraines.
- opioids and other non-specific pain relief medications for intense or severe pain scenarios.

Preventive treatments, indicated for frequent or particularly severe migraines, often require daily intake of medications such as:

- blood pressure medications that influence vessel tone and pain mechanisms;
- antidepressants that indirectly affect serotonin receptors, which play a role in migraine onset;
- anti-epileptics targeting the pain threshold and brain hyperexcitability.

However, the chronic use of acute and preventive migraine medications can lead to side effects (gastrolesiveness and hepatotoxicity typical of NSAIDs, habituation and abuse potential typical of opioids), including the risk of medication overuse headache, emphasizing the need for careful management and monitoring of treatment plans.

Migraine and the Endocannabinoid System

Recent clinical and preclinical research supports a significant association between migraine headaches and the endocannabinoid system's neurotransmission alterations. Evidence indicates that individuals suffering from migraines often exhibit diminished activity within their endocannabinoid system.[10];[11];[12];[13];[14];[15];[16];[17]

Specifically, preclinical experiments involving laboratory animals have further substantiated these findings. In such studies, migraine conditions are simulated through the activation of the trigeminal-vascular system, lead-

ing to observable hyperalgesia in mice. This heightened sensitivity to pain is linked to increased activity of enzymes like Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MAGL). These enzymes are pivotal in the breakdown of endogenous cannabinoids, notably anandamide and 2-arachidonoylglycerol (2-AG). Additionally, there's a noted upsurge in cannabinoid receptor expression across various brain regions in these models. Collectively, this body of evidence underscores a malfunction in the endocannabinoid system's activity as a key factor in migraine pathophysiology.
Taken together, this scientific evidence suggests that a dysfunction in the activity of the endocannabinoid system plays an important role in the pathophysiological process of migraine.

Modulation of the Endocannabinoid System in the Treatment of Migraine

The exploration of the endocannabinoid system's role in migraine treatment has advanced significantly in recent years. Recent studies focused on the modulation of this system, particularly through the inhibition of enzymes like Fatty Acid Amide Hydrolase (FAAH) and Monoacylglycerol Lipase (MAGL), which degrade endogenous cannabinoids. Increasing the levels of cannabinoids like 2-AG and Anandamide by inhibiting these enzymes has shown promising results in reducing migraine-associated hyperalgesia and inflammation in animal models. A study published in 2018 demonstrated that inhibiting MAGL and consequently raising 2-AG levels effectively prevented hyperalgesia in a migraine model.[18] Moreover, increasing anandamide levels via FAAH inhibition lessened both hyperalgesia and inflammation initiated by the trigeminal-vascular system activation.[19]
These results suggest that inhibition of both FAAH and MAGL enzymes, resulting in amplification of endocannabinoid neurotransmission, may be a potential therapeutic target in the treatment of migraine. In addition to exerting a powerful pain-relieving effect, dual FAAH/MAGL inhibition also induces a decrease in the levels of inflammatory neuropeptides both pe-

ripherally and in the brain.[20] This decrease is also accompanied by a significant peripheral and central reduction of pro-inflammatory cytokines, in particular TNF-alpha and IL-6.

Although further studies are needed to define the molecular mechanisms underlying the analgesic effect of FAAH and MAGL inhibitors, the results obtained from these studies contribute to strengthening the hypothesis that pharmacological modulation of endocannabinoid tone may constitute an important new therapeutic strategy in the treatment of migraine.

Observational Studies

Few clinical studies available that demonstrate the efficacy of cannabis therapy in the treatment of migraine.

A study conducted at a tertiary headache center assessed the use and perceived benefits of cannabis among patients suffering from headaches. The findings suggested that patients are exploring cannabinoid use, indicating a potential role of the endocannabinoid system in headache disorders.[21] A 2024 randomized controlled trial focused on vaporized cannabis versus placebo for acute migraine treatment.[22] The study provided valuable insights into patient-reported outcomes, and results showed that acute migraine treatment with vaporized 6% THC + 11% CBD was superior to placebo at 2 hours post-treatment with sustained benefits at 24 and 48 hours. A review explored the use of cannabis and cannabinoid therapies for migraine.[23] According to their findings, authors concluded that cannabis and cannabinoid therapies can be considered an integrative treatment to add to mainstream medicine for people with migraine who are refractory to treatment and/or exhibit disability and/or interest in trying these therapies. The review also emphasized the need for more empirical evidence to guide clinical practice and patient care.

In a Colorado study of 121 adults with a primary diagnosis of migraine, the effect of treatment or prophylaxis with CM was observed.[24] Migraine fre-

quency decreased from 10.4 to 4.6 attacks per month ($p < 0.0001$). Daily use, in various forms of administration, was found to prevent headache attacks: cannabis inhalation in acute migraine had a timely analgesic effect. Fourteen patients reported undesirable consequences, including drowsiness and difficulty controlling the effects of cannabis: it was found that patients who ate cannabis were more likely to experience adverse effects. Moreover, cannabis oil from the Bediol and Bedica (Bedrocan) varieties has been shown to reduce the intensity and frequency of migraine attacks. This was reported in a Dutch retrospective study involving 44 migraine patients who were asked to fill out a questionnaire about their cannabis oil therapies.[25] The results of the questionnaire showed that following the use of cannabis oil, the overall mean frequency of migraine attacks decreased from 9 to 5.9 per month ($P = 0.008$) and the overall mean severity decreased from 8.4 to 6.4 ($P < 0.001$). In addition, other effects of cannabis were reported, including a decrease in nausea by 25.6% (11 patients), an increase in drowsiness by 37.2% (16 patients) and an increase in memory loss by 25.6% (11 patients). This analysis suggests that cannabis oil has a positive effect in decreasing nausea, which often afflicts patients during migraine attacks.

In conclusion, various trials indicate that the use of Medical Cannabis has led to a decrease in the frequency of migraine attacks. It is therefore necessary to conduct clinical studies to investigate the mechanisms of action of cannabinoids, the cause-effect relationship in order to identify the most effective varieties, formulations and doses of cannabis for maximum therapeutic effect and to minimize undesirable effects.

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3.12.1. Case Study: Cluster Headaches

Dr. Jean Claude Scicluna founded plantmedicineclinics.com from his clinic in Malta, and decided to share his practical experience with us.

Dr. Scicluna presents the case of a 31-year-old man, diagnosed with cluster headache for approximately 10 years, who decided to start cannabinoid therapy to try to improve his condition. The patient was already a recreational cannabis user before starting the therapy.

Before starting cannabinoid treatment, the man was treated with:

- calcium channel blockers;
- pure O2 for abortive relief.

Subsequently, he started a 2-week therapy with:

- CBD 10% extract in hemp oil, 50 mg three times per day.

After two weeks of treatment, THC was added. Current therapy includes:

- CBD 10% extract in hemp oil, 50 mg, three times per day;
- THC 22% flower: 0.25 g afternoon or evening not in cluster, up to 1 g throughout day during cluster headache, via inhalation;
- Melatonin, 2mg, afternoon or evening.

Only during the cluster:

- Oxygen therapy at the health center;
- Verapamil, 40-80 mg, 3 times daily, when the patient feels the cluster approaching; occasionally this treatment interrupts the headache.

After two years of cannabinoid therapy, the patient's condition had greatly improved. The patient reported that "Prior to the use of cannabis I would face around 5 clusters a year, each cluster lasting between 1-2 months, with anywhere between 1-6 attacks a day." "With the combined use of cannabis oil and cannabis flower, melatonin and rarely calcium channel blockers, they have been reduced to 1 cluster around every 2 years." "During clusters I have always found pure oxygen inhalation the most effective abortive treatment. Cluster headaches are not only about the excruciating pain, as they make one's life dysfunctional. I have found the use of cannabis very useful to counter the depression, mental exhaustion and the fear (of the next attack). Additionally, along with the melatonin, cannabis helps me get the required sleep to prepare for another day of exhaustion." Below is a summary of the treatment carried out.

Table 50.

	Patient
Age and sex:	31-year-old, male.
In therapy since:	10 year.
Diagnosis:	Cluster Headaches.
Eventual past medications:	Calcium channel blockers; Pure O2 for abortive relief.

	Patient
Current medications (type of Medical Cannabis or cannabinoids prescribed):	CBD 10% extract in hemp oil THC 22% flower: 0.25 g (afternoon or evening) not in cluster, up to 1 g throughout day during cluster headache, by inhalation; Melatonin 2 mg, afternoon or evening; During cluster only: - Oxygen therapy at health center; - Verapamil 40-80mg TDS when patient feels cluster is approaching, occasionally this aborts headache.
Starting dosage:	Oral CBD 10% extract, 50mg, 3 times a day, for 2 weeks; then start with THC therapy.
Possible corrections in dosage:	No corrections.
Length of treatment with Medical Cannabis or cannabinoids (at the time of the interview):	2 years.
Results after Medical Cannabis or cannabinoids introduction into therapy (follow-up):	Before the therapy with Medical Cannabis, the patient suffered with 5 clusters per year, each cluster lasting between 1-2 months, with 1-6 attacks per day. With the combined use of cannabis oil and flower, melatonin and rarely calcium channel blockers, clusters have been reduced to 1 around every 2 years. Patient reports that during clusters he has found pure oxygen inhalation the most effective abortive treatment and that the use of cannabis has been very useful to counter the depression, mental exhaustion and fear (of next attack); additionally, along with the melatonin, cannabis helps him get the required sleep to prepare for another day of exhaustion.
Any other consideration:	Patient was not naïve to cannabis.

Summary of the treatment of cluster headaches with Medical Cannabis, as reported by Dr. Scicluna.

3.13. The Impact of Cannabis and Cannabinoids on Sleep and Insomnia

The sedative properties of cannabis have been recognized anecdotally for centuries, with individual testimonials and scholarly accounts underscoring its potential to induce sleep. However, systematic scientific investigation into cannabis's impact on sleep and insomnia has gained momentum relatively recently.

For a comprehensive view of the effects of the Endocannabinoid System on the sleep-wake cycle, please read chapter 1.4.

Effects of Cannabis and THC

The relationship between cannabis, specifically THC, and sleep has been an area of growing scientific interest. Initial research involving both animal models and human subjects suggests that the acute administration of cannabis or THC can enhance sleep quality. This enhancement is characterized by a reduced latency to sleep onset, an increase in non-REM sleep, and a reduction in REM sleep phases. A retrospective study highlighted that cannabis could shorten the time required to fall asleep by approximately 30 minutes in individuals with insomnia and by 15 minutes in those without sleep disorders.[1] Furthermore, a 2017 survey involving over 1,500 patients at a dispensary in New England revealed that around two-thirds of the respondents reported reducing their use of traditional sleep medications in favor of medical cannabis.[2]

However, the impact of chronic cannabis use on sleep appears to diverge from its short-term effects. Long-term use may lead to tolerance, necessitating higher doses to achieve the desired sleep-promoting effects. Studies have documented a deterioration in sleep quality during withdrawal periods following chronic usage. Observations include reductions in total sleep time and sleep efficiency, along with disturbances in non-REM and REM sleep patterns. Increases in sleep onset latency, wakefulness after sleep onset, and periodic limb movements have also been reported among abstinent heavy users.[3][4]

The mechanisms through which cannabis influences the sleep-wake cycle remain to be fully elucidated. Some hypotheses suggest that cannabis may serve as a central zeitgeber, modulating biological rhythms to support regular sleep schedules. This theory posits that cannabis may not directly induce sleep but rather facilitates it by synchronizing circadian rhythms, particularly in populations with disrupted sleep patterns, such as the el-

derly.[5] Such a role suggests potential therapeutic applications of cannabis as a chronobiotic agent, although further research is necessary to clarify these effects and develop targeted treatments.

Effects of CBD

The exploration of cannabidiol (CBD) in sleep studies represents a newer avenue of research compared to the more extensive investigations into cannabis and tetrahydrocannabinol (THC). Given CBD's anxiolytic properties, there is a growing interest in its potential utility for sleep disorders.

A study from 2004 conducted in the UK on healthy volunteers distinguished the differing effects of THC and CBD on sleep. It was observed that a 15 mg dose of THC exerted a sleep-inducing effect, while an equivalent dose of CBD resulted in increased wakefulness.[6] This finding introduces the complexity of cannabinoid effects on sleep, suggesting that CBD's impact may diverge significantly from that of THC.

Further research into CBD's effects on sleep has revealed a dose-dependent relationship: lower doses of CBD may act as a stimulant, whereas higher doses appear to have sedative properties. This biphasic action of CBD introduces considerations for its application in treating sleep disorders, underscoring the importance of dosage in achieving desired outcomes.

Studies examining the combined effects of THC and CBD have yielded promising results. For instance, Sativex, an oromucosal spray containing extracts of THC and CBD, has been shown to improve sleep among patients suffering from chronic pain.[7] Additionally, a controlled clinical trial investigating the effects of 100 mg of CBD and CBD-dominant cannabis highlighted that inhalation of CBD-dominant cannabis increased subjective sleepiness.[8]

The observed sedative effects in the latter study might be attributed to the trace amounts of THC (< 0.3%) present in CBD-dominant cannabis varieties. This raises questions about whether the minimal THC concen-

tration alone could induce drowsiness or if it acts synergistically with CBD and other phytocannabinoids present in the strain used for the study. The interaction between CBD, THC, and other compounds within cannabis strains suggests a complex interplay that could influence the therapeutic potential of cannabinoids for sleep disorders. Further research is essential to unravel the specific mechanisms by which CBD and its interactions with other cannabinoids affect sleep and wakefulness.

Cannabinoids and sleep disorders

The interaction between endocannabinoids and the body's natural sleep cycles, as well as the potential benefits of plant-based cannabinoids for initiating sleep, offer promising pathways for addressing certain sleep disorders.

Cannabis and Insomnia

Insomnia involves dissatisfaction with sleep either in terms of quantity or quality, characterized by challenges in falling asleep, staying asleep during the night, or waking up too early and not being able to fall back asleep. This condition leads to significant distress or interference with daily functioning. It is estimated that over 20% of the global population experiences insomnia, with rates exceeding 40% among older adults.

The scientific literature presents mixed findings on the efficacy of cannabinoids derived from cannabis, such as THC and CBD, in treating insomnia. While anecdotal evidence from patient reports, surveys, and review articles suggests that cannabinoids may improve sleep quality, rigorous animal studies and controlled human trials have yet to conclusively demonstrate their benefits.[9] This discrepancy highlights that the effectiveness of cannabinoids on sleep might vary based on their concentration, the dosage used, and the method of administration.

Cannabis and Obstructive Sleep Apnoea

Obstructive sleep apnea (OSA) is a disorder marked by repeated interruptions in breathing during sleep, due to the total or partial blockage of the upper airways. Studies involving laboratory animals have indicated a reduction in OSA following administration of THC or the cannabinoid-like compound OEA.[10] In 2010, research involving patients highlighted the protective role of endocannabinoids, specifically OEA, against brain symptoms associated with OSA.[11] Subsequent investigations by the University of Chicago (USA) revealed that dronabinol (a synthetic form of THC) effectively diminishes OSA symptoms, with doses ranging from 2.5 to 10 mg daily.[12] Consequently, it emerges that THC, especially in its synthetic form, serves as a potential treatment in alleviating OSA symptoms.

Cannabis and REM Sleep Behavioural Disorder

REM sleep behavioural disorder is characterized by the loss of muscle paralysis that normally occurs during REM sleep, often accompanied by nightmares and physical actions related to dreaming. While research into cannabinoids' effects on this condition is scarce, a study focusing on patients with Parkinson's disease has found that CBD can reduce abnormal behaviors associated with REM sleep behavioural disorder.[13] This finding suggests CBD's potential in managing symptoms of this disorder.

Cannabis and Nightmares

Nightmares, especially those linked with post-traumatic stress disorder (PTSD), often persist as a challenging symptom to address, even as other symptoms improve. Research indicates that THC and nabilone (a synthetic form of THC) are effective in decreasing the frequency and severity of nightmares. Furthermore, they contribute to an increase in the total hours of sleep per night among participants.[14];[15]

Cannabis and Daytime Sleepiness

Excessive daytime sleepiness, a condition marked by an overwhelming urge to sleep during the day, can result from medication use, medical and psychiatric conditions, and sleep disorders like narcolepsy. Limited research in this area suggests that THC and cannabis consumption may exacerbate symptoms of excessive daytime sleepiness. On the other hand, CBD has shown promise in promoting wakefulness and countering THC's sedative effects, highlighting its potential utility in managing this condition.[16] This distinction between the effects of THC and CBD underscores the complexity of cannabis's impact on sleep and wakefulness.

Cannabis, Insomnia and the Sleep-Wake Cycle: Conclusions

The association of cannabis use with increased drowsiness is widely acknowledged, particularly for recreational purposes, as evidenced by numerous accounts throughout human history involving this plant. Yet, the precise impacts of phytocannabinoids on the sleep cycle remain to be fully understood. Cannabis and THC are known for their sedative properties, which facilitate sleep onset and likely extend the duration of non-REM sleep while reducing REM sleep. This reduction in REM sleep correlates with reports from users experiencing decreased dreaming with chronic cannabis use, a phenomenon for which the scientific explanation remains unclear.

CBD, interestingly, shows biphasic effects: low doses enhance alertness and reduce daytime sleepiness, while high doses promote sleep and contribute to a stable sleep-wake cycle.

These observations indicate the potential of cannabis and THC (including synthetic forms) in treating sleep disorders such as insomnia and obstructive sleep apnea, and of CBD in addressing excessive daytime sleepiness. However, given the mixed findings in current literature, more comprehensive research, particularly large-scale patient studies, is needed to fully establish a cannabis-based "sleep therapy."

The choice of cannabis variety is crucial, tailored to the specific sleep issue at hand. While some situations may benefit from a high THC concentration, others may require the unique or combined effects of THC and CBD, as seen with medications like Sativex®. This approach aims to address whether the goal is to mitigate excessive sleepiness or tackle a confirmed sleep disorder.

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3.13.1. Case study: Chronic Insomnia

Dr. Sandra Carrillo, a specialist in the medical application of cannabinoids, presents a detailed case of a 45-year-old patient diagnosed with chronic insomnia. This case illustrates the therapeutic benefits and adjustments involved when using medical cannabis as a treatment.

The case involves a 45-year old man diagnosed with chronic insomnia from 2022. Prior to cannabinoid therapy, the patient was prescribed multiple medications including:

- Quetiapine 50 mg/night;
- Alprazolam 1 mg/night;
- Melatonin 5 mg/night;
- Hydroxyzine 25 mg/night.

These medications were discontinued four months before starting cannabinoid therapy due to side effects.

Cannabinoid Therapy Introduction and Adjustment

Dr Carrillo started a cannabinoid therapy with a Cannabis Sativa sublingual extract (Oil), with a ratio of CBD/THC: 1:1 (24mg/ml CBD and 27 mg/ml THC). The initial dosage was: 0.1 cc, 1 hour before bedtime, increased by 0.1 cc every four days, until a dose of 0.5 cc before bedtime.

The dosage was subsequently adjusted to 0.4 cc at bedtime after the patient reported morning drowsiness. This adjustment was necessary to optimize results and minimize side effects.

Duration of Therapy and Clinical Outcomes

The treatment spanned six months, yielding significant improvements:

- sleep onset improved. Indeed, initially, it took the patient 2-4 hours to fall asleep. Post-treatment, sleep onset was reduced to 15 minutes;
- sleep maintenance was also achieved. Previously, the patient woke up around 2-3 a.m. and struggled to fall back asleep. After treatment, the patient reports uninterrupted sleep lasting 7-9 hours;
- patient also reported a significant improvement in energy levels, mood stability, and work performance;
- regarding the sleep quality, an improvement was noted with the Pittsburgh Sleep Quality Index (PSQI), which went down from 15 to 7.

Side Effects and Recommendations

Reported side effects were minimal, including dry mouth and mild dizziness, which did not necessitate any intervention. Additionally, Dr. Carrillo recommended Cognitive-Behavioral Therapy for insomnia and adherence to a sleep hygiene routine to support and extend the benefits of the treatment.

This case underscores the importance of meticulous dosage titration and monitoring within cannabinoid therapies, crucial for balancing treatment effectiveness with patient comfort, ultimately enhancing sleep quality and overall life quality.

The table below summarize the clinical case:

Table 51.

	Patient
Age & Gender	45 years old, male.
Diagnosis	Chronic Insomnia.
Date of diagnosis:	2022
Previous therapy before the use of medical cannabis or cannabinoids:	Quetiapine 50 mg /night, Alprazolam 1mg/night, (recommended by Psychiatrist) Melatonin 5mg /night, Hydroxyzine 25 mg/ night. The patient discontinued the use of Quetiapine and Alprazolam 4 months ago due to side effects.
Current therapy:	**Cannabis Sativa Sublingual Extract (Oil).** Ratio: CBD/THC 1:1 (24mg/ml CBD y 27 mg/ml de THC). Titration protocol : 0.1cc /1 hour before bed, increasing by 0.1 every four days.
Route of administration:	Sublingual
Any dosage adjustments during therapy:	We increased the dosage by 0.1 cc every four days until we reached 0.5 cc at bedtime. The patient reported feeling drowsy in the mornings at work, so we reduced the dosage to 0.4 cc, obtaining optimum results, and reduction of the drowsiness.
Length of treatment):	Patient in with Cannabinoid Therapy treatment for six months.
Follow-up :	1. The patient reported that before starting the treatment with Cannabinoid Therapies, it was hard for him to fall asleep (sleep onset), taking him approximately 2-4 hours. After six months of treatment, the patient fell asleep in 15 minutes. 2. Before treatment, the patient reported that he used to wake up at 2 or 3 a.m and had a tough time falling asleep again (sleep maintenance); after six months of treatment, the patient sleeps all night for a total of between 7 and 9 hours. 3. Before treatment, the patient reported extreme fatigue, difficulties concentrating, mood swings, and irritability during the day. After six months of treatment, the patient reports better work performance, no mood swings, more energy, better concentration and substantially improved quality of life. 4. PSQI (Pittsburg Sleep Quality Index before treatment with Cannabinoid TherapiesPSQI 15, after treatment PSQI 7. Significant improvement. 5. Reduction in polypharmacy.
Any reported side effects (type, severity, management):	Dry mouth, dizziness (mild). Patient reported no need for treatment.
Additional Considerations	It is recommended to the patient to participate in Cognitive-Behavioral Therapy for insomnia and a Sleep Hygiene Routine.

Summary of the treatment of chronic insomnia with Medical Cannabis, as reported by Dr. Carrillo.

