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Review

Cannabis for Chronic Pain: Mechanistic Insights and Therapeutic Challenges

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Abstract: Chronic pain represents a complex and debilitating condition that affects millions of people worldwide, significantly compromising their quality of life. The conventional approach to treating this type of pain often relies on the use of opioid analgesics and anti-inflammatory drugs. While these agents are effective in the short term, they present several limitations, including the risk of dependence, severe side effects, and, in some cases, ineffectiveness in reducing pain. In this context, medical cannabis has emerged as a promising therapeutic alternative, given its potential ability to relieve pain effectively with a favorable safety profile. This work aims to provide a comprehensive and up-to-date review of the existing literature on the effects of medical cannabis in the treatment of chronic pain. *Cannabis sativa* contains several pharmacologically active compounds, the most prominent of which are delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), which interact with the body's endocannabinoid system, thereby modulating the pain response. Clinical evidence has shown that cannabinoids can significantly reduce the intensity of chronic pain, particularly in cases of neuropathy, multiple sclerosis, arthritis, and other painful conditions that are unresponsive to conventional treatments. However, the full integration of medical cannabis into clinical practice faces significant obstacles, including the need for standardized dosing, long-term safety data, and regulatory frameworks. These issues, alongside concerns over adverse effects and drug interactions, must be addressed to unlock the full therapeutic potential of cannabinoids, particularly for chronic pain patients, who endure both physical suffering and the added burden of stress.

Keywords: *Cannabis sativa*; Δ^9-tetrahydrocannabinol; cannabidiol; chronic pain; endocannabinoid system; adverse effects; drug interactions

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1. Introduction

Millions of people around the world suffer from the reality of chronic pain [1], which places a significant burden not only on the individuals affected but also on healthcare systems. In view of the public health crisis, the search for effective and safe therapies for the relief of chronic pain has become an urgent priority [2,3]. In this context, the use of cannabis for medicinal purposes has become a viable therapeutic tool that offers an alternative perspective in the management of chronic pain [4]. The analgesic and anti-inflammatory effects of cannabinoids have been extensively researched, providing an

acceptable replacement for current drugs [5,6]. Cannabinoid-based drugs approved by the Food and Drug Administration (FDA) include CBD (Epidiolex®), a combination of Δ^9-THC and CBD (Sativex®), Δ^9-THC, and its synthetic analogs such as nabilone (Cesamet®) and dronabinol (Marinol® and Syndros®) [7]. The use of medicinal cannabis in the treatment of chronic pain is important not only because of its potential efficacy but also because it fills gaps in conventional therapy. For many patients suffering from this type of pain, medicinal cannabis offers hope of relief and improved quality of life, especially for those who do not have an adequate response to traditional painkillers or who suffer from their adverse effects [8].

However, despite the mounting interest and evidence supporting the use of cannabis for medicinal purposes, several key concerns remain. Considerations of safety, efficacy, regulation, accessibility, and possibly social stigma are all entwined in the discussion around the use of medicinal cannabis, particularly phytocannabinoids, in the treatment of chronic pain.

2. *Cannabis sativa*

Cannabis sativa, commonly known as cannabis, is a member of the Rosales order, Cannabaceae family, and Cannabis genus [9,10]. It was one of the earliest plants to be cultivated, and its medical use was mentioned in the first written pharmacopeia around 2700 BC [11,12]. Cannabis was first used as medicine in India (~1000 BC), as an analgesic, anticonvulsant, hypnotic, tranquilizer, anesthetic, anti-inflammatory, antibiotic, antispasmodic, and hunger stimulant [11]. The use of this plant in Western medicine began at the end of the nineteenth century; however, by the beginning of the twentieth century, the use of cannabis to treat diseases began to decline, which can be attributed to an assortment of factors, including the difficulty in obtaining consistent and replicable effects. Furthermore, new synthetic chemical substances emerged, such as opioids and non-steroidal anti-inflammatory medications, with the same efficacy in treating the principal indications of cannabis [9,11]. Phytocannabinoids, flavonoids, terpenoids, alkaloids, glycoproteins, and phytosteroids are among the many phytochemicals described in cannabis [13,14], containing more than 125 cannabinoids and 400 non-cannabinoid compounds [15,16]. Therefore, the presence of cannabinoids is a characteristic shared by all plants belonging to the Cannabis genus. These secondary compounds, which oversee protecting and defending the plant against insects, bacteria, fungi, and some diseases, are mostly produced in the glandular trichomes of female plants.

According to Breijyeh et al. (2021) [4], cannabinoids can be divided into three classes based on their synthesis site, namely phytocannabinoids (cannabinoids found in plants), endocannabinoids (endogenous compounds found in animals that modulate the same receptors as those affected by certain phytocannabinoids (the cannabinoid receptors), and synthetic cannabinoids (synthetic substances that may or may not be structurally linked to phytocannabinoids and elicit agonistic actions at cannabinoid receptors) [4,17].

2.1. Phytocannabinoids

Phytocannabinoids comprise a class of terpenophenolic metabolites, characterized by the presence of a resorcinol ring para-substituted with an isoprenyl, alkyl, or aralkyl side chain [18], even though most of them are alkyl-type phytocannabinoids alkylated with a monoterpene unit.

The phytocannabinoids identified in *Cannabis sativa* can be classified into eleven subclasses as follows: delta-9-tetrahydrocannabinol (Δ^9-THC), delta-8-tetrahydrocannabinol (Δ^8-THC), cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), cannabinediol (CBND), cannabielsoin (CBE), cannabicyclol (CBL), cannabinol (CBN), cannabitriol (CBT),

and various cannabinoids, with Δ^9-THC and CBD (Figure 1) being the two most abundant cannabinoids with the greatest therapeutic interest [15,19,20].

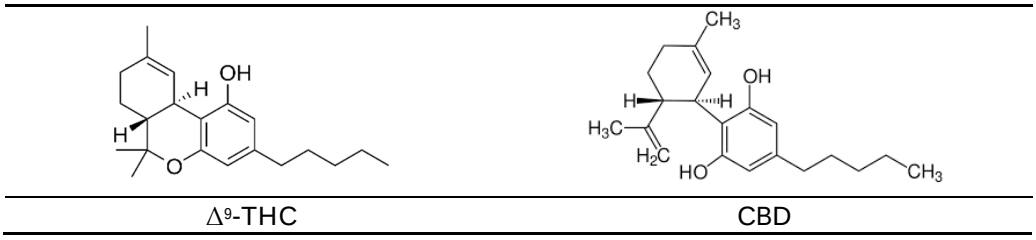

Figure 1. Chemical structures of Δ^9-THC and CBD, respectively.

Δ^9-THC is the main phytocannabinoid with psychoactive properties and notable pharmacological properties. From a pharmacological perspective, Δ^9-THC is a partial agonist (it lacks the ability to fully activate both cannabinoid receptors to elicit a maximal response) of both mammalian cannabinoid receptors, which are CB_1, which modulates psychoactive effects, causing anxiety, paranoia, altered perspective, and cognitive deficits, and CB_2, which modulates immunological and anti-inflammatory effects [13,21]. Thus, Δ^9-THC possesses analgesic properties in chronic and neuropathic pain, appetite stimulation in cancer patients, a reduction in nausea and vomiting in patients undergoing chemotherapy, beneficial effects in patients with Tourette's syndrome, and improved sleep quality [15,22].

As for CBD, despite its structural similarity to Δ^9-THC, it does not activate the CB_1 and CB_2 receptors and therefore does not exhibit the psychotropic effects associated with cannabis [15,23]. Ongoing experimental research on CBD shows its wide range of therapeutic applications and its ability to work in concert with Δ^9-THC at controlled doses, including anti-inflammatory, anxiolytic, analgesic, antipsychotic, anticonvulsant, antioxidant, anti-emetic, neuroprotective, and anti-tumor properties. Additionally, there is significant potential for treating conditions such as epilepsy, substance abuse and dependence, schizophrenia, post-traumatic stress disorder, depression, Parkinson's disease, and Alzheimer's disease [13,15,24,25].

2.2. Endocannabinoids

The discovery of the endocannabinoid system opened up new avenues for global research into the potential therapeutic applications of cannabis. This resulted in the discovery of its receptors in the body, which are called cannabinoid receptors 1 (CB_1) and cannabinoid receptors 2 (CB_2), where the designation "CB" refers to "cannabinoid binding" and was assigned by the International Union of Basic and Clinical Pharmacology (IUPHAR) subcommittee on nomenclature and classification of cannabinoid receptors [15,26]. Anandamide, also known as N-arachidonoylethanolamine (AEA), and 2-arachidonoylglycerol (2-AG) were the first endocannabinoid compounds to be identified, and their biological roles remain to be investigated. Thus, arachidonic acid derivatives belong to the endocannabinoid class, which includes lipophilic amides, esters, and ethers. Virodhamine is the O-acyl analog of AEA, and 2-arachidonyl glyceryl ether (2-AGE) is a reduced form of 2-AG [27]. Other endocannabinoids include N-acylamino acids (eg N-arachidonoylserine) and N-acylated neurotransmitters (eg N-arachidonoyldopamine) [17].

The endocannabinoid system is involved in several biological functions, including cognitive processes, behavioral control, memory, motor control, pain sensation, and appetite, among others [28,29]. Covering a wide range of physiological processes under homeostatic control, this is potentially one of the most significant discoveries in the fields of medicine and physiology in the last century [30].

CB_1 receptors are G protein-coupled receptors that are primarily located in the central nervous system (CNS). They are predominantly found in the terminals of neurons in the basal ganglia, cerebellum, hippocampus, neocortex and hypothalamus, and limbic cortex, and they mediate the main psychotropic effects of cannabinoids [31,32]. Importantly, these brain regions are involved in motor activity, coordination, short-term memory, executive function, appetite, and sedation [31]. In addition, CB_1 receptors are also present in smaller amounts in various peripheral tissues and cells, such as cardiovascular tissue, the gastrointestinal tract, liver, reproductive system, muscles, bone, and skin [29].

In contrast, CB_2 receptors are commonly found in immune-related tissues and organs and can become significantly active during inflammation or damage processes [26,33]. These receptors are additionally connected to the G protein [33,34] and are primarily located in immune system cells, including leukocytes, the spleen, tonsils, bone marrow, the thymus, B and T lymphocytes, monocytes, NK cells, and mast cells [35,36]. These have a role in the control of cytokine release and the migration of neutrophils and macrophages, thereby reducing inflammatory processes and modulating neuropathic pain [35,37]. In addition, the activation of CB_2 receptors on keratinocytes stimulates the release of β-endorphins, which act on opioid receptors μ peripheral sensory neurons to inhibit nociception [38]. Finally, these receptors are also present in the lungs, uterine, and bone tissue, including osteoclasts, osteoblasts, and osteocytes. It has been shown in studies that mutations or polymorphisms in the CB_2 receptor are related to the onset of osteoporosis in humans; in addition, studies carried out in knock-out mice for the CB_2 receptor have shown accelerated age-related loss of trabecular bone mass [39]. Although the evidence for the existence of cannabinoid receptors and the understanding of their signaling pathways have been sufficient to establish their biological importance, the identification of their endogenous ligands has been fundamental to understanding their functional relevance [40,41].