3.14. Drug Interactions with Cannabinoids

Tetrahydrocannabinol (THC) and cannabidiol (CBD), the primary active compounds in cannabis, are primarily metabolized in the liver by the cytochrome P450 (CYP) enzyme family.[1] THC undergoes metabolism predominantly by CYP3A4 and, to a lesser extent, CYP2C9. Similarly, CBD is metabolized mainly by CYP3A4 and, to a lesser extent, by CYP2C19 and CYP2C9.
It's crucial to consider interactions with medications that either induce or inhibit these enzymes, as such interactions could modify the bioavailability of THC and CBD. Generally, THC and CBD have demonstrated a limited capacity to inhibit the activity of CYP450 enzymes, indicating a relatively low potential for causing significant drug interactions through this mechanism.
Anyway, while THC and CBD may not strongly inhibit these enzymes compared to other substances, even limited inhibition (or induction) can be clinically relevant, especially in individuals taking other medications metabolized by these pathways. This is particularly important for patients using medications with narrow therapeutic indices or those that are highly dependent on CYP450 for metabolism.

Effects of THC and CBD on other Drugs[2]

- THC increases warfarin (anticoagulant) levels and the associated risk of bleeding.
- CBD inhibits CYP2C19. When used concomitantly with clobazam (benzodiazepine), levels of the active metabolite of clobazam may increase up to threefold.
- Due to CYP2C19 inhibition, CBD should be avoided during warfarin (anticoagulant) therapy due to the increased risk of bleeding.

- Particular attention should be paid to the use of CBD with tacrolimus (immunosuppressant), as its plasma concentration may increase up to three times.
- In the case of therapy with Epidiolex® or CBD alone, it is important to consider that CBD induces a dose-dependent increase in the levels of the liver transaminases alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).[3] Liver enzyme levels should always be checked before starting CBD therapy.
- In general, patients with baseline transaminase levels above 3 times the reference limit, accompanied by bilirubin elevations above 2 times the reference level, should be carefully assessed before starting treatment with CBD.

Effects of Cannabis[2]

- Smoking cannabis increases the elimination of theophylline (bronchodilator) and possibly other drugs metabolised by CYP1A2, such as olanzapine (antipsychotic).
- Cannabis may generate additive effects when combined with sympathomimetics (induction of tachycardia, hypertension), central nervous system depressants such as alcohol and opioids (drowsiness, ataxia) and anticholinergics (tachycardia, confusion).

Drugs that modify the bioavailability of THC and CBD

Here is a summarized table outlining the primary interactions between cannabinoids and drugs:[2]

Table 52.

Pharmacokinetic interactions

Tetrahydrocannabinol (THC)		Cannabidiol (CBD)
Substrate of CYP3A4 and CYP2C9		Substrate of CYP3A4 and CYP2C19
Potential increase in THC concentration with CYP3A4 and CYP2C9 inhibitors (see below)		Potential increase in CBD concentration with CYP3A4 and CYP2C19 inhibitors (see below)
CYP3A4 inhibitors [e. g.macrolide antibiotics (clarithromycin and erythromycin only), azole antifungals, HIV protease inhibitors, diltiazem, verapamil, amiodarone].	Ketoconazole increases THC concentration nearly 2-fold. Similar interaction possible with other 3A4 inhibitors, resulting in enhanced THC psychoactive effects.	Ketoconazole increases THC concentration nearly 2-fold. Similar interaction possible with other 3A4 inhibitors, resulting in enhanced THC psychoactive effects.
CYP3A4 inducers (e.g. rifamycins, efavirenz, nevirapine, St. John's wort, carbamazepine, phenytoin, phenobarbital)	Rifampin decreases THC concentration ~20%. Similar interaction possible with other 3A4 inducers. Clinical significance unclear.	Rifampin decreases CBD concentration ~ 60%. Similar interaction possible with other 3A4 inducers. Combined use may decrease effectiveness when used for seizure disorders.
CYP3A4 substrates (e.g. alprazolam, PDE5 inhibitors (e.g. sildenafil), carbamazepine, HIV protease inhibitors, diltiazem, verapamil, fentanyl, cyclosporine, tacrolimus, sirolimus, simvastatin, atorvastatin, zopiclone)	No effect of THC on CYP3A4 substrates anticipated based on current knowledge.	CBD increases tacrolimus concentration 3-fold. Interactions with other 3A4 substrates possible. Monitoring for adverse reactions and/or selecting alternative agents recommended when clinically possible.
CYP2C9 inhibitors e.g. (sulfamethoxazole, amiodarone, metronidazole, fluconazole, voriconazole, valproic acid)	May increase THC levels, enhancing psychoactive effects.	No effects anticipated of CYP2C9 inhibitors or inducers based on current knowledge.
CYP2C9 Inducers (e.g. rifamycins, barbiturates, carbamazepine)	May decrease THC levels, attenuating psychoactive effects,	
CYP2C9 Substrates (e.g. warfarin, rosuvastatin, phenytoin)	THC may enhance levels; monitor for adverse reactions; dose reduction may be required. Cases of increased INR and bleeding with smoked marijuana.	CBD may enhance levels; monitor for adverse reactions; dose reduction may be required. Cases of increased INR and bleeding with smoked marijuana.
CYP2C19 inhibitors (e.g. cimetidine, omeprazole, esomeprazole, ticlopidine, fluconazole, fluoxetine, isoniazid)	No effects anticipated with 2C19 inhibitors, inducers or substrates, based on currently available knowledge.	Although a CYP2C19 substrate, no impact of omeprazole. Because of potential for interaction, monitor for CBD side effects.

Tetrahydrocannabinol (THC) Substrate of CYP3A4 and CYP2C9 Potential increase in THC concentration with CYP3A4 and CYP2C9 inhibitors (see below)		Cannabidiol (CBD) Substrate of CYP3A4 and CYP2C19 Potential increase in CBD concentration with CYP3A4 and CYP2C19 inhibitors (see below)
CYP2C19 inducers (e.g. barbiturates, St. John's wort, carbamazepine, rifamycins)		Similar effects possible as with 3A4 inducers.
CYP2C19 substrates [e.g. aripiprazole, clopidogrel, citalopram, diazepam, N-desmethylclobazam (nCBZ)].		CBD enhance levels of nCBZ 2- to 6-fold. Interactions with other 2C19 substrates possible. Monitor for toxicity. Because clopidogrel is activated by CYP2C19, CBD may compromise antiplatelet activity of this drug.
CYP2B6 substrates (e.g., methadone, selegiline, meperidine)	THC may enhance levels; monitor for adverse reactions; dose reduction may be required.	CBD may enhance levels; monitor for adverse reactions; dose reduction may be required.
CYP1A2 substrates e.g. (clozapine, theophylline, olanzapine)	Smoked marijuana may enhance the clearance of these drugs. Monitor for loss of efficacy with chronic marijuana use. Conversely, smoking cessation may require dose reductions of 30% and 50% of olanzapine and clozapine, respectively to avoid toxicity.	Smoked marijuana may enhance the clearance of these drugs. Monitor for loss of efficacy with chronic marijuana use. Conversely, smoking cessation may require dose reductions of 30% and 50% of olanzapine and clozapine, respectively to avoid toxicity.
P-glycoprotein substrates Substantial overlap with CYP3A4 substrates, and also includes dabigatran etexilate, digoxin and loperamide.	No effect of THC on p-glycoprotein substrates anticipated.	CBD may inhibit p-glycoprotein drug transport. Monitor for increased toxicity of substrates.
Pharmacodynamic interactions		
Central nervous system depressants (e.g. alcohol, opioids, benzodiazepine receptor agonists, tricyclic antidepressants)	Additive cognitive and psychomotor impairment.	Additive cognitive and psychomotor impairment.
Sympathomimetics (e.g. amphetamines, cocaine, noradrenergic and anticholinergic agents)	Additive tachycardia, hypertension and fluid retention.	No interaction anticipated.

Summary of the primary interactions between cannabinoids and drugs.

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3.15. **Insight:** Cannabis and Cannabigerol (CBG) against Antibiotic Resistance

Uncovering the Hidden Antibiotic Potential of Cannabis is the title of a paper published in *ACS Infectious Diseases*, the infectious diseases journal of the American Chemical Society.

Antibiotic Resistance: a Threat to Global Health

The World Health Organization (WHO), a specialized agency of the United Nations (UN) dedicated to monitoring global health status, periodically releases reports analyzing the worldwide health situation. These reports highlight potential public health risks, including the emergence or re-emergence of epidemics caused by both known and unknown pathogens. The goal is to inform and prepare world governments for potential future health crises, urging them to take proactive measures. However, these warnings, such as the one in the September 2019 Annual Report on Global Preparedness for Public Health Emergencies, which cautioned that the world was ill-prepared for a severe respiratory pandemic like COVID-19, are often overlooked.[2]

Among the pressing health issues monitored by WHO, antibiotic resistance stands out for its growing threat to global health. This phenomenon, also known as antimicrobial resistance, involves an increasing number of infections caused by bacteria, parasites, viruses, and fungi becoming difficult or impossible to treat with existing medications. The WHO explains that antimicrobial resistance occurs when microorganisms change upon exposure to antimicrobial drugs, such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics. These resistant organisms, often called superbugs, pose a significant challenge to public health.[3]

In response to this escalating threat, cannabis and its compounds, particularly phytocannabinoids, have shown promising potential as novel antimicrobial agents. Research conducted over the past decade has begun to uncover the antimicrobial properties of cannabis, suggesting its potential utility in combating antibiotic-resistant infections.

Cannabis and Antibiotic Resistance: the 'Hidden' Potential

The global surge in antimicrobial resistance is alarming, prompting the WHO to publish a list of 'priority pathogens,' which includes 12 families of bacteria posing significant threats to human health.[4] Notably, *Staphylococcus aureus*, a GRAM-positive bacterium, ranks as one of the top concerns due to its high infectivity and contribution to morbidity and mortality worldwide. The emergence of methicillin-resistant Staphylococcus aureus (MRSA), resistant to β-lactam antibiotics and others, exacerbates the challenge, particularly as 75% of the pathogens listed by WHO are GRAM-negative bacteria, which are inherently tougher to treat due to their protective cell wall absent in GRAM-positives.

Amidst this daunting scenario and the stagnation in discovering new antibiotic classes—none having been found in the last 30 years—cannabis emerges as a promising avenue for alternative treatments. A study published in *ACS Infectious Diseases* highlights this potential by evaluating

the antibacterial properties of various cannabinoids against methicillin-resistant *S. aureus*.[1] This investigation included five primary phytocannabinoids: cannabichromene (CBC), cannabidiol (CBD), cannabigerol (CBG), cannabinol (CBN), and tetrahydrocannabinol (THC)—along with their carboxyl precursors and synthetic isomers, totaling 18 molecules.

The findings reveal that all tested compounds exhibit significant antibiotic activity, with neutral phytocannabinoids showing greater potency than their acidic precursors and dimarinic derivatives. A crucial aspect of S. aureus's virulence is its biofilm formation capability, which enhances antibiotic resistance. In testing the cannabinoids' ability to inhibit biofilm formation, CBG stood out as the most effective, aligning with its potency in neutralizing dormant MRSA populations or 'persisters.' These persisters are key to the chronicity and recurrence of *S. aureus* infections, underscoring the potential of CBG and other cannabinoids as viable options in combating antibiotic-resistant bacteria.

Cannabigerol (CBG)

1. CBG, a phytocannabinoid found in cannabis in low concentrations, has garnered attention in scientific research due to its promising antibacterial properties, among other benefits. CBG stands out for several reasonsNon-psychotropic effects.
2. Easily and inexpensively synthesized in the laboratory from olivetol and geraniol, readily available compounds.
3. Tests carried out by researchers showed that CBG does not induce antimicrobial resistance against methicillin-resistant *S. aureus*.

Research has suggested that CBG's mechanism of action involves disrupting the plasma membrane of GRAM-positive bacteria, leading to their destruction. This mode of action highlights CBG's potential as a powerful antibacterial agent. Further studies, supported by bioinformatics analysis,

have validated CBG's effectiveness against antibiotic-resistant strains of S. aureus in vivo, using laboratory animals with a dose of 100 mg/kg. This evidence positions CBG as a promising tool in the arsenal against antibiotic-resistant bacteria, offering hope for new treatments that circumvent the pitfalls of current antibiotics.

Phytocannabinoids are also Effective against GRAM-negatives

Phytocannabinoids have shown promise against GRAM-negative bacteria, expanding their potential as broad-spectrum antimicrobials. While these compounds were effective against Staphylococcus aureus, a GRAM-positive bacterium, they also demonstrated activity against Escherichia coli, a prototypical GRAM-negative bacterium, albeit at higher dosages. The increased dosage requirement can be attributed to the dual layers of protection in GRAM-negative bacteria, which possess both a plasma membrane and an additional cell wall, presenting a significant barrier to many antibiotics.

To address this challenge, researchers employed a strategy to enhance the effectiveness of phytocannabinoids against GRAM-negative bacteria by using them in conjunction with polymyxin-B. Polymyxin-B acts by permeabilizing the outer cell wall of GRAM-negative bacteria, thereby facilitating the entry of phytocannabinoids. When combined with polymyxin-B, all tested phytocannabinoid compounds exhibited increased antibacterial capacity. Notably, CBG, which required a dose of 128 µg/mL to act against E. coli alone, showed effectiveness at just 1 µg/mL when used in combination with polymyxin-B.

This synergistic effect supports the hypothesis that the primary mechanism of action of phytocannabinoids involves disrupting the bacterial plasma membrane. The combination of CBG and polymyxin-B not only proved to be more potent against E. coli but also effectively inhibited the growth of other dangerous GRAM-negative pathogens, including *Acinetobacter baumannii, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. These

findings highlight the potential of phytocannabinoids, particularly CBG, as components of novel antimicrobial treatments capable of targeting a wide range of bacterial pathogens, including those resistant to conventional antibiotics.

The Therapeutic Potential of Cannabis and Phytocannabinoids

This study has revealed the extensive antibacterial capabilities of cannabinoids, spotlighting CBG's effectiveness against both GRAM-positive and GRAM-negative bacteria that are resistant to antibiotics. These findings not only underscore the potential of CBG as a powerful antimicrobial agent but also lend support to the notion that the cannabis plant may produce phytocannabinoids as a natural defense mechanism against microbial invaders. According to the researchers, this investigation reinforces the understanding that cannabinoids possess beneficial pharmacological properties for humans, a conclusion that is becoming increasingly recognized within the scientific community.

Furthermore, the study posits cannabinoids as a promising foundation for developing new medications, particularly against the backdrop of rising antibiotic resistance, a global health concern that threatens the effectiveness of existing treatments. The demonstrated broad-spectrum antibacterial activity of cannabinoids opens up new avenues for the creation of novel antimicrobial drugs, potentially offering a solution to the urgent challenge of combating antibiotic-resistant pathogens.

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3.16. Insight: Cannabis Use, Data from an American Study

A 25-year-long US study monitored cannabis use in states that have legislated in favor of medical cannabis and those where it is not yet legal. Upon comparing the data, no evidence emerged to suggest that the legalization of medical cannabis and the creation of dispensaries encourages use among young people.

Cannabis Use in Young People

Young individuals often begin using cannabis due to peer influence, a desire for experimentation, or as an act of rebellion. Despite societal changes over the past two decades, discussing cannabis or drugs in general remains a taboo in many settings, including schools, families, and social gatherings. This lack of open dialogue leaves young people with limited knowledge and understanding of the substance.

The illegal status of cannabis in many countries further restricts access to reliable information, forcing young users to navigate these challenges on their own. Consequently, they often have to rely on the illicit market, where they may encounter criminals and have no certainty about the quality or composition of the cannabis they consume. The effects of cannabis, both desired and adverse, are influenced by the concentration of active compounds like THC and CBD, the dosage, method of administration, and interaction with other substances. This uncertainty poses significant risks, underscoring the importance of informed and open conversations about cannabis use.

The Risks of Cannabis Use among Young People

Cannabis use in young people, particularly adolescents, poses significant risks primarily due to its potential impact on mental and psychological health. Adolescence is a critical period for brain development, marked by substantial synaptic and structural changes, especially in areas related to cognition, self-regulation, and emotional processing. The brain undergoes rapid growth from birth until the early twenties, characterized initially by the proliferation of new synapses, particularly in the cerebral cortex, followed by a "pruning" phase where redundant connections are eliminated, and utilized synapses are refined.[1]

Different brain regions mature at varying rates; basic functions like movement and sensory processing develop earlier in childhood, while areas involved in impulse control, strategic planning, and social behavior, such as the prefrontal cortex, mature later in adolescence. This ongoing development renders the adolescent brain particularly vulnerable to potential harm.

The psychoactive effects of cannabis are largely attributed to THC's interaction with CB1 receptors, which are densely populated in the brain. Recent research has explored whether cannabis use during this developmental phase could lead to neurological issues, such as psychosis or mood disorders, with mixed findings. Prof. Stefan Dhein of the University of Leipzig summarized these studies in a 2020 article in the journal Pharmacology, highlighting the conflicting results and the need for further research.[2]

The primary concern with early cannabis use is its potential impact on brain and cognitive functions. In susceptible individuals, it may precipitate or hasten the onset of psychosis, particularly among those with a family history of psychosis or behavioral disorders. Prof. Dhein's review emphasizes the difference in cannabis's impact on adolescents versus adults, noting that chronic use during adolescence can lead to psycho-emotional deficits and stunted personality development. However, responses vary

significantly between individuals, underscoring the necessity for further studies to identify specific risk factors that contribute to the adverse effects of cannabis use in young people.

Data on Cannabis Use among Young People

While concerns about cannabis use among young people are valid, evidence from countries with more liberal cannabis policies provides reassurance. A study conducted by researchers from John Hopkins University, Harvard University, and the Massachusetts Cannabis Control Commission analyzed data from the *Youth Risk Behavior Survey*, which included responses from over one million adolescents in grades 9 through 12, spanning from 1991 to 2015.[3]

The findings revealed no increase in adolescent cannabis use in the 30 days prior to the survey or in heavy cannabis use linked to the enactment of medical cannabis laws or the presence of operational medical cannabis dispensaries. Furthermore, the study highlighted a significant finding: adolescents residing in states with legal medical cannabis were less likely to have used cannabis in the past 30 days—6% less likely—compared to their peers in states without such laws. The effect was most pronounced among ninth graders, who were 9% less likely to have used cannabis, while no significant differences were found in other grade levels.

This data and various previous and following studies suggest that medical cannabis laws, contrary to some concerns, do not increase cannabis use among adolescents and may even contribute to lower usage rates. This finding is crucial for informing policy discussions and alleviating concerns about the impact of medical cannabis legalization on youth.

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3.17. **Insight:** THC in the treatment of Acute Respiratory Distress Syndrome (ARDS)

Acute Respiratory Distress Syndrome (ARDS) can be triggered by various causes, including bacterial toxins such as staphylococcal enterotoxin. Research indicates that tetrahydrocannabinol (THC), a prominent cannabinoid from the Cannabis Sativa L. plant, can completely prevent ARDS when it results from this specific bacterial toxin. The protective effects of THC are believed to be mediated through modifications in the microbiota. Additionally, there is potential for THC to be beneficial in treating ARDS related to COVID-19, suggesting its broader therapeutic applications in respiratory conditions.

Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS) gained significant attention during the COVID-19 pandemic as a severe manifestation of the virus. ARDS can be triggered by various agents, including staphylococcal enterotoxin B (SEB), a powerful bacterial superantigen known for its ability

to provoke intense immune reactions. SEB can induce a cytokine storm, an overwhelming release of pro-inflammatory mediators that can cause extensive, potentially irreversible damage to tissues. This phenomenon is also notably associated with severe cases of COVID-19.

The process through which SEB contributes to ARDS involves its activation of a large proportion of inflammatory cells, such as T lymphocytes, which then release a surge of cytokines leading to multi-organ damage, including the lungs. Currently, there are no specific pharmacological treatments available to shield humans from the toxic effects of SEB.

The term "microbiota" refers to the community of symbiotic microorganisms residing in and on the human body, usually without causing harm. The gut microbiota is the most extensively studied and is known to play a crucial role in various body processes, including potentially the pathogenesis of ARDS. This is because the gut microbiota produces short-chain fatty acids (SCFAs) that can have systemic effects and modulate immune responses even in distant organs.

Additionally, the microbiota is not limited to the gut but is also present in other parts of the body including the urogenital system, skin, and lungs. The influence of microbiota, particularly any changes in its composition (dysbiosis) in the gut or lungs, on the development of ARDS had not been well understood before this study. This highlights a new area of research that could offer insights into novel therapeutic strategies for managing ARDS.

The Role of THC in the Treatment of ARDS: a Study

A study conducted by Dr. Mitzi Nagarkatti and Dr. Prakash Nagarkatti at the University of South Carolina explores the role of Tetrahydrocannabinol (THC) in treating ARDS, a condition for which there are currently no FDA or EMA approved drugs.[1]

The study showed that administering THC to animals with ARDS induced by the staphylococcal enterotoxin B (SEB) led to several beneficial outcomes:

- reduced lung inflammation and immune cell infiltration;
- decreased pro-inflammatory mediators and increased anti-inflammatory cytokines in the blood;
- favorable changes in the gut and lung microbiota, including an increase in protective bacterial species and a decrease in those promoting inflammation;
- Increased production of short-chain fatty acids like propionic acid, which inhibited T-lymphocyte activation and the associated inflammatory response.

Moreover, the researchers employed fecal microbiota transplantation to further confirm THC's role. Mice receiving microbiota from THC-treated animals showed a survival rate of over 80%, indicating that THC's protective effects are mediated by changes in the microbiota. Additionally, THC was found to enhance the expression of protective genes in lung epithelial cells, contributing to a physical barrier against infection.
These findings suggest that THC not only has a direct anti-inflammatory effect but also modulates the microbiota to confer a broader protective effect against ARDS, offering promising insights for future treatment strategies.

Conclusion: is THC also useful against COVID 19?

These investigations into THC and its effects on respiratory distress syndromes have shown promising results. The study revealed that a staphylococcal enterotoxin (SEB) disrupts lung microbiota, facilitating the growth of pathogenic bacteria and triggering severe respiratory distress akin to a cytokine storm—a phenomenon also prevalent in severe COVID-19 cases, which can lead to extensive organ damage or death. The application of THC was found to counteract these effects by promoting beneficial bacte-

ria that reduce inflammation and prevent lung damage, again suggesting a potent anti-inflammatory action evoked by THC.

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CHAPTER **4.**

MEDICAL CANNABIS REGULATIONS, ACCESS AND PRODUCTS IN EUROPE

4.1. Foreword by Prohibition Partners

Education and evidence. These words are repeated in every conversation about medical cannabis by regulators, clinicians, policy advisors, and industry leaders alike. They are recognised as essential and often referred to as the next priority or the missing link. But in truth, they are too often sidelined, talked about more than acted on.

This handbook is different.

The second edition of *Principles of Clinical Cannabinology* is a clear and practical contribution to the clinical field. It builds on the strong foundation of the first edition and goes further. It translates research into understanding. It helps practitioners navigate uncertainty. And most importantly, it supports better outcomes for patients.