These endocannabinoids are lipophilic compounds that are generated on demand and promptly removed by hydrolyzing enzymes. In clinical trials, endocannabinoid signaling was found to be disrupted in individuals with chronic pain. There is significant evidence to suggest that the endocannabinoid system plays a role in triggering strong effects on neurotransmission, neuroendocrine, and inflammatory processes, all of which are known to be disrupted in chronic pain [42].

3. Chronic Pain

Pain is considered "an unpleasant sensory and emotional experience associated, or similar to that associated, with actual or potential tissue damage", and since 2020, this definition is based on the following criteria [43,44]:

1. Pain is a personal experience influenced at various levels and degrees by psychological, social, and biological factors;
2. Pain and nociception are distinct concepts, and pain cannot only be inferred by activity in sensory neurons;
3. Pain is something that is learnt throughout life experience;
4. Reports of pain experiences should be respected;
5. Pain is an adaptive process, which can have an influence on psychological and social well-being;
6. The way to express pain can be through verbal description. The inability to communicate should not negate the fact that human beings or non-human living beings feel pain.

Pain, as a clinical symptom, has become a serious public health issue due to its frequency and ability to cause suffering and disability but above all due to the serious personal, family, and social consequences [45,46]. Pain is a unique, subjective, and non-

transferable experience. Each individual has their own interpretation of pain, influenced by biological, psychological, social, emotional, cultural, and spiritual aspects [47,48].

Chronic pain is defined as persistent or recurring pain for at least 3 to 6 months, often extending beyond the healing of the initial injury or manifesting itself in the absence of obvious injury, resulting in limitations and disabilities that affect work, social, and family life, and it can be caused by a wide range of common medical conditions, including arthritis, cancer, and diabetes or by other factors, such as trauma or surgery, or even an undetermined cause [47,49,50]. Chronic pain negatively impacts the lives of almost 2 billion people worldwide [51].

3.1. Classification of Pain

As shown in Figure 2, pain can be classified according to various characteristics, including the site of origin, etiology, intensity, duration, and pathophysiological mechanism (nociceptive, neuropathic pain, and nociplastic pain (or central sensitization) [46,52,53].

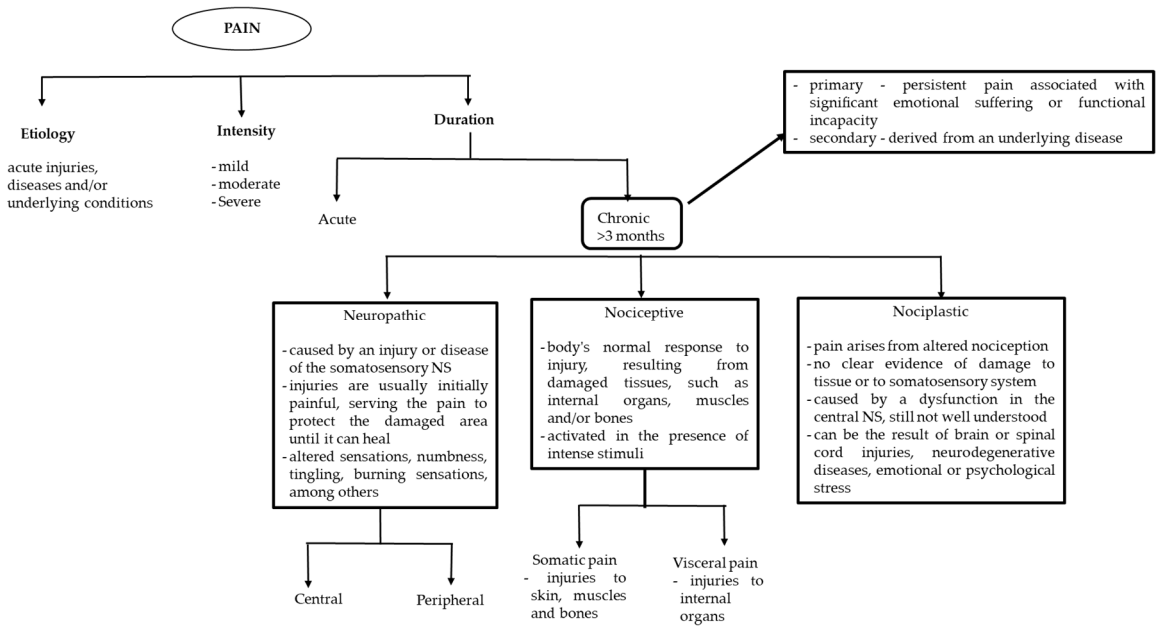

Figure 2. Pain classification [52,54–61].

Unlike acute pain, chronic pain lasts for more than 3 months and can result from a disease such as rheumatoid arthritis, diabetes, stroke, or from an injury that has already healed [55]. It is associated with "useless" and debilitating pain and often disturbs sleep, mood, and psychological well-being, leading to a reduction in vitality and physical activity [62,63]. Ultimately, it can lead to social isolation, affecting personal, intimate, and even sexual relationships. For all these reasons, chronic pain can be associated with depression, which requires a doctor to consider the patient's entire psychological and social context [64]. The WHO, in collaboration with the International Association for the Study of Pain, has developed a new classification of chronic pain that describes seven distinct categories, which can be divided into primary chronic pain and secondary chronic pain [56].

3.2. Mechanism of Pain

Nociception is the process by which mechanical, thermal, and chemical stimuli are detected by macromolecular structures present in the peripheral nerve fibers, known as nociceptors, and subsequently transmitted to the brain [65].

Pain processing can be divided into four phases, namely transduction, transmission, perception, and modulation (Figure 3) [66].

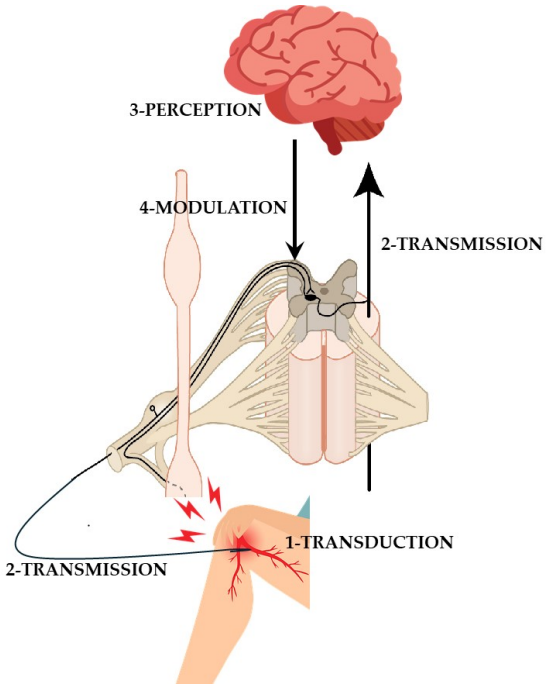

Figure 3. Phases of pain processing, namely transduction, transmission, perception, and modulation. ("Slagter—Drawing appendicitis, pain route and referred pain—no labels" by Ron Slagter and O. Paul Gobée, LUMC, license: CC BY-NC-SA).

Transduction begins when the nociceptors are activated by a noxious stimulus, causing the ion channels to open, creating electrical impulses that are propagated to the spinal cord, brainstem, thalamus, and cortex. There are two main types of nociceptors; Aδ fibers are myelinated fast conduction nociceptors that trigger a withdrawal reflex from the painful stimulus even before the pain sensation is fully perceived; C fibers are smaller, unmyelinated, slow-conducting fibers that make up the majority of peripheral nociceptors [67,68]. These fibers are located in muscles, tendons, organs, and the skin, and they transmit burning, throbbing sensations that are not well localized [66]. Nociceptors, when directly stimulated, release various chemical mediators, such as histamine, bradykinin, acetylcholine, serotonin, and substance P, which activate even more nociceptors [69,70].

Transmission is the second process involved in nociception and refers to the motion of action potentials from the peripheral terminal along the axons to the central terminal of the nociceptors in the central nervous system. This conduction is carried out by first-order neurons to the dorsal horn of the spinal cord [70]. Here, they form synapses with second-order neurons [71], which ascend to the brain via two distinct spinothalamic tracts. The neo-spinothalamic tract carries fast impulses signaling acute pain, while the paleo-spinothalamic tract carries slow impulses [66]. The impulses are then projected to the somatosensory cortex for interpretation and to other areas of the brain for an integrated response to pain stimuli [72].

The next step is pain perception, where the brain interprets and decodes the input, which is a step towards pain awareness [73]. The transmission of stimuli then ends in the reticular and limbic systems and the cerebral cortex [66]. The interpretation of pain can be influenced by various factors such as genetics, gender, life experiences, and past pain experiences [73]. Modulation is the last process in nociception and refers to the alteration of sensory input. In this final stage, the modulation of pain stimuli occurs through endogenous mechanisms. Supraspinal inhibition leads to the release of endogenous opioids that inhibit the release of neurotransmitters from the primary neuron and hyperpolarize the secondary

neuron so that it requires greater stimuli to reach the action potential. There are other neurotransmitters with this function, such as norepinephrine and serotonin [66,67].

3.3. Possible Mechanisms in Chronic Pain

Chronic pain is a complex challenge that affects countless people around the world, often becoming a constant and debilitating presence in their lives. One of the characteristics of chronic pain with neuropathic symptoms is the presence of phenomena such as hyperalgesia and allodynia, which broaden the understanding of pain beyond the simple sensation of discomfort [72]. Hyperalgesia refers to an exacerbated sensitivity to pain, where stimuli that would normally be mildly painful are perceived as extremely painful, while allodynia is characterized by the perception of pain in response to stimuli that would not normally be painful [71].

Therefore, the literature describes that chronic pain can result from two mechanisms of pain sensitization, peripheral sensitization and central sensitization [74].

Peripheral sensitization begins when there is tissue damage followed by an inflammatory reaction, which leads to the activation of Aδ and C fibers by inflammatory mediators such as bradykinin, prostaglandins, cytokines, and others, which have the ability to bind and directly stimulate G protein-coupled, ionotropic, or tyrosine kinase receptors [72]. Like immune cells, nociceptors also express cytokines, chemokines, and Toll-like receptors, which play an essential role in modulating the immune system [72,75]; this release can lead to the production of more immune cells that are directed to the site of inflammation. In addition, compounds such as adenosine triphosphate, K^+ and H^+ ions, bradykinin, histamine, and serotonin are released, which directly activate the receptors expressed on the peripheral terminals of nociceptors, causing depolarization and a consequent action potential [74,75]. Pro-allergic inflammatory mediators are also released, such as prostaglandins and interleukins, which have the ability to sensitize local peripheral nociceptors. This occurs through the activation of intracellular secondary messengers, such as protein kinases, which in turn lead to the phosphorylation and altered activity of ion channels [75].

The sum of these processes leads to a reduction in the response threshold and an increase in nociceptor transduction activity, resulting in abnormal pain with hypersensitivity at the site of injury [74,76].