Prohibition Partners is proud to have played a more active role in this new edition. Across more than 40 global markets, our research has consistently shown that clinical progress depends on clarity. For clinicians to prescribe confidently and for patients to access treatment safely, we need consistent information and accessible tools. This handbook is one of the most useful resources we've seen developed to meet that need.

It covers the science of cannabinoids, the structure of the endocannabinoid system, and the key clinical principles behind prescribing cannabis-based medicines. But it also goes beyond theory. It addresses what hap-

pens in real practice. How to work with patients? What to monitor? How to adjust? Where do the regulatory systems support progress, and where do they still fall short?

The international context matters. In Ukraine, doctors and lawmakers have pushed forward in wartime conditions because the need is too great to ignore. In many European countries, access exists on paper but not in practice. Prescribers are expected to make decisions with too little information and too few resources. Patients are left waiting.

This handbook helps close that gap.

Everyone in this sector shares a responsibility to improve care. That means not just acknowledging the role of education and evidence, but making them available, consistent, and independent. This publication does exactly that. It will support clinicians, inform decision-making, and contribute to safer, more effective treatment.

We are proud to support it.

Prohibition Partners

London, 2025

Introduction

The medicinal benefits of cannabis are well-documented and acknowledged by the global scientific community for many years. Despite this, the illegal status of cannabis, primarily due to its psychoactive component THC, has significantly hindered its application in medical treatments.

Consequently, a robust discussion has been ongoing for years in numerous European countries and beyond regarding the potential medicinal use of cannabis. This debate has engaged a spectrum of stakeholders, including government bodies, regulatory agencies, law enforcement, healthcare professionals, and patients.

In response to these discussions, several European nations have enacted specific laws and initiated programs to facilitate the use of cannabis in medical therapy. These initiatives allow patients to access various forms of cannabis-based products to help manage and alleviate symptoms associated with a variety of medical conditions.

However, without a unified directive from the European Union on Medical Cannabis, individual countries have developed their own regulatory frameworks. These national laws vary widely—some adopting a more liberal approach and others maintaining stricter controls.

To comprehensively understand the legal status of Medical Cannabis across Europe, we will explore the legislative landscapes of the following countries that have embraced its medical use. Each section will detail the specific laws, the extent of access provided to patients, and any notable regulations unique to each Country.

4.2. Medical Cannabis Regulation in Belgium

Legal Framework and References

In Belgium, the regulation of Medical Cannabis is primarily governed by the Royal Decree of 11 June 2015. This foundational legal framework was further enhanced by Circular No. 648, issued by the Federal Agency for Medicines and Health Products (FAMHP) on 16 July 2019.

Scope of Use and Restrictions

According to Circular 648, the use of medical cannabis in Belgium is restricted to products containing only cannabidiol (CBD), with permissible products having only trace amounts of tetrahydrocannabinol (THC). Specifically, the circular delineates that any medical preparation is legally compliant if a patient's exposure does not exceed 1 microgram of THC per kilogram of body weight per day.

Authorized Suppliers

Post the issuance of Circular No. 648, Fagron has been designated as the sole authorized company to supply CBD isolate powder. This powder is distributed to pharmacists for use in magistral preparations, ensuring controlled and standardized dispensation of medical cannabis-based treatments under the current Belgian law.

Medical products/varieties available for prescription and routes of administration allowed

Belgium's medical cannabis landscape, as outlined in Circular 648, includes the following products:

- Sativex®: A commercially available medication used primarily for managing multiple sclerosis symptoms;

- Epidyolex®: Approved but not yet commercialized as of 2022. To address this, magistral preparations with similar compositions are often prescribed as an alternative;
- Magistral Preparations: Pharmacists prepare these custom medications using CBD powder, adhering to the stipulations of Circular 648. These preparations are permissible as long as they contain only trace amounts of THC. Available forms includOil;
- Capsules;
- Ointments.

The legal requirement for these preparations is that they must not expose the patient to more than 1 microgram of THC per kilogram of body weight per day.

Additional Access Options

- Cross-Border Prescriptions: For patients requiring THC-containing products such as flower, it is permissible to be prescribed these in Belgium and fulfill the prescription in a neighboring country, with the Netherlands being a common choice.
- Hospital and Pharmacy Collaborations: There are a few hospitals in Belgium that have established agreements with pharmacies abroad. These partnerships facilitate the provision of THC-containing oils and flowers to Belgian patients, adhering to specific regulatory frameworks.

Authorized Routes of Administration

The methods for administering these medical cannabis products are strictly regulated:

- oral: This includes forms such as oils and capsules;
- topical: Applications such as ointments, used for localized treatment.

Prescribing Medical Cannabis in Belgium

In Belgium, while the official guideline suggests that Medical Cannabis should ideally be prescribed by a neurologist, the principle of therapeutic freedom allows any physician to prescribe approved cannabis-based medicines. This flexibility is based on the belief that doctors are best placed to make informed decisions about the suitability of such treatments for their patients.

Conditions for Prescription

In particular, a treating physician may prescribe Sativex® under the following conditions:

- The physician believes the product will be beneficial for the patient;
- The patient is fully informed about the potential risks associated with the treatment and consents to proceed.

Pathologies Treatable with Medical Cannabis

Medical cannabis in Belgium is specifically approved for the following medical use:

- Moderate to severe spasticity due to Multiple Sclerosis (MS). This is the primary condition for which medical cannabis, particularly Sativex®, is prescribed. Importantly, patients diagnosed with MS experiencing moderate to severe spasticity may be eligible for reimbursement through the national healthcare system.

Broad Physician Discretion for Other Conditions

Beyond the specifically approved use, the scope for prescribing Medical Cannabis extends to technically any condition, under these circumstances:

- Physician Discretion: A doctor may prescribe medical cannabis for conditions other than MS based on their clinical judgment and the perceived benefits for the patient.

- Non-Reimbursable Prescriptions: Prescriptions for conditions other than MS spasticity are not eligible for reimbursement. This means that while physicians have the liberty to prescribe medical cannabis for various pathologies, patients must bear the full cost of these treatments.

Differences between Private and Public Healthcare System/Insurance System

Reimbursement in Private Healthcare

In Belgium's private healthcare sector, there is currently no provision for reimbursement of cannabis or cannabinoid-based medications. Patients opting for treatment in private settings must fully fund their medication, regardless of the condition being treated or the specific product prescribed.

Reimbursement Criteria in Public Healthcare

The public healthcare system in Belgium offers reimbursement for specific cannabis-based medications under tightly regulated circumstances. The criteria for reimbursement are particularly stringent to ensure that only patients who most need the treatment receive financial support. For example, Sativex® is reimbursed when:

- Specific Condition: It must be prescribed for a patient suffering from moderate to severe spasticity due to multiple sclerosis (MS).
- Lack of Response to Other Treatments: The patient must have tried and not responded to other conventional spasticity medications.
- Demonstrated Improvement: There must be documented proof of symptom improvement during a trial period to qualify for ongoing treatment.
- Specialist Prescription: The prescription must be issued by a neurologist, emphasizing the drug's specialized application.
- Hospital Pharmacy Dispensing: The medication must be dispensed by a hospital pharmacy, further controlling its distribution.

Structure of a Typical Prescription for Medical Cannabis

In Belgium, a prescription for Medical Cannabis or any other medication is meticulously structured to include essential details that ensure proper administration and compliance with healthcare regulations. Here's what a typical prescription contains:

1. Active Ingredient Specification.
   The prescription must specify the active ingredient rather than the brand name. This practice helps ensure the focus remains on the medication's active properties and not on brand preferences, facilitating generic substitutions when appropriate.
2. Quantity, Dosage, and Route of Administration.
   - Quantity: Indicates the total amount of medication prescribed.
   - Dosage: Specifies how much of the medication the patient should take per dose.
   - Route of Administration: Describes how the medication is to be taken (e.g., orally, topically).
3. Patient Identification.
   The prescription must include the National Institute for Health and Disability Insurance (NIHDI) number of the patient. This unique identifier is crucial for tracking medical prescriptions and for eligibility and reimbursement processes within the Belgian healthcare system.

Example of a Medical Cannabis Prescription Layout

Prescription:

- Active Ingredient: Cannabidiol (CBD)
- Quantity: 30 capsules
- Dosage: 1 capsule twice daily
- Route of Administration: Oral
- NIHDI Number:[Patient's NIHDI number]

How Patients Obtain Medical Cannabis in Belgium

Obtaining medical cannabis or cannabinoid-based medicines in Belgium is a straightforward process, governed by specific regulations to ensure both access and control. Here's how patients can acquire their prescribed medications.

Prescription Requirement

Patients must first obtain a valid prescription from their physician. The prescription should clearly state the active ingredient, dosage, quantity, and route of administration, along with the patient's National Institute for Health and Disability Insurance (NIHDI) number.

Dispensing Pharmacies

- Public Pharmacies: Patients can go to any public pharmacy with their prescription to obtain their medication. Public pharmacies are equipped to dispense medications like Sativex®, but it's important to note that purchasing from public pharmacies does not qualify for reimbursement.
- Hospital Pharmacies: For patients to be eligible for reimbursement when prescribed Sativex®, the medication must be dispensed by a hospital pharmacy.

Reimbursement Conditions

To receive reimbursement, the patient must not only meet the specific conditions associated with their pathology (e.g., moderate to severe spasticity due to MS) but also ensure that the medication is dispensed through a hospital pharmacy, as per the regulations set forth by the Belgian healthcare system.

Accessing Medication from Abroad

In some cases, particularly for THC-containing products not available in Belgium, patients may be prescribed these products and instructed to obtain them from pharmacies in neighboring countries like the Netherlands, under the guidance and agreement of their healthcare provider.

Average Costs of Medical Cannabis Treatments in Belgium

The price of Medical Cannabis treatments in Belgium can vary depending on the form and source of the medication. Here are the average costs for different types of cannabinoid preparations:

1. Sativex®
   - Price Range: €400 to €500 per 100ml.
   - Description: Sativex® is one of the few commercially available cannabinoid medications specifically approved for use in Belgium, typically prescribed for severe spasticity due to multiple sclerosis (MS).
2. Magistral Preparations
   - Price Range: €110 to €120 for a bottle of 10% CBD oil.
   - Description: These are pharmacist-prepared formulations made from CBD powder with trace amounts of THC, adhering to the legal requirements specified in Circular 648. These preparations are tailored to individual patient needs and are not eligible for reimbursement unless specific conditions are met.
3. Cannabis Inflorescence Imported from Neighboring Countries (e.g., Holland).
   - Price per Gram: €5.50.
   - Additional costs: Travel expenses must be considered since these products must be purchased abroad and personally transported back to Belgium.

- Description: Patients who require THC-containing cannabis flowers often have to resort to importing them from countries where such products are legally available and can be prescribed by Belgian doctors but must be obtained outside Belgium.

Considerations

It's important to note that only specific products like Sativex®, when dispensed by hospital pharmacies, are eligible for reimbursement under the public healthcare system. This can significantly affect the affordability of these treatments for patients. For patients importing cannabis inflorescence, the added travel expenses can increase the overall cost of treatment, affecting the total affordability and accessibility of these medications).

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4.3. Medical Cannabis Regulation in the Czech Republic

Legal Framework for Prescribing Medical Cannabis

In the Czech Republic, the regulation of substances that can potentially lead to addiction, including cannabis, is governed by the Act on Addictive Substances. This foundational legal framework was significantly amended in 2015 with the adoption of Decree No. 236/2015 Coll. This amendment was a pivotal move in enabling the use of medical cannabis within the country.

Key Provisions of the 2015 Amendment

- Good Practice Standards: The amendment sets forth a set of standards of good practice for the distribution of medical cannabis. These standards ensure that the process from prescription to distribution is handled with a high degree of professionalism and control.
- Prescription and Distribution Conditions: The decree outlines specific conditions under which medical cannabis can be prescribed, prepared, and distributed. This includes the use of magistral formulas—pharmacist-prepared medications tailored to the individual needs of patients.
- Definition of Medical Cannabis: According to the amendment, Medical Cannabis is defined as the dried female flowers of either the Cannabis Sativa L. or Cannabis Indica L. plants, with THC levels ranging from 0.3% to 25.0% and CBD levels not exceeding 23.0%.

Scientific Considerations

The legal distinction in the Czech Republic between Cannabis Sativa and Cannabis Indica varieties is noted in the regulations. However, it is important to mention that this distinction is considered scientifically outdated, as discussed in chapter 2.1 of this text. The ongoing scientific debate re-

flects the complexity and evolving understanding of cannabis categorization, which may affect future regulatory adjustments.

Pathologies that can be Treated with Medical Cannabis

In the Czech Republic, Medical Cannabis is approved for use in the treatment of a variety of serious medical conditions. The conditions for which medical cannabis can be prescribed include:

- Chronic Pain: This includes pain related to oncological diseases, pain associated with motor diseases, systemic and immunopathologic conditions, neuropathic pain, and pain related to glaucoma.
- Multiple Sclerosis (MS) and Spinal Cord Injury: Cannabis is used to manage spasticity that restricts movement, mobility, or breathing, and pain from these conditions.
- Involuntary Kinesis: Treatment for involuntary movements caused by underlying neurological conditions.
- Neurological Tremor, including those caused by Parkinson's disease, as well as other neurological issues as determined by the treating physician.
- Nausea and Vomiting: Medical cannabis can be prescribed to treat nausea and vomiting, as well as to stimulate appetite in patients undergoing cancer treatment or HIV therapy.
- Gilles de la Tourette Syndrome: Medical cannabis is used to manage symptoms of this neurological disorder.
- Dermatoses and Mucosal Lesions: Medical cannabis is also approved for the superficial treatment of skin and mucosal conditions.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

The Czech Republic offers a range of Medical Cannabis products tailored to suit various therapeutic needs. These include both pharmaceutical preparations and specific cannabis flower varieties.

Pharmaceutical Preparations

- Sativex®: Used specifically for the treatment of spasticity related to multiple sclerosis, particularly when other treatments have proven ineffective.
- Epidyolex®: A cannabidiol (CBD) based medicine used primarily to treat seizures associated with certain forms of epilepsy.

Flowers

- Annabis: Elkoplast 21/1;
- Aurora: Varieties include 1/12, 20/1, and 22/1;
- Pedanios: Options available are 10/10, 20/1, 22/1, and 8/8;
- 420 Pharma: Natural 20/1;
- Olikla (Tilray): Olikla 22/0.

These products are available through medical prescriptions and can be obtained in accordance with Czech regulations, ensuring that patients have access to a wide range of options for their treatment. Products from Tilray, Aurora, Canopy Growth and Bedrocan have been imported in the past, but it is unclear what the current stocks are.

In the Czech Republic, it is also possible to use domestic varieties, provided the grower has a permit from the State Institute for Drug Control.

Private individuals may also cultivate Medical Cannabis, provided they comply with the regulations.

Routes of Administration

- Oral (oil, capsule, tea, extract);
- Inhalation;
- Topical.

Who can prescribe Medical Cannabis in the Czech Republic?

Only doctors with specific specializations are authorized to prescribe medical cannabis, and even then, only for particular health indications related to their field of expertise. These specializations include:

- Oncology;
- Neurology;
- Palliative Medicine;
- Pain Treatment;
- Rheumatology;
- Orthopaedics;
- Infectious Medicine;
- Internal Medicine;
- Dermato-Venerology;
- Geriatrics;
- Psychiatry;
- Ophthalmology.

Prescription Authorization and Regulations

- Authorization Process: Specialists must apply to the State Institute for Drug Control for the authorization to prescribe medical cannabis.
- E-Prescribing: Doctors are permitted to use electronic prescribing (e-prescribing), but this is restricted to patients who are over the age of 18.
- Condition-Specific Prescriptions: Prescriptions must be targeted toward treating specific symptoms of a disease, as outlined in the relevant medical guidelines or regulations.

- Quantity Limits: The amount of dried cannabis that can be prescribed to a patient is capped at 180 grams per month.

Differences between Private and Public Healthcare System/Insurance System

In the Czech Republic, the healthcare system does not differentiate between public and private insurance schemes when it comes to the coverage of Medical Cannabis. Public health insurance covers 90% of the costs associated with Medical Cannabis for approved conditions. Insurance typically covers up to 30 grams of medical cannabis per month under normal circumstances. For cases where a higher dosage is medically justified, coverage can be extended up to 180 grams per month. However, this higher limit requires approval from an insurance doctor, ensuring that such an increase is strictly based on medical necessity.

Structure of a Typical Medical Cannabis Prescription

In the Czech Republic, Medical Cannabis prescriptions are required to be written electronically for patients who are over the age of 18. This electronic format enhances the security and accuracy of the prescribing process, ensuring that prescriptions are easily trackable and less susceptible to errors or misuse.

A typical Medical Cannabis prescription in the Czech Republic includes several critical components that specify the exact requirements for the medication, tailored to the patient's specific medical needs:

- A specific code that categorizes the Medical Cannabis into individual groups based on the cannabis species (Indica or Sativa);
- The THC and CBD content in percentage;
- Dosage and route of administration must be specified;

- The prescription must clearly indicate the active ingredient to be used. This ensures that pharmacists dispense the correct form of cannabis, whether it's a specific cannabinoid like CBD or a combination of cannabinoids.

Obtaining Medical Cannabis

Patients obtain medical cannabis through pharmacies that have established a framework agreement with the State Institute for Drug Control to dispense locally produced cannabis. Alternatively, pharmacies are allowed to procure imported medical cannabis from distributors of their choosing. Once patients receive a prescription from a specialist doctor, they can visit any pharmacy listed in the database of the State Institute for Drug Control to fulfill their prescription. Alternatively, patients have the option to designate a dedicated agent to collect their prescription from the pharmacy on their behalf.

Medical Cannabis Treatment: Average Prices

In the Czech Republic, the maximum price cap for cannabis flower is set at CZK 143.75 per gram (approximately € 5.75 per gram), excluding VAT and any pharmacy preparation surcharge. For cannabis extracts, the price is capped at CZK 1,006.25 (approximately € 40) per gram, also not including VAT and additional pharmacy fees. These price caps are established to regulate the cost and make medical cannabis accessible while ensuring that pharmacies comply with financial guidelines when dispensing these treatments.

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4.4. Medical Cannabis Regulation in Denmark

Overview of Legal Framework

In Denmark, the regulation of prescriptions, including those for cannabis-based medicines, is governed by the Danish Medicines Act of 12 December 2005. This act oversees the authorization and control of medicines and the companies that produce, store, or handle these substances. On 1 January 2018, this framework was expanded with the introduction of the Act on a Medical Cannabis Pilot Programme, offering more flexibility in prescribing cannabis products.

Ways to Prescribe Cannabis-Based Medicines

Danish law provides four primary methods for the prescription of cannabis-based medicines:

1. Authorized Drugs: Currently, Denmark has authorized the use of two cannabidiol (CBD) containing drugs: Sativex® and Epidyolex®. These drugs meet all regulatory requirements for sale and use within the country.

2. Compassionate Use Medicines: This category includes medicines containing THC, such as Nabilone and Marinol®. Although these drugs may not have marketing authorization in Denmark, physicians can request authorization from the Danish Medicines Agency for their use on compassionate grounds. Upon approval, these drugs can be imported from abroad for use by specific patients.
3. Magistral Drug Preparations: Physicians have the option to prescribe magistral preparations, which are medications prepared by a pharmacy specifically for an individual patient based on a doctor's prescription. These can include various forms of Medical Cannabis, such as capsules or oils, tailored to the patient's needs.
4. Medical Cannabis Pilot Program Products: The pilot program provides an additional pathway for doctors to prescribe other types of cannabis products not typically classified as pharmaceuticals, including herbal teas and cannabis oils.

Differences between Private and Public Healthcare System/Insurance System

Reimbursement under the Medical Cannabis Pilot Program

In Denmark, the Medical Cannabis Pilot Program includes specific provisions for the reimbursement of cannabis products used for medicinal purposes:

- Terminally ill patients: Those diagnosed with terminal illnesses are eligible to receive full reimbursement for cannabis products included in the pilot program, ensuring they have access to necessary treatments without financial burden.
- Other patients: Patients who are not terminally ill but who participate in the pilot program are eligible for a 50% subsidy on the cost of the cannabis products, capped at DKK 10,000 (approximately EUR 1,300) per year. This subsidy helps make these treatments more accessible to a broader range of patients.

Reimbursement for Non-Pilot Program Cannabis Products

Physicians can apply to the Danish Medicines Agency for single reimbursement on behalf of their patients for medicines containing cannabis or cannabis derivatives. This option is available for products such as Sativex®, Epidyolex®, magistral cannabis preparations, and cannabis-containing medicines prescribed through a compassionate use permit (including Marinol® and Nabilone). Single reimbursement is granted on an individual basis and only after all other authorized treatments for the patient's condition have been attempted. This ensures that cannabis-based treatments are considered a secondary option, pursued only when standard treatments do not yield satisfactory results.

Role of Private Insurance (Co-payment Coverage)

In addition to the public healthcare system's provisions, patients in Denmark have the option to take out private insurance to cover the co-payments of statutory drugs, including those for cannabis-based treatments. This private insurance can help reduce the financial burden on patients, particularly for those who require ongoing or costly treatments that may not be fully covered by public insurance.

Who can prescribe Medical Cannabis in Denmark?

General Prescribing Guidelines

In Denmark, the ability to prescribe Medical Cannabis varies depending on the type of product and the physician's specialization:

- Medical Cannabis Pilot Program: All doctors in Denmark are authorized to prescribe products included in the Medical Cannabis Pilot Program. However, prescribing these products is not mandatory, and physicians may choose whether or not to include these treatments as part of their practice based on their clinical judgment and patient needs.

- Magistral Cannabis Preparations: Similar to the pilot program products, all physicians are permitted to prescribe magistral cannabis preparations, which are pharmacy-prepared formulas tailored to individual patients. This also remains at the physician's discretion.

Specialization-Specific Prescriptions

- Sativex®: This specific cannabis-based medication is restricted to being prescribed only by specialists in neurology. This restriction is likely due to the medication's specific use in treating conditions like multiple sclerosis, which require specialist knowledge and management.
- Epidyolex®: Prescriptions for Epidyolex®, another specialized medication, are limited to doctors who specialize in neurology and/or paediatrics. This is particularly due to its use in treating rare forms of epilepsy that often present in children and require specialized care.

Compassionate Use and Regulatory Decisions

Marinol® and Nabilone: For these drugs, any doctor can apply for a compassionate use permit, but the Danish Medicines Agency will make a decision on each specific application.

Restrictions and Recommendations

- Unauthorized Drugs: It is not permissible in Denmark to prescribe unauthorized drugs not produced by pharmaceutical companies, even for compassionate use.
- Age Considerations: The Danish Medicines Agency advises against the treatment of individuals under the age of 18 with Medical Cannabis products.
- Treatment Justification: The Agency emphasizes that Medical Cannabis should only be considered when traditional treatments have failed.

Pathologies that can be treated with Medical Cannabis

Licensed Medical Cannabis products may be used to treat:

- Multiple sclerosis-related spasticity;
- Pain and nausea in cancer patients;
- Spasms due to spinal cord damage;
- Neuropathic pain.