The process of central sensitization consists of a phenomenon that is triggered by a prolonged nociceptive stimulus or with a high frequency, which will lead to neuronal changes that are maintained even beyond the period of stimulation and become practically independent of the stimulation itself, leading to permanent changes in the nociceptive system without physiological purpose. This type of sensitization leads to a state of neuronal hyperexcitability, resulting in increased processing of painful stimuli, an increase in receptive fields, a reduction in the activation threshold, and an increase in spontaneous activity [77]. As mentioned above, this type of sensitization is prolonged over time, thus giving rise to the phenomenon of long-term potentiation, which consists of an increase in the effectiveness of an excitatory synapse following short-duration high-frequency stimulation. Another phenomenon that occurs is called “wind-up”, which is characterized by a repetitive low-frequency stimulus but with a constant intensity that is sufficient to activate the C-fibers [78].

For this sensitization to occur, there must be activation of NMDA (N-methyl-D-aspartate) glutamate receptors, an increase in the intracellular concentration of Ca^{2+}, and the activation of protein kinases that phosphorylate certain receptors and/or ion channels [79].

When a C-fiber is activated by a nociceptive stimulus, glutamate is released into the synapse between its central terminal and the spinal neuron, causing glutamate to bind

to its receptors, namely AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolpropionate) and NMDA, present in the spinal neuron [75,80].

Under normal conditions, NMDA receptors are blocked by Mg^+ ions, so there is no effect when glutamate binds to the NMDA receptor, whereas when it binds to the AMPA receptor, Na^+ enters, leading to depolarization of the spinal neuron membrane and thus the emergence of the action potential. This synaptic transmission ends with the inactivation of AMPA receptors and the opening of voltage-sensitive K^+ channels, resulting in repolarization of the membrane [81,82]. However, the transient depolarization of the membrane causes the opening of Ca^{2+} channels, controlled by the membrane's electrical potential, and if this depolarization occurs repeatedly as a result of repeated stimulation of the C-fibers, the neuronal membrane becomes depolarized due to the increase in the intracellular concentration of Na^+ and Ca^{2+}. As a result, the ion channels of the NMDA receptors are no longer blocked by Mg^+ and are activated by glutamate, resulting in the entry of large quantities of Ca^{2+}, which activates various enzymes such as substance P and protein kinase, thereby altering neuronal excitability [82]. It has also been described in the literature that central sensitization can be facilitated by a reduction in the activity of inhibitory interneurons that produce glycine and γ-aminobutyric acid (GABA), which when inhibited lead to greater excitability and thus greater neuronal sensitivity [69,75].

3.4. Treatment of Chronic Pain

The main goals of treating patients with chronic pain are to provide pain relief, improve quality of life, and promote physical and emotional functionality. As mentioned in the previous sections, pain is a complex experience involving various mechanisms, so it is common for treatment to involve a combination of drugs with different modes of action, with the aim of increasing the effectiveness of pain treatment or control.

Pain control guidelines are applied in the treatment of chronic painful conditions, which may be oncological, but also in the case of degenerative or musculoskeletal diseases and neuropathic pain, among others [83]. One of the most important strategies for pain control is to start with oral medication, increasing the dose and strength until the pain can be controlled [84]. The ladder of guidelines is divided into three levels, with the first being non-opioid drugs, such as non-steroidal anti-inflammatory drugs, used to control mild pain. The second step is for moderate pain, and the pharmacological example is the use of weak opioids, such as codeine. Finally, the third step is for the treatment of severe pain, which requires the use of more powerful drugs, such as strong opioids like morphine. This ladder also includes adjuvant medications, which can be added at any time during treatment and consist of hypnotics, muscle relaxants, and anxiolytics to combat insomnia, muscle spasms, and anxiety, respectively [83,84]. Although adjuvants are co-administered with analgesics, they are indicated as a first-line treatment option for treating specific pain conditions. Tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, gabapentanoids, topicals, and transdermal substances are recommended as first-line therapy for the management of neuropathic pain [85].

Cannabinoids are included in guidelines as fourth-line therapy for chronic pain. The guidelines report that cannabis-based medicines may be considered as a treatment option for patients with neuropathic pain, with chronic non-cancer pain, and with chronic non-cancer, non-neuropathic pain but with some caveats [86]. However, there are authors who argue that there is sufficient evidence of the quality of medicinal cannabis to support its use as a first-line treatment for pain as an adjuvant or alternative to opioids [87]. The medicinal use of cannabis is mainly due to the analgesia mechanisms stimulated by cannabinoids, which are the inhibition of the release of neurotransmitters and neuropeptides in pre-synaptic nerve endings, the activation of the descending inhibitory pathway,

the modulation of postsynaptic neuronal excitability, or the reduction in neural inflammation [35,88–90].

The endocannabinoid system can modulate pain through peripheral and central mechanisms. In the periphery, CB_1 receptors are located in sensory afferent terminals and thus control the transduction of pain from nociceptive stimuli, whereas CB_2 receptors, located in cells of the immune system and keratinocytes, intervene in the release of endorphins, which act on opioid receptors in primary afferent neurons to inhibit nociception [91,92]. In terms of spinal mechanisms, endocannabinoids have antinociceptive effects due to the high expression of CB_1 receptors in the dorsal root ganglia and nociceptive terminals of the dorsal horn, where they inhibit the release of neurotransmitters involved in pain transmission [88,91]. CB_2 modulates central immune responses that are responsible for neuronal development and sensitization during chronic pain [90,93]. Finally, the endocannabinoid system is able to modulate painful stimuli at the supraspinal level, where CB_1 inhibits ascending nociceptive transmission, mainly in the thalamus and brainstem, and it modifies subjective pain perception by modulating neuronal activity in the limbic system, particularly in the amygdala and in the cortical areas, activating the descending inhibitory pathway by inhibiting GABA release in the gray matter and raphe nucleus. The emotional and cognitive effects of pain are modified by the activation of the CB_1 receptor, which acts in the limbic system and cortical areas of the brain [90,91].

4. Mechanism of Pharmacological Action of Cannabinoids

AEA and 2-AG are known to be synthesized from membrane lipid precursors in response to stimuli, whether physiological or pathological [32,94]. The biosynthesis of both occurs in postsynaptic neurons following the influx of calcium and the subsequent activation of enzymes responsible for their formation; however, their metabolisms follow different pathways [95]. In brief, AEA is formed from phospholipid precursors in the membrane as arachidonic acid, mainly by the sequential action of N-acyltransferase and N-acyl-phosphatidylethanolamine-specific phospholipase D [96,97]. However, the synthesis of 2-AG is mainly driven by two diacylglycerol lipases (DAGL α/β) [96].

Endocannabinoids are produced "on demand" when tissue damage occurs, usually due to an increase in the intracellular concentration of calcium [98]. These compounds act as signaling molecules by binding to cannabinoid receptors, thereby initiating a retrograde signaling process. Contrary to what is typical, the stimulus is released in the postsynaptic neurons, where endocannabinoids are synthesized. These endocannabinoids then bind to the endocannabinoid membrane transporter (EMT), becoming available to act on the cannabinoid receptors located on the endings of the presynaptic neurons [99].

In neurons, when an endogenous ligand interacts with the CB_1 receptor, the activation of the Gi protein occurs, which is the first component of signal transduction, resulting in the inhibition of adenylyl cyclase (AC) activity, which in turn inhibits the production of cyclic adenosine monophosphate (cAMP), thereby affecting intracellular signal transduction and protein kinase A (PKA) activity [100]. When potassium channels open, the resulting force (electrical and concentration gradient) causes an efflux of potassium and a loss of positive charges from the cell, leading to a decrease in excitability (hyperpolarization). In addition, voltage-dependent calcium channels are inhibited, resulting in reduced presynaptic excitability and decreased neurotransmitter release [35]. Due to the rapid reuptake and subsequent intracellular enzymatic degradation, the effect is considered to be short-lived [28,97]. The degradation of AEA is mediated by fatty acid amide hydrolase (FAAH), which has the ability to cleave AEA into arachidonic acid and ethanolamine in the postsynaptic membrane. However, there are other pathways for AEA catabolism, in which it can undergo oxidation by the action of the enzyme cyclooxygenase 2 (COX-2),

lipoxygenases, or the cytochrome P450 system [97,101] element. As for 2-AG, the main enzyme responsible for its hydrolysis is monoacylglycerol lipase (MAGL), which breaks it down into arachidonic acid and glycerol in the presynaptic membrane [101].

In recent years, some publications have shown the presence of the CB_1 receptor in other CNS structures, such as in postsynaptic neurons, where signaling may be autocrine, and in astrocytes, where signaling may be indirectly presynaptic or postsynaptic. However, these mechanisms are not fully understood, with the theory of retrograde signaling being widely accepted [29,100].

In addition to the aforementioned cannabinoid receptors, it is now known that AEA also acts as an agonist for TRPV1 receptors and is therefore considered an "endovanilloid". These receptors are found in peripheral afferent neurons, known as nociceptors, which, when activated, have the ability to regulate the synaptic transmission associated with nociception [100,102]. TRPV1 receptors are also expressed in postsynaptic neurons in the CNS, which play a role in regulating long-term synaptic plasticity phenomena such as long-term depression and long-term potentiation. However, the effects of AEA's action on TRPV1 are controversial, and the literature describes that the combined effects of TRPV1 and CB_1 can be synergistic or antagonistic depending on certain conditions [103].

Entourage Effect

As mentioned above, *C. sativa* contains a wide range of compounds in its composition, which can generate the so-called "entourage effect". In 1998, Professors Raphael Mechoulam and Shimon Ben-Shabat realized that there was a complex interaction between the different chemical compounds present in the plant, and that they worked together to produce more potent therapeutic effects than if they were used in isolation [104]. This effect is still not fully understood, but there are several studies suggesting that there is an interaction between the endocannabinoid 2-AG and 2-arachidonoylglycerol esters, which do not bind to or are active on CB_1 cannabinoid receptors. However, 2-arachidonoylglycerol esters can potentiate the effects of 2-AG at this receptor, thereby enhancing the typical effects of cannabinoids [105–107].

A multicenter, double-blind, randomized scientific study published in 2009 aimed to evaluate the efficacy of an extract containing 2.7 mg of Δ^9-THC and 2.5 mg of CBD compared to a pure Δ^9-THC extract (2.7 mg) and a placebo in relieving pain in patients with advanced cancer. This clinical trial was carried out on 177 patients with moderate-to-severe pain (on a 0–10 mean pain numerical rating scale (NRS) > 4) despite being treated with opioids. The study concluded that after two weeks of treatment with a THC:CBD extract, there was a higher reduction in pain intensity (NRS changed from 5.68 to 4.31) compared to the placebo group (NRS decrease from 6.05 to 5.38) and the Δ^9-THC-only group (NRS reduction from 5.67 to 4.66). These results highlight a synergy between Δ^9-THC and CBD and lead to the conclusion that CBD can enhance the analgesic power of Δ^9-THC through a strong inverse antagonism on CB_2 receptors, which can produce anti-inflammatory effects and inhibit the migration of immune cells. In addition, CBD can modulate the undesirable effects of Δ^9-THC by antagonizing CB_1 receptors, potentially providing a better safety profile for this extract in chronic use. However, there was no change in median dose or the mean number of doses for breakthrough pain, meaning that THC:CBD analgesic effects were pretty mild [108].