The products included in the pilot program can be prescribed to any patient for any disease.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

The products that can be prescribed in Denmark are:

- Sativex®;
- Epidiolex®;
- Marinol®;
- Nabilone.

Inflorescences, as part of the pilot program:

- Bedica “CannGros” (THC: CBD 14% : 1%);
- Bediol “CannGros” (THC: CBD 6,5% : 8%);
- Bediol “Scanleaf” (THC: CBD 6,5% : 8%);
- Bedrocan “CannGros” (THC: CBD 22 %: 1%);
- Billinol “LGP” (THC: CBD 16% : 1%);
- CBD Olie “Stenocare” (20 mg/mL CBD);
- THC Olie “Stenocare” (30 mg/mL THC);
- Sedemen Aurora Nordic (capsules: THC: 5 mg + CBD 0.2 mg).

Unauthorised products may be prescribed with a permit for compassionate use. Magistral preparations (capsules and oils) can be prescribed and

prepared at Glostrup pharmacies (these products are more commonly prescribed than the products on the pilot program).

Routes of administration allowed

- Oral (capsules, tea, oil);
- Inhalation;
- Topical.

What does a Prescription look like?

A prescription for Cannabis products in Denmark follows the standard electronic format and includes:

- Patient's surname, name and date of birth;
- The date of prescription;
- The surname, first name, professional qualification, contact details (e-mail and telephone or fax number, including country code), work address (including the name of the Member State concerned) and signature (written or digital) of the doctor or dentist;
- The generic name or brand name of the prescribed product if:
  (i) the prescribed product is a biological drug, or
  (ii) the doctor or dentist considered this to be necessary; the context must be specified;
- Pharmaceutical form (e.g., tablet, solution), quantity, dosage (specified as quantity per unit dose, unit volume, or unit weight), and instructions for use (posology).

How Patients get their Medicine

Patients can obtain medical cannabis products exclusively from hospitals or pharmacies. In order to avail the prescription fee allowance, it is necessary to have an insurance card.

Medical Cannabis Treatment: Average Prices

Medical prescriptions in Denmark are not covered by the public health care system. If patients are eligible, they receive an allowance up to a certain amount and only pay part of the costs.
The average cost for cannabis products is:

- Inflorescences: approximately €20/gram;
- Oil: € 9.5 per milliliter;
- Capsules with THC content ranging from 2.5mg to 5mg: between €250 and € 300 for 60 capsules;
- Epidyolex®: € 1681.97;
- Sativex®: € 414.97.

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4.5. Medical Cannabis Regulation in France

Law References that Regulate Prescription

In France, the regulation of Medical Cannabis is currently shaped by a controlled experimental framework aimed at evaluating its medical use within a strictly regulated environment. This experiment is governed by the *Décret n° 2020-1230 du 7 octobre 2020*, which outlines the parameters for

the use of Medical Cannabis in a clinical setting. This decree sets the legal groundwork for an experimental program that allows certain patients to access Medical Cannabis treatments under closely monitored conditions. The primary aim of this program is to gather data on the effectiveness and safety of Medical Cannabis, helping health authorities decide whether it should be integrated more broadly into the French public health system. In total, 700 doctors and 1,400 pharmacists across France are taking part in this experiment.

France is set to officially authorize the use of medical cannabis starting in 2026, following the promising results of a pilot program. The trial initially involved around 3000 patients, but as of March 2025, approximately 1600 patients remain under active treatment, while others discontinued due to limited access, regional disparities, or personal choice.

According to health authorities, nearly 60% of participants in the experimental program reported a noticeable clinical benefit from medical cannabis use. These benefits included better symptom control, reduced reliance on conventional medications, and improvements in quality of life, particularly among those who had exhausted other therapeutic options. A report published by the French Directorate General of Health in November 2023 confirmed these findings, noting that 30 to 35% of patients previously in therapeutic dead-ends experienced significant improvement in symptoms and quality of life. The report also emphasized that prescription by doctors and pharmacy dispensing posed no issues, viewing medical cannabis as a medication like any other. Additionally, it stated that side effects observed during the trial were expected, with serious adverse effects affecting only about 5% of patients.

Building on these outcomes, the French government has decided to integrate medical cannabis into the national healthcare system starting in 2026. This means cannabis-derived treatments will be available by prescription and dispensed in pharmacies, with pharmaceutical-grade quality standards, clearly defined doses, and systematic medical follow-up.

Differences between Private and Public Healthcare/Insurance System

During the experimental trial of Medical Cannabis, all participating patients receive their Medical Cannabis treatments free of charge. So, there is no need for reimbursement claims or insurance coverage. Outside of the experimental program, approximately 65% of the cost of Epidyolex is reimbursed through France's social security system. For the integration of cannabis into the French healthcare system in 2026, the next step is to discuss the price of the medications and the possibilities for reimbursement with the High Authority for Health.

Guidelines for Prescribing Medical Cannabis

In France, the prescription of Medical Cannabis is strictly regulated and limited to physicians who specialize in certain medical fields. These specialists include neurologists, pain specialists, oncologists, and palliative care professionals, who are often involved in the treatment of conditions for which Medical Cannabis has been authorized. To qualify for prescribing Medical Cannabis, doctors must first undergo compulsory training specifically designed to educate them on the various aspects of using cannabis in a medical setting. After completing this training, physicians are required to register and provide a personal certificate of validation from the training in the national electronic register. This registration is a prerequisite to legally prescribing Medical Cannabis to patients, ensuring that all prescribers are adequately prepared and certified.

Pathologies for which Medical Cannabis can be Prescribed

In France, Medical Cannabis is approved for use in treating several specific medical conditions. These include neuropathic pain, which often does not respond well to conventional pain medications, and various forms of

epilepsy that are resistant to standard treatments. It is also used in oncology to alleviate symptoms such as nausea and pain associated with cancer treatments, and in palliative care to improve the quality of life for terminally ill patients. Additionally, it is prescribed for managing spasticity associated with multiple sclerosis.
Specifically, Epidyolex, a cannabis-derived medication, is approved for treating Dravet Syndrome and Lennox-Gastaut Syndrome, both of which are severe forms of childhood epilepsy. Epidyolex is also used for controlling epileptic seizures associated with tuberous sclerosis, a genetic disorder that causes non-cancerous tumors to develop in the brain and other organs.

Medical Products/Varieties available for Prescription and Permitted Routes of Administration

- In France, the products available for prescription are:LGP Classic 1/20 (1mg/ml THC; 20mg/ml CBD);
- CBD 50 LGP Classic (< 0.2mg/ml THC; 50mg/ml CBD);
- Naxiva-Panaxir T25C25 (25mg/ml of THC; 25mg/ml of CBD);
- Naxiva-Panaxir T25C0 (25mg/ml THC; 0mg/ml CBD);
- Epidyolex®.

The permitted ways of administration are:

- Oral (oil, capsule, extract);
- Inhalation via vaporisation

What does a Prescription look like?

In France, a prescription for Medical Cannabis must be renewed every 28 days. Each prescription includes specific details:

- Active ingredients: Listed by their international nonproprietary name (INN) or, if INN is unavailable, by their name in the European or French pharmacopoeia;

- Dosage clearly specified for each medication;
- Pharmaceutical form indicated for each prescribed substance;
- Route of administration;
- Duration of treatment;
- Number of packaging units;
- Number of Prescription Renewals.

Additionally, the prescription must contain personal details about the patient:

- First and last name;
- Gender;
- Date of birth;
- Height and weight.

Medical Cannabis Treatment Prices

In the context of the medical cannabis trial program in France, patients are provided Medical Cannabis free of charge during the trial period. Outside of the trial program, for approved cannabis-based medications like Epidyolex, which is used primarily for treating severe forms of epilepsy such as Dravet and Lennox-Gastaut syndromes, the cost is € 1,066.74. No indication has yet been given as to whether treatment will be covered by public health insurance under the new system in 2026.

Sources

[1] https://actu.fr/societe/ce-sont-des-medicaments-comme-les-autres-le-cannabis-medical-bientot-autorise-en-france-des-2026_62394993.html.

4.6. Medical Cannabis Regulation in Germany

Law References that Regulate Prescription

Since the 1st April 2024, the regulatory framework governing Medical Cannabis and its derivatives in Germany is defined by the Medical Cannabis Act (MedCanG), which amended the Narcotics Act (BtMG) and Narcotics Prescription Ordinance. The MedCanG removed cannabis and cannabis resin from Appendix I and Appendix III of the BtMG, which removes cannabis from the list of non-marketable and marketable prescription narcotics, thereby removing cannabis from the BtMG and no longer classifying it as a narcotic. Additionally, the changes to the Narcotics Prescription Ordinance remove the narcotic prescription requirements for cannabis, thus, cannabis is prescribed as an ordinary prescription medicine.

Differences between Private and Public Healthcare/Insurance System

Public Healthcare System Reimbursement

In Germany, patients covered under the public healthcare system may receive reimbursement for Medical Cannabis under specific conditions. Firstly, a formal application for reimbursement must be submitted and approved by the public health insurer, the patient must be suffering from a serious illness, and there are no other standard treatments or therapies available or suitable for the patient.

Moreover, there must be a reasonable expectation that Medical Cannabis will have a positive effect on the patient's condition.

If these conditions are satisfied, public health insurers are generally required to cover the costs of Medical Cannabis therapies, except in exceptional circumstances.

Despite these provisions, it's important to note that in over 30% of cases, patients covered by public insurance do not receive reimbursement.

Private Healthcare System Reimbursement

- Patients with private insurance face different challenges. Indeed, privately insured patients typically pay the full cost upfront. Subsequently, they must apply for reimbursement through their insurance provider, which requireA doctor's prescription;
- The medicine must be obtained from a pharmacy.

The therapy must be medically necessary for a specific case and either adhere to the rules of conventional medicine or be used because no conventional methods or medicines are available.
The rate of non-reimbursement is generally higher for privately insured patients compared to those insured publicly.

Guidelines for Prescribing Medical Cannabis

In Germany, all licensed doctors (except dentists and veterinarians) are authorized to prescribe Medical Cannabis. This has been facilitated by the removal of cannabis from the Narcotics Act, which has also introduced the possibility for doctors to prescribe Medical Cannabis via video consultations. This change eliminates the previous requirement for an in-person visit to assess addiction risk, thereby streamlining the process and increasing accessibility for patients.

Prescribing to Publicly Insured Patients

For patients with public health insurance, the following criteria must be met for a prescription of Medical Cannabis to be issued:

- There is no general standard therapy available for the patient's disease.
- The standard therapies available are not suitable for the patient, based on the treating physician's assessment of side effects and the patient's disease status.

- There is a reasonable expectation that Medical Cannabis will have a positive effect on the disease process or alleviate serious symptoms.

Prescribing to PrivatePatients

Private patients can receive a medical cannabis prescription if the therapy is medically justifiable for a specific health condition, and other conventional medicines are not sufficiently effective.

Pathologies for which medical Cannabis can be Prescribed

In Germany, medical cannabis can be prescribed for any pathology, provided there is adequate scientific data and justification supporting its efficacy and safety for the patient in question.
While medical cannabis may be considered for a wide range of conditions, it is most commonly prescribed for the following ailments:

- Pain;
- Spasticity;
- Anorexia;
- Epilepsy;
- ADHD;
- Gilles de la Tourettes syndrome;
- Sleep disorders;
- Anxiety and stress disorders.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

The following products are available in Germany:

- Sativex®;
- Epidolex®;
- Canemes ® (Nabilone).

As of April 2025, it is also possible to find:

- Medical Cannabis inflorescences: 900+ products on the market, of which 97% are THC dominant, 2% are balanced THC-CBD, and 1% are CBD dominant;
- Medical Cannabis Extracts: 120+ products on the market, of which 58% are THC dominant, 60% are balanced THC-CBD, and 22% are CBD dominant.

Sample List of Medical Cannabis Products and Prices in Germany

Product	Manufacturer	THC (%)	CBD (%)	Form	Price / unit (g, ml)
enua 22/1 JFG CA Jet Fuel Gelato	enua Pharma	22	0.1	Flowers	€7.5
enua 22/1 BCP CA Black Cherry Punch	enua Pharma	22	0.9	Flowers	€7.8
Bathera 24/1 Permanent Marker	Bathera	23.43	0.1	Flowers	€9.9
madrecan 21/1 MDR MAC Driver	Remexian Pharma	21	0.1	Flowers	€5.7
enua 25/1 SBD CA Strawberry Diesel	enua Pharma	25	0.1	Flowers	€10.0
enua 25/1 SC CA Strawberry Cake	enua Pharma	25	0.1	Flowers	€8.0
Bathera 21/1 Zashimi	Bathera	21	0.1	Flowers	€8.1
Drapalin 27/1 Pink Gas	Drapalin Pharma-ceuticals	27	1	Flowers	€9.5
Huala 25/1 CA ALM Alien Mints	Four 20 Pharma	25	1	Flowers	€6.0
420 Compound 27/1 GAP Gastro Pop	Four 20 Pharma	27	0.1	Flowers	€12.7
avaay Signature 28/1 WB Waffle Bites	avaay	28	0.1	Flowers	€12.0
LOT 420 GLT Gelato33	Cantourage	25	0.1	Flowers	€11.0
Bathera 25/1 BZ Blue Z	Bathera	25	1	Flowers	€9.1
IMC THC25 T04 Strawberry OG	IMC	25	0.9	Flowers	€9.0
madrecan 18/1 Granddaddy OG	Remexian Pharma	18	0.1	Flowers	€5.0
Weeco Duke 24/1 Purple Rain	Weeco	23.8	0.1	Flowers	€8.4

Product	Manufacturer	THC (%)	CBD (%)	Form	Price / unit (g, ml)
Demecan CRAFT Walkie Talkie 31:01 Sugar Cake	Demecan	31	0.1	Flowers	€13.2
420 Compound 30/1 GAP Gastro Pop	Four 20 Pharma	30	0.1	Flowers	€12.2
IMC THC22 T02 OG Kush	IMC	22	0.9	Flowers	€7.7
Pedanios 31/1 COS-CA Cosmic Cream	Aurora	31	0.1	Flowers	€11.9
avaay 23/1 RG Royal Gorilla	avaay	23	0.9	Flowers	€8.9
Bedrocan	Bedrocan	22	0.9	Flowers	€11.2
Remexian 22/1 Frosted Lemon Cake	Remexian Pharma	22	1	Flowers	€6.4
All Nations GM 104 Mac Doughnut	Cantourage	28.3	0.1	Flowers	€9.1
Ceres No. 2 25/1 Slurricane Mint	Cantourage	23	0.9	Flowers	€9.0
Barongo 24/1 Banjo	WMG Pharma	24	1	Flowers	€11.0
Remexian 14/1 White Widow	Remexian Pharma	14	1	Flowers	€9.9
420 Evolution 27/1 CA ICC Ice Cream Cake	Four 20 Pharma	27	0.9	Flowers	€13.2
Remexian 20/1 White Widow	Remexian Pharma	20	1	Flowers	€6.5
Remexian 27/1 GJY GRG Grape Galena	Remexian Pharma	27	0.1	Flowers	€9.2
Cantourage MAC 1+	Cantourage	25	0.9	Flowers	€11.8
420 Evolution 30/1 CA ICC Ice Cream Cake	Four 20 Pharma	30	0.1	Flowers	€12.4
enua 25/1 SLC CA Slurricane	enua Pharma	23.7	0.1	Flowers	€8.2
BOTANICS Purple Cream 22/1 Purple Ice Water	Nimbus Health	22	0.1	Flowers	€9.4
Cannabis 1A 16/1 White Widow	Weeco	16	0.9	Flowers	€6.0
Cannabis 1A 16/1 White Widow	Weeco	16	0.9	Flowers	€6.0
420 Evolution 30/1 CA WES Wedding Singer	Four 20 Pharma	30	0.1	Flowers	€12.2
Vasco PR PT Pave Runtz	Cantourage	24.49	0.02	Flowers	€10.3
Canopy KMI 28/1 Kush Mints	Canopy Medical	26.2	0.1	Flowers	€9.9
Demecan Typ 1 Bubba Kush	Demecan	21	0.9	Flowers	€9.5
SOMAI Cannabisextrakt Hybrid 25:1	SOMAÍ Pharmaceuticals	25	1	Extracts	€7.2
IMC Cannabisextrakt 25:1	IMC	25	1	Extracts	€7.9

Product	Manufacturer	THC (%)	CBD (%)	Form	Price / unit (g, ml)
SOMAI Cannabisextrakt Hybrid 10:10	SOMAÍ Pharmaceuticals	10	10	Extracts	€5.7
Farmako 100 (Cannabisextrakt)	Farmako	100	0	Extracts	€3.3
Cannamedical Cannabisextrakt THC5:CBD20 Tangie Chem	Cannamedical	5	20	Extracts	€7.0
Grünhorn Cannabisextrakt Hybrid 50:1	Grünhorn	50	1	Extracts	€4.0
SOMAI Cannabisextrakt Hybrid 25:25	SOMAÍ Pharmaceuticals	25	25	Extracts	€10.5
Sinceritas 10/10	Cannamedical	10	10	Extracts	€8.0
Cannamedical Hybrid Cannabisextrakt THC25:CBD25	Cannamedical	25	25	Extracts	€9.1
Cannamedical Cannabisextrakt THC12,5:CBD12,5 Strawberry Ice	Cannamedical	12.5	12.5	Extracts	€9.0

Source: Prohibition Partners.

* The prices in this table refer to the prices of privately prescribed Medical Cannabis and do not include a fee of 4.26 EUR per purchased cannabis variety.

The routes of administration allowed in Germany are:

- Oral (oil, capsule, extract, tincture);
- Inhalation (vapourisation).

What does a Prescription look like?

In Germany, medical cannabis can be prescribed using either a normal pink prescription for public insurance beneficiaries or a blue prescription for private payers. With the advancement of technology, these prescriptions are often issued as e-prescriptions, simplifying the process and enhancing security. Notably, a narcotics prescription is no longer required for medical cannabis. Insured patient prescriptions are valid for a month, while privately paid prescriptions are valid for three months.

Required Information on the Prescription

A standard medical cannabis prescription in Germany includes the following essential details:

- The first and last name of the patient along with their address;
- The full name of the doctor issuing the prescription and the specific medical specialization of the doctor, such as a specialist in general medicine, neurology, etc.;
- Doctor's Signature (handwritten signature or qualified electronic signature for e-prescriptions);
- The name and exact amount of the medicine prescribed.

While not explicitly listed in the basic requirements, including the form (e.g., oil, capsule) and dosage instructions can aid pharmacists and patients in correct usage.

The date on which the prescription was officially issued, which is critical for tracking and validity purposes).

When an insured patient receives a prescription for cannabis or its derivatives for the first time, he or she must obtain approval from his or her health insurance company (it can only be refused in special cases). Afterwards, the patient can go to an authorized pharmacy.

Pricing and Co-payment Details for Medical Cannabis

In Germany, the average prices for Medical Cannabis products prescribed to private patients as of April 2025 are:

- Flower: € 9.17 per gram;
- Oil: € 11.99 per milliliter.

These prices represent the typical cost to patients before any insurance contributions are applied, and they can vary based on the specific product and quantity prescribed.

Co-payment for Insured Patients

For patients with health insurance, the financial burden is significantly alleviated through the co-payment system:

- Insured patients are required to pay a co-payment for their medical cannabis prescriptions, which is 10% of the total medication cost.
- The minimum amount payable by the patient is set at €5, regardless of the total cost of the prescription.
- The maximum co-payment amount is capped at €10, ensuring that patients do not face excessive out-of-pocket expenses for their prescribed cannabis treatments.

Sources

[1] Prohibition Partners, *The German Cannabis Report* 2024.

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4.7. Medical Cannabis Regulation in Greece

Legal Framework

The regulatory landscape for Medical Cannabis in Greece has undergone significant changes in recent years, reflecting a broader shift towards recognizing and integrating cannabis for medical purposes. The legal framework governing Medical Cannabis is delineated by several key pieces of legislation that aim to control its use while making it accessible for medical purposes.

Key Legislation and Developments

- Law no. 4139/2013—Law on Addictive Substances and Other Provisions: This foundational law set the groundwork for the regulation of various substances, including narcotics, within Greece. Initially, cannabis was listed under a schedule that restricted its use heavily.
- In June 2017, a pivotal change occurred when Medical Cannabis was legalized through a joint Ministerial Decision by the Ministry of Health and the Ministry of Justice, Transparency, and Human Rights. This decision was published in the Government Gazette (Issue Two 2238/2017).
- The change involved rescheduling cannabis and cannabis resin from Table A (which includes strictly controlled substances) to Table B of the tables of narcotic substances outlined in Law 3459/2013, as amended by Law 4139/2013. This rescheduling marked a significant step, reducing the restrictions on cannabis to facilitate its medical use.
- Law 4523/2019—The Provisions for the Production and Trade of Cannabis Products for Medical Use: Passed in 2018, this law established a comprehensive regulatory framework for the cultivation, production, and distribution of Medical Cannabis products in Greece. It also

set the guidelines for providing related licenses, which are necessary for businesses to legally cultivate and distribute Medical Cannabis. The law's enactment has not only legalized but also regulated the Medical Cannabis industry, ensuring that all products meet strict safety and quality standards before they reach patients.

Differences between Private and Public Healthcare/Insurance System

Both the public and private healthcare systems in Greece typically do not offer reimbursement for Medical Cannabis. Sativex stands as an exception in the context of reimbursement. Patients or their healthcare providers can apply for reimbursement for Sativex through Greece's Electronic Pre-Authorization System (EPS). The process involves a detailed review of the patient's medical condition and the expected benefits of using Sativex as opposed to other less costly treatments. If the application is successful, the cost of Sativex may be covered partially or fully, depending on the specifics of the public or private insurance policy under which the patient is covered.

Who can prescribe Medical Cannabis?

The initial prescription of Medical Cannabis can only be issued by specialist doctors with specific qualifications. These specialists include:

- Anaesthesiology;
- Neurology;
- Pathologist-Oncologist;
- Pathologist-Infectiology;
- Rheumatology.

After the initial prescription by a specialist, follow-up prescriptions can be provided by other doctors, however, these prescriptions are subject to review. Follow-up prescriptions can be issued every six months and the

treatment must be re-evaluated periodically by a specialist to confirm its ongoing necessity and effectiveness.
A prescription for Medical Cannabis may only be considered if the use of already approved and established drugs has been found to be unfeasible, intolerable, or ineffective for the patient.

Pathologies Treatable with Medical Cannabis

The approved treatable pathologies include:

- Prevention and treatment of severe nausea or vomiting from chemotherapy, radiotherapy and combination therapy against HIV or hepatitis C;
- Treatment of chronic pain, related to cancer or diseases of the central or peripheral nervous system, such as neuropathic pain caused by: nerve damage, “phantom limb,” trigeminal neuralgia, postherpetic neuralgia;
- Treatment of spasticity associated with multiple sclerosis or spinal cord injuries;
- As an appetite stimulant in the palliative care of patients undergoing treatments for cancer or acquired immune deficiency (AIDS).