However, a recent review of five double-blind randomized controlled trials involving 1539 participants with moderate-to-severe pain unresponsive to opioid therapy found moderate–certain evidence that oromucosal nabiximols (Δ^9-THC and CBD) and Δ^9-THC alone offered no clinically relevant benefits. A meta-analysis of four studies with 1333 par-

ticipants revealed no significant improvement in patient-reported global impression of change or reductions in pain intensity compared to a placebo [109].

Van Dam et al. (2024) evaluated whether adding inhaled cannabis containing 6.3% Δ^9-THC and 8% CBD to oxycodone for chronic non-cancer pain management could reduce adverse effects while maintaining analgesia. Fibromyalgia patients were randomized to receive oxycodone, inhaled cannabis, or a combination of both for six weeks. No differences were observed in composite adverse event scores across groups. Hence, this study shows the results with cannabis are not superior to opioids in controlling pain in fibromyalgia patients. Nevertheless, the study has several limitations: it did not assess the intensity of adverse events for participants who remained in the study; the high dropout rate among cannabis users could bias results; the absence of a placebo control limits baseline comparisons; and the study population was predominantly female fibromyalgia patients, restricting generalizability beyond this demographic [110].

5. Efficacy Studies

This review included only randomized double-blind clinical trials that compared the effects of cannabinoids with a placebo or standard treatment, lasted at least 4 weeks after the start of treatment, and used one of the internationally validated pain intensity scales, most commonly the "Numerical Scale".

The study, conducted in 2007 by Nurmikko et al., was designed to evaluate the efficacy of Sativex® in relieving neuropathic pain of various etiologies characterized by allodynia. This was a randomized, double-blind, placebo-controlled study. The main objectives of this trial were to assess the efficacy of the drug in question in relieving pain and its impact on quality of life, such as improving sleep, depression, and anxiety. At the start of the study, the average intensity of pain reported was in the severe range, with the group taking the drug in question scoring 7.3 on the numerical scale and the placebo group scoring 7.2. At the end of treatment, the Sativex® group showed a reduction of 1.48 points on this scale (about 22%), while the placebo group showed a reduction of 0.52 points (about 8%). Twenty-six percent of patients in the Sativex® group showed an improvement of more than 30% in intensity compared with 15% of patients in the placebo group. It is also important to note that in terms of secondary objectives, there was also a significant improvement in terms of both sleep disturbance and allodynia in the group taking the drug in question [111].

In another study, Frank et al. carried out a randomized, double-blind trial to compare the analgesic efficacy and adverse effects of the synthetic cannabinoid nabilone with those of the weak opioid dihydrocodeine for the relief of chronic neuropathic pain. After treatment with both drugs, the authors concluded that dihydrocodeine was significantly better at relieving pain than nabilone and also had fewer adverse effects [112].

In 2010, Ware et al. conducted a four-period, randomized, double-blind, placebo-controlled crossover study in which the main objective was to understand whether smoked cannabis in different concentrations (2.5%, 6%, and 9.4% Δ^9-THC) would have analgesic effects in patients with post-traumatic or post-surgical neuropathic pain. The authors also wanted to understand whether there were improvements in quality of life, namely sleep quality and levels of happiness, anxiety, and mood. After four periods, the authors determined that the average pain intensity was significantly lower in patients who smoked cannabis, with a concentration of 9.4% compared to the placebo, where the pain intensity recorded was 5.4 versus 6.1. In terms of secondary objectives, the authors noted that patients using the 9.4% Δ^9-THC concentration reported more sleepiness, more ease in falling asleep, and fewer periods of insomnia than those using the placebo. There were also significant improvements in terms of anxiety and depression in this group. Despite

the positive results obtained in this test, the authors determined that the reduction in pain using cannabis was modest when compared to other medications used to relieve chronic pain, such as gabapentin and pregabalin [113].

In 2014, Lynch et al. conducted a study to understand the effectiveness of Sativex® in the treatment of chronic pain induced by chemotherapy. In this clinical trial, patients were instructed to start with one spray of the study drug under the tongue or inside the cheek at bedtime on the first night and then adjust the dose as needed to relieve the pain, as long as it did not exceed 12 sprays per day. After treatment, it was then reported that there was no statistically significant difference between the treatment and placebo groups [114].

Turcotte et al. carried out a randomized, double-blind, placebo-controlled trial in patients with multiple sclerosis who were experiencing neuropathic pain due to their disease. The main objective of this study was to see if nabilone in combination with gabapentin had positive analgesic effects compared to gabapentin and placebo. After 9 weeks of treatment, the authors reported that the combination of nabilone and gabapentin achieved a significant reduction in pain compared with the placebo and gabapentin [115].

In a study conducted by Fallon et al. in 2017, the main objective was to evaluate the efficacy of using Sativex® as an adjuvant treatment to opioids in cancer patients whose pain was not relieved by the recommended treatment. A randomized, double-blind, placebo-controlled phase 3 trial was carried out. In terms of results, the authors found no significant impact on pain intensity in the drug group compared with the control group. However, they did report that the average pain intensity decreased significantly in the North American group under the age of 65 who received the drug. After analyzing the data, it was found that this group of patients had slightly greater pain and were given a lower dose of opioid medication at the start of treatment. In addition, this group admitted to having been exposed to the cannabis plant in the past. The researchers reported that the reduction in opioid use may have led to a reduced downregulation of opioid receptors and improved synergy between cannabinoids and opioid receptors, leading to a more favorable outcome in these patients. As for the improvement in quality of life, it has also been reported that the trial showed no significant differences in treatment between Sativex® and the placebo [116].