Approved Cannabis-based Medicines and Products in Greece

As of April 2025, the approved products are:

- Sativex®;
- Epidyolex®.

Dried Flower

- Avidekel THC 18.5% CBD<1% (Tikun Olam);
- Davikel THC 18.5% CBD<1% (Tikun Olam);
- Midnight THC 9% CBD 13% (Tikun Olam).

The way of administration allowed are:

- Oral Spray (Sativex);
- Oral Syringes (Epidyolex).

Dried Flower

- Inhalation via medically approved vaporization device.

Obtaining Medical Cannabis

In Greece, the process of prescribing Medical Cannabis, particularly for products like Sativex, involves a structured and detailed protocol. Here is a breakdown of how a Medical Cannabis prescription is structured and processed.

Electronic Prescription:

- *Format*: Medical Cannabis prescriptions, including for medical flower, are issued electronically. This method ensures accuracy and traceability.
- *Included Details*: The prescription must include the product name, dosage, and patient's ID details.
- *Record Keeping*: Doctors are required to print a copy of each Medical Cannabis prescription and retain it for three years from its registration date for compliance and audit purposes.

Special Case: Prescription and Reimbursement Process for Sativex

Initial Application for Compensation:

- The treating physician must fill out an application for Sativex compensation and send it to the EOPYY (Greek National Organization for Healthcare Services Provision).
- It typically takes a week for the EOPYY Board of Directors to review and either approve or reject the application.

Approval and Documentation:

- Upon approval, the doctor prints out the approval notice and attaches the Medical Opinion from the IFET (Institute of Pharmaceutical Research and Technology).
- The patient receives these documents and is required to take them to an ordinary pharmacy.

Pharmacy Process:

- The pharmacist completes the IFET "Application for Individual Drug Order" and submits all the necessary documents together to the EOF (National Organization for Medicines).
- If the EOF approves the application, the file is forwarded to the IFET.

Medicine Procurement and Reimbursement:

- IFET delivers the medicine to the pharmacy.
- The pharmacist then pays for the medicine and claims reimbursement from EOPYY.
- The patient is informed by the pharmacist that the medicine is ready for collection.

Final Prescription Issuance:

- The patient returns to their doctor, who must issue an electronic prescription categorized as "drugs via IFET." This prescription must also be printed out.
- Simultaneously, the doctor issues a handwritten prescription marked with a double red line.

Collection of Medicine:

- The patient presents both the printed electronic prescription and the handwritten two-line prescription at the pharmacy.
- The pharmacy then dispenses the medication accordingly.

Medical Cannabis Treatment Prices

Here's a summary of the costs (updated to April 2025) for several commonly prescribed Medical Cannabis products:

- Sativex: € 565.55;
- Epidyolex: € 1,099.37;
- Flower: € 15.1-€ 16.6/gram.

Sources

[1] Prohibition Partners 2025.

[2] Tikun Olam.

4.8. Medical Cannabis Regulation in Ireland

Legal Framework

Prior to significant regulatory changes in 2017, patients in Ireland required specific written authorization from the Department of Health to use cannabis products for medical purposes, as mandated by the Misuse of Drugs Act. This process was both cumbersome and restrictive, limiting access for many patients in need.

Recognizing the need for a more structured and accessible framework, Ireland introduced the Medical Cannabis Access Program in 2017, which officially began as a five-year pilot program in 2019. This initiative marked a pivotal shift in the country's approach to medical cannabis, aiming to facilitate better access under regulated conditions.

The operational details of this program are outlined in the Misuse of Drugs Regulations (Prescription and Control of the Supply of Cannabis for Medical Use) of 2019. These regulations specifically allow for:

- Import: Legal importation of approved cannabis products into Ireland;

- Prescription and Supply: Authorized prescription and supply of cannabis products listed as 'specified controlled drugs,' which are included in Schedule 1 of the Misuse of Drugs Regulation.

To be considered for inclusion in Schedule 1, cannabis products or preparations must meet stringent criteria set forth in the regulations. An amendment in 2021 (S.I. No. 577 of 2021) further updated and expanded the list of products contained in Schedule 1, reflecting ongoing adjustments to the regulatory framework based on new evidence and therapeutic needs.

Current Access Routes to Medical Cannabis

There are currently three primary avenues through which patients can access medical cannabis products in Ireland:

- Ministerial Approval: This route remains for exceptional cases where patients require specific types of cannabis products not generally permitted under the regular frameworks.
- Pharmaceutical Grade Cannabis Products: Products such as Sativex® and Epidyolex® are approved for use but are generally underutilized due to reimbursement challenges. These products are specifically approved for a limited range of conditions and have stringent prescribing and reimbursement criteria.
- Medical Cannabis Access Program: This program provides a structured pathway for patients to obtain cannabis products that have been rigorously assessed and approved under Irish law, ensuring safety, efficacy, and controlled distribution.

Differences between Private and Public Healthcare/Insurance Systems

In Ireland, the reimbursement of Medical Cannabis products is contingent upon several factors, including the route through which the cannabis is accessed and the type of healthcare coverage a patient holds. Here's a closer look at how these factors influence reimbursement.

Ministerial Approval Route

Patients who receive Medical Cannabis under ministerial approval are granted automatic reimbursement. This ensures that those granted access through this exceptional approval process do not face financial barriers to obtaining their prescribed cannabis products.

Medical Cannabis Access Programme

Reimbursement under the Medical Cannabis Access Programme is not automatic. It is determined on a case-by-case basis and is typically available only to patients who are part of specific health schemes:

- Medical Card Holders: Patients with a Medical Card, which provides access to health services for those who cannot afford them due to financial reasons, are eligible for reimbursement.
- Long Term Illness Scheme: This scheme covers patients with certain conditions that require prolonged treatment, including the use of medical cannabis, if applicable.
- Drugs Payment Scheme: Under this scheme, a cap is placed on the monthly cost that families and individuals have to pay for approved drugs, including medical cannabis, once it is covered under the scheme.

Licensed Products

Despite being regulated and approved, products like Epidiolex® face significant hurdles in receiving reimbursement. The Irish Health Services Executive (HSE) does not recommend these products for reimbursement, which means that patients prescribed with such treatments often have to bear the full cost unless other specific approval or coverage conditions are met.

Who can prescribe Medical Cannabis in Ireland?

Ministerial Approval Process

For patients seeking access to Medical Cannabis through ministerial approval, only medical specialists are authorized to prescribe or recommend its use. These recommendations can then be used by the patient's personal General Practitioner (GP) to continue management. While GPs themselves cannot initiate a Medical Cannabis prescription under this route, they play a crucial role in managing the ongoing treatment after a specialist's recommendation.

Medical Cannabis Access Program

Under the Medical Cannabis Access Program, the authority to prescribe Medical Cannabis is restricted to medical specialists. These specialists must first register with the Health Service Executive (HSE) to access a dedicated HSE portal for managing Medical Cannabis prescriptions.

Specialists must also register their patients within this system. The approval of this registration is a prerequisite before any prescriptions can be issued.

To be eligible to prescribe under this program, specialists must demonstrate a clear rationale for using Medical Cannabis, indicating that it is intended for patients whose standard therapies have not yielded effective results.

Reimbursement Requirements

It is a fundamental requirement that treatment with Medical Cannabis may only be initiated after standard therapies have been proven ineffective. This stipulation is critical not only to ensure the prudent use of Medical Cannabis but also to qualify for reimbursement under Irish healthcare schemes.

Pathologies Treatable with Medical Cannabis

The Medical Cannabis Access Program in Ireland allows for the prescription of Medical Cannabis products, but only for specific, well-defined medical conditions. The Irish Minister of Health has approved the use of Medical Cannabis under this program for patients who have not found relief through standard treatments. The conditions specified include:

- Spasticity associated with Multiple Sclerosis;
- Intractable nausea and vomiting;
- Severe and refractory epilepsy.

Conditions Under Ministerial Authorization

Unlike the Medical Cannabis Access Program, the ministerial authorization process allows for the potential treatment of any condition with Medical Cannabis, subject to approval. This process is generally reserved for exceptional cases where conventional treatments have failed, and where the prescribing specialist can provide a strong justification for the use of Medical Cannabis.

Approved Cannabis-Based Medicines and Products in Ireland

In Ireland, the regulatory framework for Medical Cannabis includes specific approvals for a limited number of cannabis-based medicines, ensuring that patients receive treatments that meet rigorous safety and efficacy standards. The following medicines are currently approved:

- Sativex®;
- Epidyolex®;
- Nabilone.

Additionally, several manufacturers have received authorization to provide their Medical Cannabis products through the Medical Cannabis Access

Program. These authorized products include:

- Aurora High CBD Oil Drops (600 mg/ml);
- CannEpil (5 mg/ml);
- Tilray Oral Solution THC:CBD, 10:10, 25mL;
- Aurora Sedamen Softgels (THC:CBD 5:0.2);
- Oleo Bedrobinol, Dried Flowers (THC:CBD 13.5:<1);
- Oleo Bedrocan, Dried Flowers (THC:CBD 22:<1).

Permitted Routes of Administration:

- Oral;
- Inhalation.

Structure of a Medical Cannabis Prescription in Ireland

Ministerial Approval Process

For patients needing access to Medical Cannabis via ministerial approval, the prescription process is quite specific and regulated. The prescribing doctor must prepare a comprehensive application to be sent to the Ministry of Health, which includes several critical elements:

- A detailed account of the treatments the patient has received thus far, providing a clear medical history relevant to the application.
- The doctor's rationale, explaining why, in the patient's specific circumstances, prescribing Medical Cannabis is deemed appropriate and necessary.
- Comprehensive information about the specific Medical Cannabis product intended to be prescribed, including its form and dosage.
- Information about where and how the Medical Cannabis product is sourced or manufactured.
- A plan outlining how the patient will be monitored and cared for after beginning Medical Cannabis treatment, ensuring ongoing evaluation and safety.

Access Through the Medical Cannabis Access Program

For patients accessing Medical Cannabis through the Medical Cannabis Access Program, the procedure involves several steps:

- The patient must first be registered by their physician on the Health Service Executive (HSE) portal. This step is crucial for maintaining a controlled and monitored access pathway.
- Once the patient is registered and approved via the HSE portal, the medical specialist can then issue the prescription. This prescription will detail the specific Medical Cannabis product to be used, along with the dosage and administration instructions.

How Patients Obtain their Medicine

In Ireland, patients prescribed Medical Cannabis can obtain their medication from any pharmacy that is authorized to dispense cannabis-related medicines. Pharmacies play a critical role in maintaining the control and quality assurance of these medications, aligning with national healthcare standards. Additionally, there is an alternative method for obtaining Medical Cannabis that was established during the pandemic and continues to be a viable option. Patients can have their prescribed Medical Cannabis products delivered directly from the Netherlands, under a system designed for products prescribed with a ministerial license. This method was initially developed to ensure patient access during restrictions on movement and has proved beneficial for those who may find pharmacy access challenging or prefer the convenience of direct delivery.

Medical Cannabis Treatment: Average Prices

In Ireland, the pricing for Medical Cannabis products is not standardized, which means there are no fixed prices across the board. The cost of these products can vary based on several factors, including the type of product, the manufacturer, and the dispensing pharmacy.

While prices vary, there are provisions for reimbursement under specific circumstances, particularly for patients accessing Medical Cannabis through the Medical Cannabis Access Program. Patients with approved medical conditions who are enrolled in this program may receive reimbursement for their Medical Cannabis treatments, alleviating some of the financial burden associated with these therapies.

Despite the availability of pharmaceutical grade Medical Cannabis products like Sativex®, Epidyolex®, and Nabilone, these are often challenging to get reimbursed by the Irish Health Services Executive (HSE).

Sources

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[3] https://www2.hse.ie/services/schemes-allowances/medical-cannabis-products-reimbursement-scheme/.

[4] https://prohibitionpartners.com/2021/07/23/medical-cannabis-access-progresses-in-ireland/.

[5] 'Clinical Guidance on Cannabis for Medical Use' from Department of Health Ireland, Department of Health MCAP document.

4.9. Medical Cannabis Regulation in Italy

Legal Framework

Italy's approach to Medical Cannabis has evolved significantly over the years. The initial regulatory framework was established with Decree No. 98 on April 28, 2007, which marked a pivotal shift in the legal status of THC and its homologues by moving them to Table 2, section B, of narcotic

drugs. This classification acknowledged the therapeutic potential of these substances and set the stage for further legislative advancements.
Further detailing the regulatory landscape, the Ministerial Decree of November 9, 2015, provided a structured approach to the cultivation, production, possession, and use of Medical Cannabis. This decree is crucial as it outlines the specific authorizations required at various stages of Medical Cannabis handling and use, establishing a controlled system to ensure the quality and safety of Medical Cannabis products. One of the unique aspects of Medical Cannabis regulation in Italy is the decentralized implementation approach. While the Ministerial Decree sets the framework at a national level, the actual execution of these regulations is the responsibility of the individual Regional Health Systems. This means that there can be noticeable differences in how Medical Cannabis is accessed and managed from one region to another. Such variability can affect the availability of products, the process for obtaining prescriptions, and the administration of Medical Cannabis programs across different parts of the Country.

Differences between Private and Public Healthcare/Insurance Systems

In Italy, the reimbursement of Medical Cannabis costs varies significantly between the private and public healthcare systems:

- *Private Healthcare System*: When a prescription for Medical Cannabis is issued privately, patients must bear the full cost. There is no reimbursement available, placing the financial burden directly on the individual. This can make access to Medical Cannabis treatments less feasible for those without sufficient financial resources.
- *Public Healthcare System*: Reimbursement is possible through the public healthcare system, but it is contingent on several factors. Patients can receive coverage for their Medical Cannabis prescriptions if the treatment is for specific pathologies recognized by their regional health authority.

Italy's decentralized health system means that there is considerable variation across different regions regarding the reimbursement of Medical Cannabis. Each region in Italy may have a different list of specific pathologies that qualify for Medical Cannabis reimbursement. This means a condition eligible for reimbursement in one region might not be covered in another. There are also regional differences concerning the types of Medical Cannabis preparations and varieties that are eligible for reimbursement. Some regions might approve a broader range of products, while others might restrict reimbursement to certain forms or varieties of Medical Cannabis.

Who can prescribe Medical Cannabis in Italy?

In Italy, the authority to prescribe Medical Cannabis varies significantly between regions due to the decentralized nature of healthcare regulation. Each region independently determines the specific qualifications and permissions required for doctors to prescribe Medical Cannabis that is eligible for reimbursed therapy. In general, any doctor who is registered with the professional association and licensed to practice in Italy can prescribe Medical Cannabis privately. This means that while any doctor can issue a prescription for Medical Cannabis, the ability to have such prescriptions reimbursed by the public healthcare system depends on additional regional criteria and approvals.

Pathologies Eligible for Medical Cannabis Prescription

The Italian Ministry of Health has defined specific pathologies for which Medical Cannabis treatments can be reimbursed when prescribed within the public healthcare system.
These conditions are identified based on evidence of efficacy and the necessity for alternative treatments when conventional methods fail. The recognized conditions include:

- Analgesia in chronic pain (with particular reference to neurogenic pain), where treatment with non-steroidal anti-inflammatory or cortisone or opioid drugs has proved ineffective;
- Antiemetic effect in nausea and vomiting caused by chemotherapy, radiotherapy, HIV therapies, which cannot be achieved by conventional treatments;
- Appetite-stimulating effect in cachexia, anorexia, loss of appetite in cancer or AIDS patients and in anorexia nervosa;
- Hypotensive effect in glaucoma;
- Reduction of involuntary body and facial movements in Gilles de la Tourette syndrome.

Beyond the public healthcare system, any physician in Italy can prescribe Medical Cannabis for any pathology, provided there is accredited scientific support for its use or when conventional therapies have not yielded expected results or have led to drug resistance. However, it is important to note that such prescriptions are at the expense of the patient, as they do not qualify for public reimbursement.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

In Italy, the only products that may be used for the preparation of compounded cannabis preparations are those exported by the Office for Medicinal Cannabis of the Dutch Ministry of Health, Welfare and Sport. In addition to these varieties, there are those produced by the Military Establishment in Florence and those imported through ministerial tenders. The available varieties as of May 2025 are:

- Bedrocan (THC:CBD 22: <1);
- Bediol (THC:CBD 6,5: 8);
- Bedrolite (THC:CBD <1:9);
- Bedica (THC:CBD 14: <1);

- FM2 (THC:CBD 7: 10);
- Linneo (THC:CBD 17-26%:< 1%).

In Italian pharmacies, ready-made cannabis extracts (oils) are also available. As of May 2025, the extracts available in Italian pharmacies are:

Tilray/FL Group Extracts

- Standardized Cannabis Plant Extract with 25 mg/mL THC;
- Standardized Cannabis Plant Extract with 10 mg/mL THC and 10 mg/mL CBD;
- Standardized Cannabis Plant Extract with 5 mg/mL THC and 20 mg/mL CBD.

Farmalabor Extracts

- Cannabis Extract with 15% THC (THC 150 mg/mL, CBD < 1%);
- Cannabis Extract with 5% CBD (THC < 0.5%, CBD 50mg/mL);
- Cannabis Extract with 2.5% THC (THC 25 mg/mL, CBD < 1%);
- Cannabis Extract with 2% THC (THC 20 mg/mL, CBD < 1%);
- Cannabis Extract with 1% THC (THC 10 mg/mL, CBD < 1%);
- Cannabis Extract with 1% THC and 1% CBD (THC 10 mg/mL, CBD 10 mg/mL).

Avextra/Fagron Extract

- Cannabis Extract with 1% THC and 1% CBD (THC 10 mg/mL, CBD 10 mg/mL).

The only licensed drug available on the Italian market is Sativex®. Upon medical request it is also possible to obtain Epidyolex® and Nabilone.
The permitted routes of administration are:

- Oral;
- Inhalation;
- Topical.

What does a Prescription look like?

In Italy, the process and structure of a Medical Cannabis prescription can vary by region, reflecting localized healthcare practices and regulations. Despite these regional differences, there are consistent elements across the country that must be included in every Medical Cannabis prescription:

- Patient's Informed Consent;
- Non-Repeatable Prescription: According to Law 94/98, a Medical Cannabis prescription is non-repeatable and is valid for a maximum of 30 days;
- Age and Gender;
- Specifics on the dosage, frequency, and duration of the treatment must be included to tailor the therapy to individual needs and to facilitate outcome monitoring;
- Expected or achieved outcomes should be noted to assess the effectiveness and adjust future prescriptions as needed;
- Each prescription must include a unique numeric or alphanumeric code assigned to the patient, safeguarding their anonymity while allowing for accurate tracking and data collection.

Beyond the prescription itself, the prescribing physician is required to complete a data collection form. This form collects detailed information about the treatment and patient outcomes for statistical purposes. The completed data collection form must be submitted to the Istituto Superiore di Sanità (Italian National Institute of Health), contributing to national statistics and research on the use of Medical Cannabis.

How Patients get their Medicine

In Italy, the process for patients to obtain their Medical Cannabis therapy involves visiting an authorized dispensing pharmacy in person. Depending

on the specific regulations of each Italian region, Medical Cannabis may be dispensed not only in hospital pharmacies but also in public and private pharmacies that are authorized to handle such products. In some regions, both public and private pharmacies can dispense Medical Cannabis. However, these pharmacies must meet specific regulatory requirements to ensure safe and appropriate handling of the products. Indeed, any dispensing pharmacy in Italy must have a laboratory dedicated to the compounding of Medical Cannabis preparations. There is a mandatory requirement for pharmacies to analyze each compounded Medical Cannabis product. If the Medical Cannabis is intended for inhalation, the analysis requirement may differ, focusing on ensuring the product's safety and efficacy without the need for compounding.

Medical Cannabis Treatment: Average Prices

In Italy, the pricing for Medical Cannabis, specifically for the inflorescences, is regulated and standardized across the country. The price is legally set at € 9 per gram, excluding VAT. This regulated pricing helps maintain consistency and affordability for patients who require Medical Cannabis for therapeutic purposes. For compounded Medical Cannabis preparations, such as oils or extracts, additional costs are incurred beyond the base price of the raw cannabis, such as compounding costs, narcotic taxes, compulsory analytics, with average costs of dispensed 10% extracts at 250 €. Therapies involving Medical Cannabis can be reimbursed up to 95% of the total cost, significantly reducing the financial burden on patients.

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4.10. Medical Cannabis Regulation in Malta

Legislative Framework

In Malta, the regulation of Medical Cannabis is governed by the Drug Dependence (Treatment not Imprisonment) Act, established in 2015 and amended in 2018. This act reflects Malta's progressive stance on providing patients with alternative treatments while ensuring stringent regulatory oversight.

Key Provisions of the Law

Under the amended law, only licensed medical practitioners who are duly registered under the Health Care Professions Act of 2003 are authorized to prescribe Medicinal Cannabis preparations. A practitioner may prescribe Medicinal Cannabis if it is determined that there is no viable alternative to such prescription. This decision must consider existing protocols for prescribing medicines, the interests of the patient, and the cost implications. Importantly, the legislation specifies that none of the Medicinal Cannabis preparations may be indicated for smoking or any form intended for smoking. This restriction aims to mitigate health risks associated with smoking, aligning with public health objectives. Physicians must prescribe cannabis preparations on a named basis, adhering to the instructions of the Superintendent of Public Health.

Importing and Dispensing Medical Cannabis

The dispensation of Medicinal Cannabis preparations is restricted to pharmacists operating from an authorized pharmacy. Only authorized wholesalers or manufacturers can import Medicinal Cannabis preparations. This regulation helps maintain the quality and compliance of imported Medical Cannabis products with Malta's pharmaceutical standards and Good Manufacturing Practices.

Differences between Private and Public Healthcare/Insurance Systems

Medications prescribed by a physician typically aren't covered for reimbursement, except in instances of hospitalization and for up to three days post-discharge. Patients, unless qualifying due to low income or chronic conditions, are generally responsible for covering prescription costs out of pocket.

Who can prescribe Medical Cannabis in Malta?

Licensed physicians have the authority to prescribe Medical Cannabis products if they determine there are no viable alternatives. However, Medical Cannabis treatments are only pursued after exhausting all other therapeutic options. To initiate a prescription, doctors must submit a request to the Superintendent of Public Health.

Pathologies that can be Treated with Medical Cannabis

Treatable pathologies are:

- Multiple Sclerosis;
- Chronic pain;
- Chemotherapy side effects;
- Any 'debilitating conditions,' although these are not well specified.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

Cannabinoid products that can be used in Malta are:

- Sativex®;
- Epidyolex®.

Dried Flower:

- Aphria 20/1, Variety Henik;
- Aphria 22/1;
- Aurora 20/1;
- Aurora 22/1;
- Bediol;
- Bedrocan;
- Cannabis 1A 18/1;
- WEECO 25/1;
- Carbasi Verde;
- Pedanios 8/8;
- Pedanios 20/1;
- Pedanios 22/1;
- Salus Biopharma Medical Cannabis Flower;
- ZeraMed ZeraUltra s22:0.

Cannabis extract standardized in MCT oil:

- Aphria 0:25;
- Aphria 10:13;
- Aphria 20:6;
- Panaxir CBD25;
- Panaxir THC25;
- Panaxir THC25/CBD25;
- Panaxir THC50.

The permitted routes of administration are:

- Oral (MCT oil suspension);
- Inhalation via vaporization.

What does a Prescription look like?

To issue a prescription, the physician must complete the relevant prescription and control sheet for narcotics and psychotropic drugs.
The prescription itself comprises:

- The product brand (if applicable);
- Potency, specifying the THC:CBD ratio;
- Pharmaceutical form and dosage;
- Quantity and duration of treatment for each prescribed product listed;
- Clear instructions regarding the administration or use of the prescribed product.

Repeated prescriptions should be appropriately annotated, indicating the total treatment period.

How Patients get their Medicine

In order to access a Medical Cannabis product, patients are required to go to an authorized pharmacy. There, they must provide the prescription (referred to as the green card), the control card, and the application approved by the Superintendent of Public Health.

Medical Cannabis Treatment: Average Prices

The average price for inflorescence is approximately €10-16.50/gram. Epidiolex® is sold at €3000/10ml, and Sativex® at €500/10ml.

Sources

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4.11. Medical Cannabis Regulation in the Netherlands

Legislative Framework

The Netherlands has a unique stance on the regulation of Medical Cannabis, shaped by both historical context and progressive legislative adaptations. This approach reflects a blend of stringent control with pragmatic tolerance, especially evident in the legal framework governing Medical Cannabis.

Dutch Opium Act

Firstly, the overarching regulatory framework for all drugs, including cannabis, is the Dutch Opium Act. Under this act, which has been in place since 1996, cannabis is classified as a "soft drug." This classification implies that the use, possession, and trade of cannabis are technically prohibited. However, the Dutch policy is known for its practical approach, which tolerates the use and trade of cannabis under controlled circumstances. This system aims to separate the softer drug markets from the more harmful hard drug markets, reducing the overall harm and public health risks associated with drug use.

Medical Cannabis Legalization

In a significant development, Medical Cannabis was legalized in 2003 under the Dutch Medicines Act. This act stipulates that any medicinal product, including cannabis, must generally receive a marketing authorization before it can be marketed in the Netherlands.

Special Access Scheme

A notable exception to the typical requirement for marketing authorization involves the Medical Cannabis produced by Bedrocan, the only company licensed by the Dutch government to cultivate cannabis for medicinal purposes. Bedrocan's products are made available under a special access scheme that permits the use of their cannabis without the standard marketing authorization. This scheme is designed to facilitate access to Medical Cannabis for patients who may benefit from its therapeutic properties, ensuring that the cannabis provided is consistent, controlled, and of high quality.

Differences between Private and Public Healthcare/Insurance Systems

The public healthcare system in the Netherlands does not provide reimbursement for Medical Cannabis. This means that patients who are

prescribed Medical Cannabis must cover the costs out of pocket. Some private health insurers in the Netherlands do offer reimbursement for Medical Cannabis under specific conditions. The coverage details can vary significantly from one insurer to another, often depending on the policy's terms and the specific health conditions being treated.

Who can prescribe Medical Cannabis?

Any licensed doctor is authorized to prescribe Medical Cannabis. This regulation enhances patient access to Medical Cannabis treatments, reducing barriers that might otherwise delay relief from symptoms. Patients can discuss Medical Cannabis as a treatment option with their primary care doctor, who has the full authority to prescribe it if deemed appropriate.

Pathologies that can be Treated with Medical Cannabis

Medical Cannabis is prescribed for a range of conditions where traditional treatments may not have provided sufficient relief or have resulted in significant side effects. Particular conditions treated are:

- Pain and muscle spasms/cramps associated with Multiple Sclerosis or spinal cord damage;
- Nausea, reduced appetite, weight loss and debilitation associated with cancer and AIDS Nausea and vomiting caused by medication or radiotherapy for cancer and HIV/AIDS;
- Chronic pain (nerve pain, phantom pain, facial pain or pain that persists after a cured shingles infection);
- Tics associated with Tourette Syndrome;
- Glaucoma (if standard treatment is not effective);
- Various forms of epilepsy.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

Products available in the Netherlands are:

Pharmaceutical Preparations

- Sativex®;
- Epidyolex®.

Dried Cannabis Flowers by Bedrocan

- Bedrobinol: Contains 13.5% THC and less than 1% CBD;
- Bedrocan: Contains 22% THC and less than 1% CBD;
- Bediol: Contains 6.3% THC and up to 8% CBD;
- Bedica: Contains 14% THC and less than 1% CBD;
- Bedrolite: Contains less than 1% THC and 7.5% CBD.

Magistral oils (extracts)

The routes of administration allowed are:

- Magistral oils (extracts). Oral (oil, capsule, extract);
- Magistral oils (extracts). Inhalation via vaporization;
- Magistral oils (extracts). Topical.

What does a prescription look like?

A standard prescription for Medical Cannabis includes several key elements to ensure that the medication is dispensed correctly and used safely by the patient. It contains:

- Details of the prescribing doctor, including their full name and the address of their practice, are mandatory;
- Patient's name and Address;
- The specific name of the Medical Cannabis product to be supplied;
- The exact amount of the medicine that the patient is allowed to receive;

- The concentration of active ingredients within the medication, such as the percentages of THC and CBD;
- Details on how the medicine should be used by the patient, including dosage and frequency of use.

How Patients Obtain their Medicine

In the Netherlands, the process for obtaining Medical Cannabis is well-regulated and straightforward. Here's how the process works:

- Magistral oils (extracts). Patients begin by consulting with a licensed physician who assesses their medical condition and determines whether Medical Cannabis could be beneficial.
- Magistral oils (extracts). If Medical Cannabis is deemed appropriate, the doctor writes a prescription. This prescription includes the patient's details, specific details about the prescribed Medical Cannabis (such as the type and dosage), and instructions for use.
- Magistral oils (extracts). With the prescription in hand, patients go to a pharmacy to obtain their Medical Cannabis. In the Netherlands, pharmacies that dispense Medical Cannabis must meet stringent regulatory standards to ensure they handle and distribute the medication correctly.
- Magistral oils (extracts). The pharmacist verifies the prescription, checks the patient's identity, and ensures that the prescription details are correct and clear.

Bureau voor Medicinale Cannabis (BMC)

The government agency responsible for the oversight of Medical Cannabis production and distribution is the Bureau voor Medicinale Cannabis (BMC). This agency ensures that all Medical Cannabis supplied in the Netherlands meets high-quality standards. Some patients may obtain their Medical Cannabis directly through pharmacies associated with or approved by the BMC, which guarantees the quality and safety of the products.

Medical Cannabis Treatment: Average Prices

In the Netherlands, the cost of Medical Cannabis treatments varies depending on the type and form of medication:

- Sativex: € 476.60;
- Epidyolex: € 1,068.01;
- Flowers: € 6.50/gram;
- Oils: € 4-20/mL.

4.12. Medical Cannabis Regulation in Poland

Legislation Governing Prescription

In Poland, the regulation of Medical Cannabis prescription is governed by specific laws. Notably, on July 7, 2017, the Act amending the Act on counteracting drug addiction and the Act on reimbursement of drugs, foodstuffs for particular nutritional uses, and medical devices was passed. This legislation came into effect on November 1, 2017, marking the legalization of pharmaceutical-grade Medical Cannabis for use in the country.

Differences between Private and Public Healthcare/Insurance Systems

In Poland, there exists a notable difference between the private and public healthcare systems regarding access to Medical Cannabis therapy.
In the private sector, numerous cannabis clinics offer services where patients can obtain a prescription on their first visit. However, this service comes at a cost, which patients must bear privately, without any reimbursement.

On the other hand, within the public healthcare system, overseen by the National Health Fund (Narodowy Fundusz Zdrowia, NFZ), Medical Cannabis therapy is not eligible for reimbursement either. Consequently, regardless of the healthcare setting, patients are required to cover the expenses of Medical Cannabis treatment entirely out of their own pockets.

Who can prescribe Medical Cannabis in Poland?

In Poland, Medical Cannabis can be prescribed by any physician authorized to prescribe narcotics. This requires a prescription for a preparation containing narcotics or psychotropic substances (Rpw in Polish), which can be either traditional (paper) prescriptions or e-prescriptions. However, prescriptions for Cannabis are only issued to patients who have completed the qualification process for cannabis therapy successfully.

Pathologies that can be Treated with Medical Cannabis

In Poland, Medical Cannabis can be prescribed for various pathologies and conditions supported by accredited scientific literature. While not an exhaustive list, some of the pathologies for which Medical Cannabis may be prescribed include:

- cancer;
- neuropathic or chronic pain;
- nausea and vomiting induced by chemotherapy;
- drug-resistant glaucoma;
- drug-resistant epilepsy;
- rheumatoid arthritis;
- anorexia;
- depression;
- Alzheimer's and Parkinson's disease;
- Gilles de la Tourette's syndrome.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

Currently, in Poland patients have access to numerous varieties of Medical Cannabis, as well as to Sativex® and Epidyolex®. The varieties available (as of April 2025) are:

Company	Name of the variety	% THC	% CBD
Aurora Deutschland Gmbh	Cannabis Flos LA Confidential	20	1
Aurora Deutschland Gmbh	Cannabis Flos Ghost Train Haze	22	1
Aurora Deutschland Gmbh	Cannabis Flos Equiposa	8	8
Aurora Deutschland Gmbh	Cannabis Flos THC	12	1
Canopy Growth	Cannabis Flos Penelope	8	8
Canopy Growth	Cannabis Flos Bakerstreet	20	1
Canopy Growth	Cannabis Flos	10	7
S-Labs	Cannabis Flos Pink Kush	18	1
S-Labs	Cannabis Flos	22	< 1
CanPoland	Cannabis Flos	22	1
CanPoland	Cannabis Flos	17	1
ODI Pharma	Cannabis Flos	20	< 1
Tilray	Cannabis Flos	18	1
Four 20 Pharma GmbH	Cannabis Flos	22	< 1
Polfarmex	Cannabis Flos	18	< 1

There are also extracts available:

- Cannabis Extract Standardized THC 2%, CBD ≤ 1% (CanPoland);
- Cannabis extractum normatum THC 10% CBD < 1% (Vetos Farma);
- Cannabis floris extractum normatum THC 10% CBD < 1% (PharmaCann);
- Cannabis floris extractum normatum THC 5% CBD < 1% (PharmaCann).

What does a Prescription look like?

In Poland, a prescription for a preparation containing narcotics or psychotropic substances (Rpw, in Polish) is required for Medical Cannabis. Narcotic prescriptions are valid for 30 days, after which the pharmacist will no

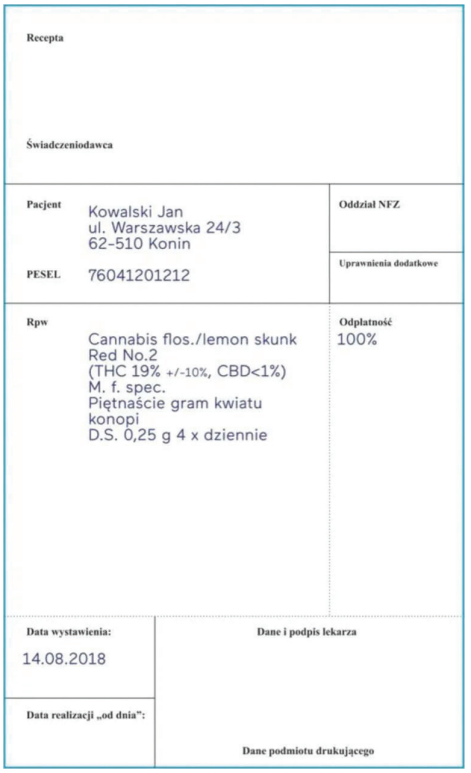
longer issue the medication to the patient. When a doctor determines that Medical Cannabis is appropriate for a patient, the prescription is generated electronically.

This digital prescription includes several critical pieces of information:

- Product Name;
- Dosage;
- Patient Identification.

After creating the electronic prescription, doctors are required to print a copy for their records. This printed document must be retained for three years from the date of its registration, serving as an important legal and medical record.

A typical prescription in Poland looks like the follow:


Recepta

Świadczeniodawca

Pacjent
Kowalski Jan
ul. Warszawska 24/3
62-510 Konin

PESEL 76041201212

Oddział NFZ

Uprawnienia dodatkowe

Rpw
Cannabis flos./lemon skunk
Red No.2
(THC 19% +/-10%, CBD<1%)
M. f. spec.
Piętnaście gram kwiatu konopi
D.S. 0,25 g 4 x dziennie

Odpłatność
100%

Data wystawienia:
14.08.2018

Dane i podpis lekarza

Data realizacji „od dnia":

Dane podmiotu drukującego

Image 20. Sample Prescription Format Used in Poland.

How Patients get their Medicine

In Poland, Medical Cannabis can be purchased at any pharmacy that sells narcotic and psychotropic drugs. However, Medical Cannabis is rarely available immediately. Due to the low demand, the pharmacist often has to order it from the wholesaler, and then it is available in a given pharmacy within a few days. The waiting time is due to the import of Medical Cannabis from abroad, mainly from Germany and the Netherlands, which often limits availability in many pharmacies in Poland, especially in smaller towns.

Medical Cannabis Treatment: Average Prices

Medical Cannabis is usually dispensed in original containers of 5 or 10 g. The patient self-doses Medical Cannabis.
The cost of Medical Cannabis treatments can vary depending on the severity of the symptoms and the dosage. Average price for 1 gram is about €16. It is worth to note that since the legalization of Medical Cannabis in Poland, all types of dried products have been subject to the 23% VAT rate. In August 2020, Aurora Deutschland was granted permission to reduce the VAT rate from 23% to 8%. Thanks to this, the price of dried material has become much more favorable for the patients. Sativex® is sold at €631.22

References

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4.13. Medical Cannabis Regulation in Portugal

Legal framework

Portugal has established a comprehensive legal framework to regulate the prescription, distribution, and use of Medical Cannabis. This framework ensures that medical cannabis is used safely and responsibly, adhering to stringent guidelines laid out in several key legal documents.

Key Laws and Regulations

- Law No 33/2018 (18 July 2018): This foundational law sets the framework for the prescription and dispensing of Medical Cannabis at pharmacies. It also covers possession, transportation, scientific research, professional education, and the regulation and supervision of all activities associated with cannabis for therapeutic purposes. Under this law, Medical Cannabis can only be dispensed in pharmacies and requires a valid prescription from a licensed physician.
- Decree-Law No. 8/2019 (15 January 2019): This decree details the conditions under which these products can be prescribed and dispensed in pharmacies. Specifically, it restricts prescriptions to products that are authorized and listed by INFARMED, the Portuguese authority under the Ministry of Health. These products are only prescribed when conventional treatments have failed to yield the desired results or have been ineffective.
- Ministerial Order 83/2021: This order specifies the requirements and procedures necessary for applying for and granting authorization for the cultivation, production, wholesale, transportation, circulation, import, and export of cannabis-based medicines, preparations, and substances.

Differences between Private and Public Healthcare/Insurance Systems

Portugal's healthcare system offers both public and private options, which differ significantly in how they handle coverage, including the costs associated with Medical Cannabis and other treatments.

Public Healthcare System

The public healthcare system in Portugal provides coverage for medications, including Cannabis-based medicines, through a tiered co-payment system. This system is designed to make treatments accessible by subsidizing a portion of the cost based on the medication's use and need. The co-payment categories for Cannabis-based medicines are as follows:

- 15% Reimbursement: Typically for less essential medications;
- 37% Reimbursement: Includes certain Cannabis-based medicines like Sativex®, which is specifically reimbursed at this rate by the state;
- 69% Reimbursement: For more essential medications;
- 90% Reimbursement: Reserved for critical or life-saving drugs.

Private Healthcare System

Approximately 20% of the Portuguese population chooses private healthcare insurance, which can offer several advantages over the public system, especially in terms of Medical Cannabis coverage:

- Private insurance often covers a larger portion of the costs for treatments and medications, including Medical Cannabis, than the public system. This can significantly reduce out-of-pocket expenses for patients;
- Patients with private healthcare may have quicker access to specialists and treatments, including newer or more expensive options that might not be as readily available in the public system;

- Private health insurance plans can be customized to fit individual needs, offering varying levels of coverage and additional benefits that might not be available through public insurance.

Choosing Between Systems

For patients requiring treatments such as Medical Cannabis, the choice between public and private healthcare can significantly impact their access to medication and overall treatment costs. While the public system provides basic coverage, private insurance might be preferable for those seeking broader coverage and faster access to a wider range of treatment options.

Who can prescribe Medical Cannabis?

Medical Cannabis can only be prescribed by licensed physicians. These healthcare professionals must follow the guidelines and regulatory framework set by INFARMED, the Portuguese authority responsible for drug regulation under the Ministry of Health. A physician can prescribe Medical Cannabis only when traditional treatments have not provided the desired results or have caused significant adverse effects.

Pathologies treatable with Medical Cannabis

In Portugal, the use of licensed Medical Cannabis products is approved for several specific medical conditions:

- Spasticity associated with MS or spinal cord injuries;
- Nausea from chemotherapy, radiotherapy, HIV treatment, and hepatitis C treatment;
- Appetite stimulation for palliative care patients undergoing cancer or AIDS treatment;
- Chronic pain;

- Gilles de la Tourette Syndrome;
- Epilepsy disorders;
- Therapy-resistant glaucoma.

Medical products/varieties available for prescription and routes of administration allowed

Here's an overview of the Medical Cannabis products authorized for use, as to April 2024:

- Sativex (has approved marketing authorization in Portugal);
- Epidyolex (for exceptional cases);
- Tilray Flower (THC 18%; CBD <1%);
- Hexa 01 Alto THC 20%;
- Tilray Oral Solution (THC 5%; CBD 20%);
- Ferraz Lynce CBD Dominant Solution.

The routes of administration allowed are:

- Oral (oil, capsules);
- Inhalation.

What does a Prescription look like?

The prescription of cannabis-based medicinal products, preparations and substances follows a special medical prescription drawn up according to a special form approved by the Ministry of Health. The prescription must identify:

- the patient;
- the prescribing doctor;
- the medicine;
- the preparation or substance;
- the respective quantity;

- the dosage;
- the mode of application.

Prescriptions can only be issued if conventional treatments have proven ineffective or have caused significant adverse effects. The specific therapeutic indication of the Medical Cannabis product must be approved by INFARMED. To control usage and prevent misuse, prescriptions for cannabis-based medicines, preparations, and substances are valid for a single use only.

How Patients get their Medicine

Medicinal products, preparations and substances based on cannabis for medical purposes may be dispensed in pharmacies by pharmacists only upon presentation of the relevant prescription and verification of the purchaser's identity.
The holder of a special prescription for cannabis-based medicinal products, preparations and substances may possess and transport cannabis-based medicinal products, preparations and substances for his or her own consumption, according to the prescription and up to the prescribed quantity. Only previously inspected pharmacies may dispense a prescription for Medical Cannabis. In order to obtain his product, the patient must go to a pharmacy and have an additional document to verify their identity.

Medical Cannabis Treatment: Average Prices

The average price of Medical Cannabis inflorescences is 10 euros/gram. Oils cost between € 2 and € 6 / ml. The cost of Sativex® is € 475 (10 mL), with a 37% reimbursement from the State. Medicines in Portugal are subsidized from 15% to 90%, depending on use and need.

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4.14. Medical Cannabis Regulation in Spain

Legal Framework

The regulation of Medical Cannabis in Spain is currently evolving, with significant developments being slowly implemented to provide a legal framework within the current Spanish legislation for the prescription and dispensation of unauthorised cannabis/based medicines.

Current Legal Status

As of June 2025, unlicensed Medical Cannabis is not legal in Spain. However, in February 2024 the Spanish Ministry of Health published the draft of a Royal decree that was subjected to public consultation and amendment and, subsequently, subjected to the European authorities. This draft suggests that the access scheme for the medical use of cannabis in Spain will be much more restrictive than the rest of European countries, closely resembling that of Latin American countries such as Colombia and Peru. Pending the final publication of the definitive text, it seems likely that the Spanish program will include the following features:

- *No dried flowers for inhalation*: Only oral, normalized cannabis extracts will be accepted for registration by the Spanish Medicine Agency (AEMPS). The ministry expects to collect around 240,000 euros in fees associated with product registration.
- *Prescription by specialist only*: As opposed to Germany, and similarly to the UK, general practitioners and family doctors will not be able to prescribe medicinal cannabis. Prescription will be authorized only to specialists, mainly pain units, neurologists, internists, psychiatrists and ObGyn. It is yet unclear if both public and private healthcare professionals will be allowed to prescribe medicinal cannabis.
- *Limited number of indications*: Initially, eligible indications will be the control of several symptoms in cancer patients, refractory paediatric epilepsy syndromes, spasticity associated with multiple sclerosis and other neurodegenerative diseases, and chronic pain, including endometriosis.
- *Dispensation in hospital pharmacies only*: Magistral formulae will be prepared and dispensed by hospital pharmacies and not in community pharmacies. Considering the residual number of patients that may benefit from these products, the AEMPS does not expect this activity to have a significant impact in the activity of pharma-

cies and, therefore, does not allocate additional funding to this program.

The final version of the Royal Decree is expected to be published by the end of 2025. From the moment of the publication, the AEMPS will have three months to publish the pharmacopeia monographs establishing the requirements for product registration. Companies interested in registering products will then have a 6-month period to do so with the competent authorities.

Authorized Medical Cannabis Products

Currently, the only cannabis-based medications that are legally prescribed and covered by public reimbursement in Spain are those that have a marketing authorization:

- Sativex approved for the treatment of MS-related spasticity;
- Epidyolex: Approved for use in treating severe forms of epilepsy, including Dravet Syndrome and Lennox-Gastaut Syndrome, as well as for managing epileptic seizures associated with tuberous sclerosis.

Prescription and Coverage

Both Sativex and Epidyolex are covered by public health insurance, making them accessible to patients without significant financial burden. The coverage extends to:

- Sativex: Priced at approximately € 400;
- Epidyolex: Priced around € 1,000.

It is yet unclear if the cost of unauthorized cannabis-based medicines will be reimbursed by either private insurers of public health care services.

Prescription Requirements

The standard prescription format is utilized for these medications, which includes:

- The issue date of the prescription;
- Detailed medication information (name of the drug, dosage, and form);
- The duration of treatment prescribed;
- The prescribing doctor's signature and official seal.

Sources

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4.15. Medical Cannabis Regulation in Sweden

Legal Framework

The Swedish law regulating the use of Medical Cannabis is the Act 2009:366 on Trade in Medicinal Products. The Swedish Medical Products Agency approved a product containing a cannabis extract—Sativex®—for multiple sclerosis in 2012 (Läkemedelsverket, 2016). Subsequently, Epidyolex® was also approved for the treatment of drug-resistant epilepsy. Swedish pharmacies are permitted to distribute prescribed drugs that have not been officially approved in Sweden, but only under special circumstances and with a specific license (Läkemedelsverket, 2017).

Differences between private and public healthcare system/insurance system

In Sweden, the landscape of healthcare insurance coverage for Medical Cannabis treatments involves distinct differences between the public and private systems, particularly in terms of exceptions for coverage.

Public Healthcare System (OKP)

Treatment with Medical Cannabis products is not typically covered by the compulsory health insurance known as OKP (Offentlig Konsekvensprogram). This means that, generally, patients must bear the full cost of these treatments. There are provisions within the public healthcare system that allow for exceptions in what are termed 'cases of hardship.' These cases are defined by the following criteria:

- The use of Medical Cannabis is expected to provide a significant therapeutic advantage in treating a disease that could be fatal or cause severe and chronic health impairments.
- There are no other effective and approved treatment methods available. This usually means that conventional therapies have either been exhausted or are unsuitable due to various medical reasons.

In these exceptional cases, the treating physician can make a request for cost approval. This involves a formal process where the physician must justify the necessity of Medical Cannabis based on its potential benefits versus the severity of the condition.

Private Healthcare Insurance

The private healthcare system in Sweden may offer more flexibility regarding the coverage of Medical Cannabis. Private health insurance policies vary significantly, and some may include coverage for treatments like Medical Cannabis, especially if they can be justified as medically necessary under the terms of the insurance policy.

Navigating Insurance Claims

Whether through public or private insurance, obtaining coverage for Medical Cannabis typically requires thorough documentation. This includes medical records detailing the patient's condition, previous treatments attempted, and a robust case from the healthcare provider about the expected benefits of Medical Cannabis. For public insurance, the process can be stringent, with approvals needed from health authorities or specific insurance boards. In contrast, private insurers may have a more streamlined process but would still require substantial evidence of the treatment's necessity and potential effectiveness.

Who can prescribe Medical Cannabis?

Any licensed physician may prescribe Medical Cannabis if previous treatments have failed. The responsibility for the treatment lies exclusively with the prescribing physician. This means that the doctor must take full accountability for the decision to prescribe Medical Cannabis, including the management of the patient's treatment and monitoring of any side effects or complications of an approved medicine is not suitable for the patient, a pharmacy can apply for a license from the Swedish Medicines Agency to be allowed to dispense and preparation that is not approved in Sweden. The application must be justified by a physician.

Pathologies treatable with Medical Cannabis

In Sweden, Medical Cannabis is available for:

- Multiple Sclerosis-related spasticity;
- Some types of epileptic seizures;
- Neuropathic and chronic pain.

Medical Products/Varieties available for Prescription and Permitted Routes of Administration

The only drugs approved by the Swedish Medicines Agency are:

- Sativex®;
- Epidyloex®.

Available under license, following approval by the Swedish Agency (on a case-by-case basis):

- Marinol®;
- Bediol;
- Bedrolite;
- Bedrocan;
- Emerald Health 1:1 THC:CBD oil.

As of 2023 (Aureum Health products):

- Tetracanoid;
- Bidiocanoid;
- Misccanoid;
- Varincanoid;
- Bigerolcanoid.

The routes of administration allowed are:

- Oral (oil);
- Inhalation.

What does a Prescription look like?

99% of prescriptions in Sweden are electronic. This includes prescriptions for cannabis products. The prescription includes:

- the generic name of the drug;
- the pharmaceutical form;

- potency (THC:CBD ratio);
- the route of administration;
- the dosage.

How Patients get their Medicine

To obtain a cannabis-based medicine, a Swedish patient can go to an authorized pharmacy.

Medical Cannabis Treatment: Average Prices

A significant issue for patients in Sweden is the cost of Medical Cannabis based products. Sativex is not covered by the high-cost protection scheme, and patients are responsible for paying for the complete treatment themselves. The cost can reach up to approximately 480 Euros per month or 5,760 Euros per year. For licensed prescriptions, the prescribing clinic bears the entire cost. As an example, for Bediol, the annual cost can be around 17,280 Euros, which results in most clinics refraining from prescribing Medical Cannabis.

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4.16. Medical Cannabis Regulation in Switzerland

Law References that Regulate Prescription

The foundation of Medical Cannabis regulation in Switzerland is the Federal Act on Narcotics and Psychotropic Substances, originally enacted on October 3, 1951, with a significant amendment set into force on 1st August 2022. This amendment was a pivotal change in the landscape of Medical Cannabis regulation, as it removed the requirement for an exceptional permit from the Federal Office of Public Health (FOPH) for prescribing Medical Cannabis and added Cannabis for medical purposes and THC to the Narcotics List Ordinance, BetmVV. This adjustment has significantly streamlined the process, making Medical Cannabis more accessible to patients who need it.

Additionally, the authority to prescribe such narcotics is given to physicians and veterinary surgeons who operate independently and are compliant with the Medical Professions Act of June 23, 2006.

The critical adjustment entered into force in August 2022, reclassified Cannabis for medical purposes from List D (prohibited narcotics) to List A (substances subject to all control measures) of the Narcotics List Ordinance. This reclassification not only simplifies the regulatory process but also underscores the acknowledgment of the medical value of Cannabis, aligning its control measures with other controlled medicinal substances. The Federal Act on Medicinal Products and Medical Devices, enacted on December 5, 2000, also plays a crucial role. It sets the standards for all medicinal products and medical devices in the country, ensuring that they meet high standards of safety, efficacy, and quality. Under this act, all Medical Cannabis products undergo rigorous assessment to confirm that they are safe and effective for use.

Differences between the Private and Public Healthcare/Insurance Systems

Public Healthcare System (OKP)

In Switzerland, the coverage of Medical Cannabis under the country's health insurance systems presents a complex landscape. While the compulsory health insurance (OKP) typically does not cover the cost of Medical Cannabis treatments, there are notable exceptions that can make these treatments accessible under certain conditions. Coverage for Medical Cannabis is considered in cases of hardship. This means that if a patient faces a potentially fatal disease or one that causes severe and chronic health impairments, and if no other effective and approved treatments are available, then the use of Medical Cannabis might be covered. For these exceptions to be made, several conditions must be met:

- The Medical Cannabis treatment must be expected to offer significant health improvements or stabilization that other treatments have not provided.

- It must be clear that other approved and effective treatment methods have been considered and ruled out, either due to ineffectiveness or unsuitability for the patient's condition.
- The treating physician must formally request cost approval. This involves preparing a detailed justification that outlines the necessity of Medical Cannabis, supported by medical evidence and a comprehensive treatment plan.

Private Healthcare Insurance

Unlike the OKP, private health insurance in Switzerland might offer more flexibility regarding the coverage of treatments like Medical Cannabis. The specifics can vary significantly between different insurers and individual insurance plans. Some private plans may include coverage for alternative therapies, including Medical Cannabis, especially if these treatments can be shown to be cost-effective or particularly beneficial for the insured's condition. Private health insurers may assess the inclusion of Medical Cannabis on a case-by-case basis, taking into account the medical necessity and potential benefits against the cost. The decision often involves an evaluation of the patient's medical history and previous treatment outcomes.

Who can prescribe Medical Cannabis in Switzerland?

As of August 2022, any licensed doctor in Switzerland can prescribe Medical Cannabis without the need for special permission from the Federal Office of Public Health (FOPH). The responsibility for prescribing Medical Cannabis lies solely with the physician. In the initial years following these regulatory changes, there was a requirement for physicians to report a wide range of treatment data to the FOPH's reporting system MeCanna. This is part of a pilot project intended to gather comprehensive observational data on the use of Medical Cannabis and Cannabinoid-based formulations with ≥ 1 % THC in clinical settings across Switzerland.

Pathologies for which Medical Cannabis can be Prescribed

In Switzerland, cannabis can be prescribed for a broad range of conditions, although it is most commonly recommended for the following:

- Severe chronic pain;
- Spasticity in multiple sclerosis or other neurological conditions;
- Neuropathic pain;
- Cancer-related pain;
- Nausea and loss of appetite, particularly in chemotherapy patients;
- MS-related Spasticity (Sativex);
- Lennox-Gastaut syndrome or Dravet syndrome (Epidyolex).

For any off-label indications, physicians should report off-label use accordingly.

Medical Products/Varieties Available for Prescription and Permitted Routes of Administration

Authorized products that can be prescribed in Switzerland are:

- Sativex®;
- Epidyolex®.

Other API-based formulations ≥ 1 % THC must be reported to Swissmedic using the federal notification system on a national level. On a cantonal level, the duty for narcotics accounting applies. Such Cannabinoid-based APIs include:

- Inflorescences (Cannabis flos, PH EUR 3028);
- Extracts;
- Resins;
- Oils;
- Tinctures.

Magistral preparations are mainly dispensed at specialised compounding pharmacies. These include:

- NRF (*Neues Rezeptur Formularium*, New Prescription Form) 22.7: Dronabinol Capsules 2.5 mg / 5 mg / 10 mg;
- NRF 22.8: Dronabinol oil drops 25 mg/ml;
- NRF 22.10: Cannabidiol oil 50 mg/ml; 100 mg/ml;
- NRF 22.11: Cannabis resin oil 25 mg/ml Dronabinol;
- NRF 22.12: Cannabis dry inflorescences for inhalation via vaporization;
- NRF 22.13: Single dose cannabis dry inflorescences for inhalation via vaporization;
- NRF 22.14: Cannabis dry inflorescences for tea preparation;
- NRF 22.15: Cannabis dry inflorescences in single doses for tea preparation;
- NRF 22.16: Ethanolic dronabinol solution 10 mg/ml for inhalation.

The permitted routes of administration are:

- Oral (oil, capsule, tea, extract, resin);
- Inhalation;
- Topical (patches, ointments);
- Rectal (suppositories);
- Vaginal (suppositories).

What does a Prescription look like?

Whenever a cannabis medicinal product is prescribed, a comprehensive therapy report is mandatory and has to be reported to the MeCanna system by the physician. Moreover, follow-up reports are required at intervals of 1 and 2 years from the start of treatment. Initially, a narcotics prescription is issued to the patient, encompassing essential details such as:

- Prescription specifics: brand name, active ingredient(s), form, dose, and administration instructions;

- Patient particulars;
- Doctor details.

Additionally, the prescription includes a barcode and narcotics prescription number for validity and 3 copies (physician/pharmacist/patient or insurance) for verification as an anti-tampering security feature. Subsequently, the doctor must notify the prescription via the MeCanna system. This step ensures proper documentation and tracking of prescribed cannabis medications.

How Patients get their Medicine

In Switzerland, accessing cannabis-based treatments is straightforward, requiring only a prescription from any licensed doctor. Patients are not obligated to seek prior authorization from the Federal Office of Public Health (FOPH).

Once a prescription is obtained, patients can procure Medical Cannabis products from public pharmacies or hospital pharmacies holding a manufacturing license for medicinal products in accordance with the *formula magistralis* (*Magistralrezeptur*).

It's important to note that treatment with Medical Cannabis products is not covered by compulsory health insurance (OKP). However, reimbursement may be possible through health insurance providers on an exception basis, subject to consultation with the prescribing physician.

Medical Cannabis Treatment: Average Prices

The costs of Medical Cannabis treatment can vary based on factors such as dosage and product type. Here are approximate prices:

- For a daily dose of 5-10 mg THC, monthly costs range from approximately CHF 200 to CHF 515.

- For oils, the costs are approximately CHF 250 per 30 ml Cannabis oil 1% THC, equivalent to CHF 8.35 per millilitre.
- Flowers are priced between CHF 6.50 to CHF 15 per gram.

According to Medcan, Switzerland's biggest Medical Cannabis patient association, the expenses for Medical Cannabis treatment can vary from around CHF 380 to over CHF 8,413 per month, per patient.

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4.17. Medical Cannabis Regulation in the UK

Law References that regulate Prescription

In the United Kingdom, the prescription of Medical Cannabis is regulated by the Misuse of Drugs Regulations 2001 (referred to as 'the 2001 Regulations'). These regulations categorize drugs into five schedules for legal control purposes.

In 2015, cannabis was reclassified and placed under Table 2 of the regulations.

Furthermore, in 2018, amendments were made to the Misuse of Drugs Regulations 2001. Consequently, since November 2018, doctors on the General Medical Council (GMC) special register have been authorized to prescribe approved Medical Cannabis products.

Differences between Private and Public Healthcare/Insurance Systems

In the UK, there are notable distinctions between accessing Medical Cannabis through the public and private healthcare systems, as well as insurance coverage.

Medical Cannabis can be obtained free of charge from the National Health Service (NHS), but obtaining these prescriptions can be challenging due to strict criteria and limited availability. The private market for Medical Cannabis prescriptions is expansive, offering greater accessibility but at a higher cost. Prescription expenses in the private sector are typically not covered by insurance, leading to out-of-pocket payments for patients. While some private insurers may offer coverage for Medical Cannabis if it meets specific requirements, this coverage is not common, and medical insurance companies generally do not include Medical Cannabis treatment in their standard coverage plans.

Who can prescribe Medical Cannabis in the UK?

In the UK, prescribing Medical Cannabis follows specific guidelines and involves various healthcare professionals:

- Medicinal Cannabis products can only be prescribed after conventional treatments have been attempted without success;
- Generally, medical specialists are authorized to prescribe medicinal products with marketing authorizations from the Medicines and Healthcare products Regulatory Agency (MHRA);
- Doctors, whether working in the public or private sector, may prescribe unlicensed drugs if they are registered specialists with the General Medical Council (GMC). They must adhere to GMC guidelines and NHS governance procedures;
- GMC-registered specialists are required to prescribe only within their area of expertise;
- Specialist doctors outside the National Health Service (NHS) must also adhere to these guidelines;
- Medical specialists intending to prescribe Medical Cannabis in a private capacity should contact their local supervisor of controlled drugs to obtain a prescriber identification number;
- The final decision to prescribe Medical Cannabis involves a multidisciplinary team of specialists, who review the patient's medical history and initial consultation details.

Pathologies that can be Treated with Medical Cannabis

In the UK, authorized indications for Medical Cannabis include:

- Multiple Sclerosis-related spasticity (if conventional treatments are ineffective);
- Dravet syndrome and Lennox-Gastaut syndrome;
- Chemotherapy-related nausea.

However, prescribing any unauthorized drug, including Medical Cannabis, is a clinical decision. Healthcare professionals consider various factors such as the patient's health status, clinical condition, evidence of efficacy and safety, and the suitability of authorized drugs when determining the most appropriate course of treatment for the patient.

Medical Products/Varieties available for Prescription and Permitted Routes of Administration

The licensed products are:

- Sativex® (authorised in the UK for use in MS-related spasticity), recommended over all other unauthorised products;
- Nabilone (chemotherapy-induced nausea);
- Epidyolex® (for conditions of severe treatment-resistant epilepsy).

Prior to licensing, Epidyolex® was available through compassionate use and extended access programs. These programs are now closed to new patients.

Unauthorized products must be prepared according to the specifications of a medical specialist on the GMC's register of specialists.

As of May 2025, the following products are also available (non-complete list):

Product	THC	CBD	Form	Size	Price	Price per unit (mg/ml/ capsule)
Althea CBD10:THC5	5 mg/ml	10 mg/ml	Oil	50ml	€234	€4,68
Althea THC20:CBD1	20 mg/ml	1 mg/ml	Oil	50ml	€234	€4,68
Althea CBD100	0.8 mg/ml	100 mg/ml	Oil	25ml	€234	€9,36
Althea CBD12:THC10	10 mg/ml	12.5 mg/ml	Oil	50ml	€234	€4,68
Althea CBD25: THC2	2 mg/ml	25 mg/ml	Oil	50ml	€234	€4,68
Cellen Satoline 0:20	20 mg/ml	0 mg/ml	Oil	30ml	€317	€10,58
Cellen Satoline 10:10	10 mg/ml	10 mg/ml	Oil	30ml	€317	€10,58

Product	THC	CBD	Form	Size	Price	Price per unit (mg/ml/ capsule)
Cellen Satoline 100:0	0.2 mg/ml	100 mg/ml	Oil	30ml	€317	€10,58
Cellen Satoline 200:0	0.2 mg/ml	200 mg/ml	Oil	30ml	€317	€10,58
Cellen Satoline 25:12.5	12.5 mg/ml	25 mg/ml	Oil	30ml	€317	€10,58
MediCabilis 50	2 mg/ml	50 mg/ml	Oil	50ml	€176	€3,53
Noidecs T1:C100 Cannabis Oil	1 mg/ml	100 mg/ml	Oil	30ml	€206	€6,86
Noidecs T1:C20 Cannabis Oil	0.9 mg/ml	18.6 mg/ml	Oil	10ml	€153	€15,28
Noidecs T10:C15 Cannabis Oil	10 mg/ml	15 mg/ml	Oil	50ml	€206	€4,11
Noidecs T26 Cannabis Oil	26 mg/ml	0.5 mg/ml	Oil	50ml	€206	€4,11
Spectrum Therapeutics Blue Cannabis Oil	10 mg/ml	15 mg/ml	Oil	40ml	€191	€4,78
Spectrum Therapeutics Yellow Cannabis Oil	1 mg/ml	20 mg/ml	Oil	40ml	€103	€2,57
Althea CBD10:THC5	5 mg/ml	10 mg/ml	Oil	50ml	€234	€4,68
Althea THC20:CBD1	20 mg/ml	1 mg/ml	Oil	50ml	€234	€4,68
Althea CBD100	0.8 mg/ml	100 mg/ml	Oil	25ml	€234	€9,36
Althea CBD12:THC10	10 mg/ml	12.5 mg/ml	Oil	50ml	€234	€4,68
Aurora High THC	25 mg/ml	0.5 mg/ml	Oil	30ml	€229	€7,64
Aurora High CBD	5 mg/ml	25 mg/ml	Oil	30ml	€194	€6,47
Columbia Care ClaraCeed Cannabis Oil	1 mg/ml	20 mg/ml	Oil	15ml	€135	€4,51
Columbia Care EleCeed Cannabis Oil	10 mg/ml	10 mg/ml	Oil	15ml	€170	€5,68
Columbia Care TheraCeed Cannabis Oil	15 mg/ml	0.75 mg/ml	Oil	15ml	€182	€6,07
Grow 1:50	1 mg/ml	50 mg/ml	Oil	30ml	€253	€8,43
Grow 1:100	1 mg/ml	100 mg/ml	Oil	30ml	€246	€8,19
Grow 1:100	1 mg/ml	100 mg/ml	Oil	50ml	€222	€4,44
Grow 2:25	2 mg/ml	25 mg/ml	Oil	50ml	€222	€4,44
Grow 10:12.5	10 mg/ml	12.5 mg/ml	Oil	50ml	€222	€4,44
Grow 25:25	25 mg/ml	25 mg/ml	Oil	30ml	€288	€9,60

Product	THC	CBD	Form	Size	Price	Price per unit (mg/ml/ capsule)
Grow 25:25	25 mg/ml	25 mg/ml	Oil	30ml	€316	€10,54
Grow 25:5	25 mg/ml	5 mg/ml	Oil	20ml	€217	€10,87
Grow 25:5	25 mg/ml	5 mg/ml	Oil	30ml	€264	€8,82
Grow THC 20	20 mg/ml	0 mg/ml	Oil	50ml	€222	€4,44
Grow THC 25	25 mg/ml	0 mg/ml	Oil	30ml	€200	€6,66
Grow CBD 100	0 mg/ml	100 mg/ml	Oil	30ml	€351	€11,72
Grow CBD 200	0 mg/ml	200 mg/ml	Oil	30ml	€457	€15,24
Grow CBD 200	0 mg/ml	200 mg/ml	Oil	30ml	€210	€7,01
Spectrum Therapeutics Blue Cannabis Oil	10 mg/ml	15 mg/ml	Oil	40ml	€191	€4,78
Spectrum Therapeutics Yellow Cannabis Oil	1 mg/ml	20 mg/ml	Oil	40ml	€103	€2,57
Spectrum Therapeutics Red 2	18%	1%	Flower	5g	€71	€14,11
Spectrum Therapeutics Red 4	20%	1%	Flower	5g	€71	€14,11
Adven Flower Indica	20%	1%	Flower	10g	€59	€5,88
Adven THC	19%	1%	Flower	5g	€59	€5,88
Adven EMT-3	17%	1%	Flower	10g	€59	€5,88
Adven EMT-2	16%	1%	Flower	10g	€59	€5,88
Adven EMC -1	1%	14%	Flower	10g	€71	€7,05
Althea THC 18	18%	1%	Flower	10g	€103	€10,35
Bedrocan	22%	1%	Flower	5g	€71	€14,15
Cellen Satoline Flos	18%	1%	Flower	10g	€88	€8,82
Khiron 1/14	1%	14%	Flower	10g	€100	€9,99
Khiron 20/1	20%	1%	Flower	10g	€100	€9,99
MedCan Isando	16%	0%	Flower	10g	€94	€9,40
Noidecs T5:C7	5%	7%	Flower	10g	€94	€9,40
Noidecs T17 - Night Queen	17%	1%	Flower	10g	€94	€9,40
Noidecs T19 - Mazar	19%	1%	Flower	10g	€59	€5,88
Noidecs T20:C1	20%	1%	Flower	10g	€94	€9,40
Tilray THC 25: INDICA	25%	1%	Flower	15g	€199	€13,25

Product	THC	CBD	Form	Size	Price	Price per unit (mg/ml/ capsule)
TILRAY THC 22: SATIVA	22%	1%	Flower	15g	€199	€13,25
TILRAY THC 22: INDICA	22%	1%	Flower	15g	€199	€13,25
TILRAY THC 22: Island Sweet Skunk	22%	1%	Flower	15g	€199	€13,25
Althea THC 18	18%	1%	Flower	10g	€147	€14,70
AURORA 20/1	20%	1%	Flower	10g	€147	€14,70
AURORA 22/1	22%	1%	Flower	10g	€147	€14,70
AURORA 1/12	1%	12%	Flower	10g	€147	€14,70
BEDICA	14%	1%	Flower	5g	€71	€14,15
Grow 16:1	16%	1%	Flower	10g	€76	€7,64
Grow 18:1	18%	1%	Flower	10g	€88	€8,82
Grow 18:1	18%	1%	Flower	10g	€88	€8,82
Grow 22:0 - La Sage	22%	1%	Flower	10g	€88	€8,82
Grow 22:0 - Strawberry Glue	22%	1%	Flower	10g	€88	€8,82
PEDANIOS 20/1	20%	1%	Flower	10g	€147	€14,70
PEDANIOS 22/1	22%	1%	Flower	10g	€147	€14,70
PEDANIOS 8/8	8%	8%	Flower	10g	€147	€14,70
Spectrum Therapeutics RED NO 2	18%	1%	Flower	5g	€162	€16,16
Spectrum Therapeutics RED NO 4	22%	1%	Flower	5g	€162	€16,16
Tilray THC 25: INDICA	25%	1%	Flower	15g	€199	€13,25
TILRAY THC 22: SATIVA	22%	1%	Flower	15g	€199	€13,25
TILRAY THC 22: INDICA	22%	1%	Flower	15g	€199	€13,25
TILRAY THC 22: Island Sweet Skunk	22%	1%	Flower	15g	€199	€13,25
TILRAY THC 18 INDICA	18%	1%	Flower	15g	€199	€13,25
Kanabo+ Noidecs T340 Hybrid	680 mg/ml	5mg/ml	Cartridges	0.5ml	€94	€47,02

Product	THC	CBD	Form	Size	Price	Price per unit (mg/ml/ capsule)
Columbia Care EleCeed	200 mg/ cartridge	200 mg/ cartridge	Cartridges	0.5ml	€145	€72,30
Columbia Care EleCeed	200 mg/ cartridge	200 mg/ cartridge	Cartridges	0.5ml	€145	€72,30
Columbia Care TheraCeed	400 mg/ cartridge	20 mg/ cartridge	Cartridges	0.5ml	€145	€72,30
Columbia Care TheraCeed	400 mg/ cartridge	20 mg/ cartridge	Cartridges	0.5ml	€145	€4,82
Columbia Care ClaraCeed Oral Tablets	0.5 mg/ capsule	10 mg/ capsule	Capsules	30 capsules	€140	€4,66
Columbia Care EleCeed Oral Tablets	5 mg/ capsule	5 mg/ capsule	Capsules	30 capsules	€147	€4,90
Columbia Care TheraCeed Oral Tablets	10 mg/ capsule	0.5 mg/ capsule	Capsules	30 capsules	€175	€5,84

The permitted routes of administration are:

- Oral (oil, capsule, extract);
- Inhalation via vaporization.

What does a Prescription look like?

When prescribing Medical Cannabis, the prescribing doctor must ensure that the prescription includes:

- Brand name of the Medical Cannabis product;
- Content and THC:CBD ratio;
- Route of administration;
- Dosage.

Additionally, medical specialists intending to prescribe Medical Cannabis privately, outside of a hospital setting, should reach out to the Controlled

Drugs Accountable Officer to obtain a Prescriber Identification Number. If the doctor practices at a private clinic, they have the option to send the prescription directly to the clinic for processing and fulfillment.

How Patients Obtain their Medicine

In order to obtain their Medical Cannabis product, patients have several options:

- Patients can personally go to a clinic or pharmacy and present their prescription to procure their Medical Cannabis product.
- Alternatively, patients can arrange for a special agent to pick up their prescription and deliver the Medical Cannabis product to them.
- Some clinics or pharmacies may offer home delivery services, allowing patients to have their Medical Cannabis product delivered directly to their home for convenience.

Medical Cannabis Treatment: Average Prices

In the UK, Medical Cannabis is provided free of charge when prescribed through the National Health Service (NHS) for qualifying conditions, though access remains limited. However, many patients opt for private clinics for Medical Cannabis prescriptions, where prices can vary significantly. Average prices as of April, 2024:

- Epidiolex: € 987.81;
- Flowers: € 12.21/g;
- Oils: € 7.55/ml.

Sources

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4.18. Medical Cannabis Regulation: Smaller Markets

4.18.1. Austria

The Austrian Narcotics Act (SMG) allows for the production, acquisition, processing, transport, possession, import, or export of narcotic substances for medical or scientific purposes. The SMG refers specifically to Medical Cannabis, and states that the Austrian Agency for Health and Food Safety (AGES), is the only entity in Austria permitted to cultivate and possess cannabis for the production of medicinal products.

AGES grows several hundred kilograms of cannabis flower each year, which it exports to Germany, where it is processed into dronabinol, some or all of which is re-imported.

Semi-synthetic dronabinol preparations have been available as magistral preparations to patients in Austria since 2004 as a magistral treatment in the form of oils or capsules, with 95% pure cannabis-extracted dronabinol available since 2015. Dronabinol prescriptions must be written by a senior physician, with a strict approval process in place.

Dronabinol treatment in Austria is most likely to be used for patients with spasticity, paralysis, multiple sclerosis and other nervous disorders, for the relief of chronic pain that does not respond to any other therapy (cancer, diseases of the nervous system), or loss of appetite, nausea and vomiting in cancer and AIDS.

Sativex is currently the only approved medicine in Austria and may be prescribed to patients suffering from multiple sclerosis and have exhausted at least two other antispastic medications. Sativex's retail price is € 353.87.

Epidoylex has been authorised for sale in the EU since 2019; patients suffering from Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) can get it prescribed in Austria. Both medications can be covered by public insurance providers after the prescriptions have been approved by the chief medical officer and control physician.

Sources

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[4] https://www.msges.at/2019/01/keine-freigabe-von-cannabisblueten/.

[5] https://www.aponeo.de/rx/02258004-sativex-27-mg-25-mg-spray-zur-anwend-i-d-mundhoehle.html.

4.18.2. Croatia

Croatia legalised the use of medical cannabis on 15 October 2015; however, its implementation has been severely stalled due to bureaucratic barriers, affordability issues, and a lack of engagement from regulators and health-care professionals.
Specialists may prescribe medical cannabis in Croatia to treat the following diseases:

- Cancer;
- AIDS;
- Multiple Sclerosis;
- Epilepsy.

However, treatment is not covered by the public health insurance, thus, the patients must pay out of pocket, sometimes paying over € 200 monthly.
Although Croatia did witness some level of market activity in its early years, with Tilray exporting its Liquid Capsules in 2016, the market has seen slow to no growth in the following years due to the lack of prescriptions and patients, fueled by high prices and the reluctance of prescribers. Thus, there are currently no imports or products available on the market.
In April 2019, the amendments to the Act on Combating Drug Abuse came into force, which legalised the cultivation of low THC medical cannabis. Under the ruling, companies require a special permit from the Ministry of Health as well as hold a licence for the production of medicines and active substances from the Agency for Medicinal Products and Medical Devices (HALMED).
The only cannabis-based medicine with regulatory approval in Croatia is Epidyolex.

Sources

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4.18.3. Finland

Medical Cannabis (flower & oil products) is an unlicensed medicine and is strictly controlled in Finland, requiring a special permit granted by the Finnish Medicines Agency (Fimea).

Doctors who are pain management specialists at university hospitals, as well as health centre doctors, can prescribe Medical Cannabis with a special permit application. To prescribe unlicensed Medical Cannabis products, doctors must justify that the patient has exhausted all other authorised medicines and that a prescription would be beneficial for treatment. The treatable pathologies in which unlicensed Medical Cannabis products have been prescribed in Finland include multiple sclerosis, Parkinson's disease, severe rheumatism, spinal cord injuries, fibromyalgia, and nervous and chronic pain.

The number of prescriptions of unlicensed Medical Cannabis products has dropped in Finland as health agencies have warned doctors against prescribing Bedrocan, highlighting that Sativex, which has a marketing authorisation, should be prescribed instead.

Sativex received marketing approval in 2012. The product is prescribed for the treatment of muscle stiffness or spasticity, symptoms in patients with multiple sclerosis, as an adjunct to other medications when these have not helped sufficiently. The price for Sativex in Finland is € 644.35

and is not reimbursable. Epidyolex is also available through its marketing authorisation at the EU level in 2019. It is prescribed for the treatment of certain rare hereditary forms of childhood-onset epilepsy in combination with clobazam. The price for Epidyolex is € 1399.26 and is eligible for reimbursement if all reimbursement criteria are fulfilled based on a doctor's statement only.

Sources

[1] https://www.kela.fi/medicinal-products-database.

[2] https://sic.fimea.fi/-/laakeviranomainen-ja-kannabis-1.

4.18.4. Lithuania

On 11 October 2018, Lithuania legalised the manufacturing, import, export and distribution of medical cannabis. The law came into effect on 1 May 2019, however, the industry has been slow to be implemented, with no patients receiving medical cannabis.

Under the framework, patients suffering from cancer, multiple sclerosis, epilepsy and AIDS are technically able to receive medical cannabis treatment.

Additionally, companies can obtain licences for the manufacturing, wholesale, import & export and retail of medical cannabis products through the State Medicines Control Agency.

The cultivation of Medical Cannabis in Lithuania is not permitted.

Sources

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4.18.5. Luxembourg

Luxembourg introduced its Medical Cannabis law on July 20th, 2018, with the programme officially commencing in February 2019. Under the country's Medical Cannabis programme, only doctors licensed in Luxembourg and those who have specific training for its prescription may prescribe Medical Cannabis to patients.

Medical cannabis may be prescribed to Luxembourgish insured patients who suffer from

- Serious chronic diseases—classified as long-term diseases under Article 19b(1) of the Social Security Code, which are in an advanced or terminal stage and result in severe and disabling chronic pain. Patients must also have exhausted all available drug treatments, or where such treatments are not available;
- Nausea & vomiting—due to cancer treatment through chemotherapy;
- Symptomatic muscle spasticity—associated with Multiple Sclerosis.

Medical Cannabis is dispensed at hospital pharmacies and is covered by the public health insurance.

As of 1 January 2025, high-THC flowers have been removed as prescribable medical cannabis, thereby limiting the roughly 1,100 medical cannabis patients to balanced and high CBD flower products as well as cannabis oil extracts (High THC, Balanced, High CBD). The removal of high THC flowers is part of longer-term plans to phase out flower-based products altogether.

On 6 January 2025, it was announced that Tilray Deutschland GmbH was awarded the tender to supply a maximum quantity of 100 kilograms of dried cannabis flower.

Currently, the cannabinoid medicines that are authorised in Luxembourg are Sativex and Epidyolex.

Sources

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4.18.6. North Macedonia

In 2016, North Macedonia legalised the cultivation and manufacture of medical cannabis. Since then, it has become one of the largest producers and exporters of Medical Cannabis in Europe.

66 companies are licensed to produce medical cannabis in the country (as of 2022), though only a handful of this number have succeeded in producing and exporting cannabis commercially.

Several North Macedonian companies have attained EU-GMP certification for cannabis-related manufacturing activity, and the country looks set to become a key Medical Cannabis production hub in Europe.

Patient treatment with Medical Cannabis was also legalised in North Macedonia in 2016, though patient access is extremely limited, if it exists at all. Under the law, government-approved doctors with a specialisation in particular illnesses like multiple sclerosis, epilepsy, HIV and certain types of cancer can prescribe medical cannabis to patients suffering from these conditions.

Sources

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[2] https://eudragmdp.ema.europa.eu/inspections/displayWelcome.do.

[3] https://www.karanovicpartners.com/news/medical-cannabis-in-north-macedonia/.

4.18.7. Norway

In November 2016, Norway issued new guidelines regarding Medical Cannabis and approval exemptions. In Norway, unregistered Medical Cannabis products (flowers and oils) containing more than 1% THC may be prescribed through an application for an exemption, which is approved by the Norwegian Medicines Agency (DMP).

There is no official list of approved conditions in which the use of these medicines is relevant; however, patients who receive approval usually have severe pain and have exhausted all other forms of treatment.

To prescribe unregistered cannabis products over 1% THC, specialists must provide a justification why other forms of approved medicines are not suitable for the patient. Once the DMP approves the exemption, the hospital pharmacy delivers the product to the patient, for which the pharmacy wholesaler must obtain an import permit from the DMP.

Unregistered cannabis medicines that have been made available to patients include flowers by Bedrocan, magistral oils made from the Danish Glostrup pharmacy and oil drops from Stenocare. If a public hospital offers cannabis treatment, the health authorities cover the cost of the treatment; however, if specialists outside of a public hospital offer treatment, the patient must pay out of pocket.

Sativex is an available treatment for multiple sclerosis, and Epidyolex for certain forms of epilepsy in children, which all physicians who have the right to prescribe medicines in group A can prescribe. Both medicines are reimbursable through a hospital prescription.

Sources

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4.18.8. Slovenia

Slovenia first legalised Medical Cannabis (flowers & extracts) in March 2017 by removing cannabis from a schedule 1 narcotic with no medical value to a schedule 2 narcotic with a high potential for abuse with medical value.
Although theoretically, Medical Cannabis flowers and extracts can be obtained magistrally through a special prescription or import exemptions provided by the Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (JAZMP), in practice this has not become routine and only very few patients have received Medical Cannabis treatment in the country.
Specialist doctors in Slovenia may only prescribe Medical Cannabis as long as all other authorised medical treatments have been exhausted and there is sufficient evidence that medical cannabis treatment is effective for the patient's ailment. Treatable pathologies in which a doctor can prescribe medical cannabis in Slovenia include:

- Severe forms of epilepsy;
- Nausea and vomiting due to cancer treatment;
- Multiple sclerosis;
- Pain associated with cancer.

In April 2025, MPs from coalition parties Freedom Movement party and The Left drafted a law that seeks to regulate the cultivation, production and distribution of medical cannabis to improve patient access as well as to benefit from economic participation in the industry. Under the proposed law, companies will be able to cultivate determined quantities of Medical Cannabis through a permit and an annual strategic program set by the Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices.
Epidoylex has been authorised for sale in the EU since 2019; patients suffering from Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) can

get it prescribed in Slovenia. Patients are able to be prescribed Sativex, through a temporary permission for entry or import, as it has no marketing authorisation in Slovenia.

Sources

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[3] https://www.healtheuropa.com/icanna-cannabis-in-slovenia/102610/.

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CHAPTER **5.**

CONCLUSIONS

Medicinal Cannabis, characterized by its complex array of phytocannabinoids, presents a significant pharmacological landscape. Among these, Delta-9-tetrahydrocannabinol (THC) stands out. Despite its classification as a narcotic under International Law due to its psychotropic effects, THC has demonstrated valuable therapeutic applications across a range of pathological conditions.

Parallel developments have seen a surge in interest in the non-psychotomimetic components of cannabis, such as Cannabidiol (CBD) and other 'minor' cannabinoids like CBG, THCV, THCA, and CBDA, as well as terpenoids. Notably, CBD has been effective in treating several types of drug-resistant epilepsy and offers considerable anti-inflammatory benefits, which are particularly appealing given its mild side effects.

The role of the medical professional remains paramount in the therapeutic use of cannabis, crucial for devising appropriate treatments tailored to individual patient needs. It is our aspiration that healthcare providers across all European countries will soon be equipped to prescribe cannabis, following comprehensive evaluations to formulate personalized therapeutic plans that consider optimal dosing and aim to minimize side effects.

In this vision, we strongly advocate for greater harmonisation of access and regulatory frameworks across Europe, so that scientific research and

responsible market development can thrive beyond the limitations of national politics.

We also believe that in such harmonisation, cannabis-based therapies should become one of the many legitimate tools available to prescribers—integrated into public healthcare systems and insurance coverage, so as not to remain a niche solution accessible only to the few. It is time for the plant to return to its core role: serving health and wellbeing, inclusively and equitably.

This text is part of the broader research and dissemination work we carry out at Cannabiscientia SA, and stems directly from the contributions of Fabio Turco, PhD, and neuroscientist Viola Brugnatelli.

For years, we have been committed to advancing scientific knowledge on cannabis, with a particular focus on its medical application and the development of independent education for healthcare professionals.

Despite the significant progress made in cannabis research over the past three decades—thanks to the work of many pioneers in the field—much remains to be clarified regarding the mechanisms of action and overall efficacy of cannabis in various physiopathological conditions. The absence of large-scale clinical trials still limits the ability to draw strong conclusions from otherwise promising findings.

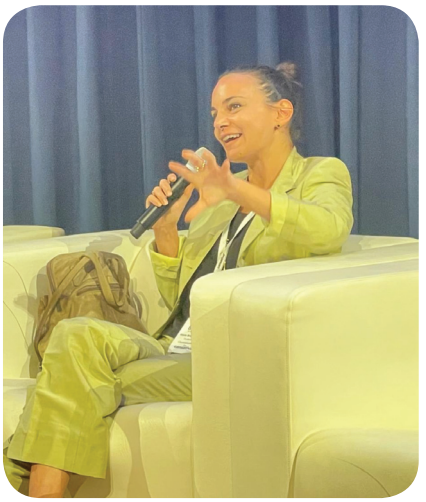
However, we are confident that with the ongoing evolution of research and the emergence of new therapeutic indications, continuously updated and cross-disciplinary education is essential for prescribers. We believe in a model of medicine where knowledge truly serves care—and where cannabis therapies can take their place among accessible, personalized, and

reimbursable treatment options. Not reserved for the few, but integrated into the clinical journey of many.

With this vision, we continue to work towards greater harmonization across Europe—so that cannabis may return to being what it has always been: a natural resource in service of health.

Viola Brugnatelli, MSc
Fabio Turco, PhD
Cannabiscientia SA

Authors & Contributors



Viola Brugnatelli is a neuropharmacologist with over a decade of experience in the field of medical cannabis. Her research journey began in 2012 at Ninewells Hospital, NHS (Scotland), where she investigated novel cannabinoid receptors, and continued at University College Dublin (Ireland), focusing on the role of CBD in inflammatory processes.

In 2017, she successfully launched a training course on endocannabinoid science at the Department of Neuroscience at the University of Padua. In 2018, she co-founded Cannabiscienza Srl, Italy's leading institution dedicated to scientific cannabis education for healthcare professionals, establishing the largest trained network of doctors, veterinarians, and pharmacists on medical cannabis in Europe. In 2022, she expanded this mission internationally by founding Cannabiscientia SA in Switzerland.

Viola is the author of numerous scientific articles, reports, and reference manuals for prescribers and researchers. In addition to her work in research and education, she plays a pivotal role in translating complex cannabis science into actionable frameworks for the regulatory, healthcare, and economic sectors. She is a frequent public speaker at industry events and scientific conferences, where she shares her strategic vision and dedication to aligning patient needs, medical innovation, and financial opportunity.

Viola's mission stems from a deeply personal story: the loss of her seventeen-year-old sister due to a chemotherapy side effect (hypokalemia caused by uncontrollable vomiting). Medical cannabis, now reimbursed in Italy as a palliative oncology treatment by the national health service, could have saved her life. This profound sense of justice has fueled Viola's commitment to education—so that no patient should suffer needlessly from a lack of effective treatment.

Fabio Turco obtained his PhD in 2010, and subsequently continued his research activity as a postdoctoral fellow. His research focused on the intestinal Endocannabinoid System, probiotic modulation of the gut microbiota, and the gut-brain axis. Notably, his work led to the first identification of Toll-like receptor expression on human enteroglial cells and contributed to elucidating the role of palmitoylethanolamide (PEA) in chronic inflammatory intestinal diseases.
Dr. Turco is an acknowledged expert in medical cannabis and cannabinoids, actively engaged as a scientific consultant and advisor in this field. He currently serves as Scientific Director at Cannabiscientia SA, where he oversees research and education initiatives aimed at advancing evidence-based knowledge on cannabinoid science and clinical applications.

We extend our deepest gratitude to all the distinguished contributors from all over the world, whose expertise has significantly enriched the *Principles of Clinical Cannabinology*.
Each contributor has played a pivotal role in enhancing the depth and breadth of this manual through their specialized knowledge:

Marcello Albanesi, Clinical Allergist and Fundamental Immunologist at Marcello Albanesi Allergology and Immunology Unit, Bari, Italy.

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Stephen Murphy, CEO & Co-founder Prohibition Partners, London, United Kingdom.

This second edition, co-authored by Cannabiscientia SA and Prohibition Partners, serves as a comprehensive resource for European healthcare professionals and stakeholders interested in the clinical application of cannabis. It presents an expanded and critically updated synthesis of current scientific evidence, regulatory frameworks, therapeutic uses, and product availability across Europe.

New content includes practical tools such as tables outlining drug-drug interactions involving CBD and THC, along with revised and extended clinical case studies. Contributions from an increased number of prescribing physicians and subject matter experts further enhance the book's practical value.

This edition documents the regulatory landscape and product offerings in 24 European countries (previously 12), with references to over 500 EU-GMP cannabis products (up from 200).

It aims to facilitate informed decision-making and support clinical integration of cannabinoid-based therapies in an increasingly complex European context.

Viola Brugnatelli is a neuropharmacologist with over a decade of experience in the field of medical cannabis. Her research journey began in 2012 at Ninewells Hospital, NHS (Scotland), where she investigated novel cannabinoid receptors, and continued at University College Dublin (Ireland), focusing on the role of CBD in inflammatory processes.

In 2017, she successfully launched a training course on endocannabinoid science at the Department of Neuroscience at the University of Padua. In 2018, she co-founded **Cannabiscienza Srl**, Italy's leading institution dedicated to scientific cannabis education for healthcare professionals, establishing the largest trained network of doctors, veterinarians, and pharmacists on medical cannabis in Europe. In 2022, she expanded this mission internationally by founding **Cannabiscientia SA** in Switzerland.

Viola is the author of numerous scientific articles, reports, and reference manuals for prescribers and researchers. In addition to her work in research and education, she plays a pivotal role in translating complex cannabis science into actionable frameworks for the regulatory, healthcare, and economic sectors. She is a frequent public speaker at industry events and scientific conferences, where she shares her strategic vision and dedication to aligning patient needs, medical innovation, and financial opportunity.

Viola's mission stems from a deeply personal story: the loss of her seventeen-year-old sister due to a chemotherapy side effect (hypokalemia caused by uncontrollable vomiting). Medical cannabis, now reimbursed in Italy as a palliative oncology treatment by the national health service, could have saved her life. This profound sense of justice has fueled Viola's commitment to education—so that no patient should suffer needlessly from a lack of effective treatment.

Fabio Turco obtained his PhD in 2010 and subsequently continued his research activity as a postdoctoral fellow.

His research focused on the intestinal Endocannabinoid system, probiotic modulation of the gut microbiota, and the gut-brain axis (neuro-gastro-cannabinology). Notably, his work led to the first identification of Toll-like receptor expression on human enteroglial cells and contributed to elucidating the role of palmitoylethanolamide (PEA) in chronic inflammatory intestinal diseases. Dr. Turco is an acknowledged expert in medical cannabis and cannabinoids, actively engaged as a scientific consultant and advisor in this field. He currently serves as Scientific Director at Cannabiscientia SA, where he oversees research and education initiatives aimed at advancing evidence-based knowledge on cannabinoid science and clinical applications.

Cristina Dirlea is a cannabis science communicator with a background in physiology (University of Toronto, ETH Zurich) and applied cannabis science (Loyalist College).
Her experience spans lab research with controlled substances, retail strategy, education, and consulting. She contributed to the scientific proofreading of Principles of Clinical Cannabinology, ensuring the accuracy of clinical and product-related content.