De Vries et al. (2017) also published a phase 2, randomized, double-blind, placebo-controlled trial, the main objective of which was to evaluate the analgesic efficacy, pharmacokinetics, safety, and tolerability of an oral tablet containing purified Δ^9-THC in patients with chronic abdominal pain. To determine the efficacy of these tablets, the authors used the "Visual Analogue Scale", and after treatment, it was found that there was indeed a change in pain intensity in both patients in the test, with a reduction of 40% in patients taking the study drug and 37% in patients taking the placebo. It was then possible to understand that there was no significant impact. Regarding the improvement in quality of life, the authors state that there were also no significant differences between the patients [117].

A summary of the studies is given in Table 1.

Table 1. Summary of clinical trials investigating the efficacy of cannabis-based medications for chronic pain.

Name of the Medicine	Type of Pain	No. of Participants	Study Time	Maximum Dose	Adverse Effects	Study Design	Pain Reduction	Reference
Sativex®	Neuropathic pain of various etiologies	103	5 weeks	48 sprays per day	Dizziness; nausea; fatigue; dry mouth; vomiting; headache; diarrhea; sleepiness; memory changes; anorexia	Parallel	Yes	[111]
Nabilone	Chronic neuropathic	96	14 weeks	2 mg daily	Fatigue; insomnia; headache; shortness of breath; nightmares; malaise	Cross-over	No	[112]

Table 1. *Cont.*

Name of the Medicine	Type of Pain	No. of Participants	Study Time	Maximum Dose	Adverse Effects	Study Design	Pain Reduction	Reference
Δ^9-THC 2.5%, 6% and 9.4%	Post-traumatic or post-surgical neuropathic pain	23	56 days	25 mg 3 times daily	Anxiety; decreased motor skills; dizziness; sleepiness; headache; insomnia; tiredness; lack of concentration; nausea; dry mouth	Cross-over	Yes	[113]
Sativex®	Chronic pain caused by chemotherapy	16	4 weeks	12 sprays day	Fatigue; dry mouth; dizziness; nausea; increased appetite; diarrhea; headache; anxiety; confusion	Cross-over	No	[114]
Nabilone	Multiple sclerosis-induced neuropathic pain	15	9 weeks	2 mg daily	Dizziness; sleepiness; dry mouth; headache	Parallel	Yes	[115]
Sativex®	Cancer pain	294	5 weeks	10 sprays day	Progression of the neoplasm; sleepiness; nausea; vomiting; dizziness; constipation	Parallel	Yes	[116]
Namisol® (Δ^9-THC)	Chronic abdominal pain	65	52 days	24 mg daily	Amnesia; increased appetite; decreased appetite; lack of balance; attention disorders; dizziness; sleepiness; headache; confusion; irritability; nausea; dry mouth	Parallel	No	[117]

6. Limitations of Medical Cannabis Use

Although these results are promising, they are difficult to generalize given the inconsistency of cannabis preparations, dosages used, and the amount prescribed to patients [118]. The debate surrounding the use of medicinal cannabis is a fertile ground for discussion and research all over the world. While many defend its potential benefits in the treatment of a variety of medical conditions, it is important to recognize and address the significant limitations associated with its use.

One of the main limitations that stands out in the use of medicinal cannabis is the adverse side effects often reported by patients. Although this plant has been acclaimed for its therapeutic properties, it cannot be ignored that many patients experience a series of undesirable symptoms during treatment. For some patients, adverse effects can be so debilitating that they end up discontinuing the use of medicinal cannabis, thereby jeopardizing the potential therapeutic benefits they could obtain. However, most authors have described that the majority of adverse effects are mild to moderate in intensity, dose-dependent, and transient [113,114,117].

The increasing use of CBD and Δ^9-THC (alone and in combination) as an adjuvant therapy in addition to conventional treatments raises concerns regarding potential drug interactions. Several studies have shown that these phytocannabinoids are not only substrates but also act as inhibitors of some enzymes and may therefore affect the pharmacokinetics of many drugs [119].

Another significant limitation is the scarcity of evidence from high-quality clinical studies that conclusively validate the efficacy and safety of using this plant. Although there is growing interest in scientific research in this field, there are still few studies that offer consistent and reliable results. Many of the available clinical trials are small in size, short in duration, or lack a robust methodological design, making it difficult to draw solid conclusions about its therapeutic effects in various medical conditions [35,118].

It is also important to recognize that despite advances in legislation in many countries, the social stigma surrounding cannabis use still persists in some communities. This can

make it difficult for patients to access treatment and limit the healthcare options available to them [120,121].

In view of these limitations, it is essential that there is greater investment in high-quality clinical research so that the benefits and risks of medical cannabis can be properly assessed. Only a solid foundation of scientific evidence can ensure that patients receive effective and safe treatments for their medical conditions. In the meantime, it is important for patients to be aware of the potential limitations and adverse effects associated with medical cannabis use and to discuss these issues with their doctors to make informed decisions about their treatment. Public education is also essential to combat stigma and ensure that all patients have access to the best treatment options.

6.1. Adverse Effects of Cannabinoids

A wide range of cannabis-based products, including dried flowers, standardized plant extracts, products containing only Δ^9-THC or CBD, and pure synthetic cannabinoids, are available for therapeutic purposes. However, medicinal cannabis may also pose health risks associated with its use [122].

As previously mentioned, chronic pain is a complex and multifactorial condition with significant biological, psychological, and social dimensions. It often involves maladaptive neuroplasticity, central sensitization, and dysfunction of the endogenous pain modulation system [122]. While cannabis-based therapies, particularly Δ^9-THC and CBD, show promise in modulating pain, their administration is associated with various adverse events, which can complicate treatment outcomes [123–125]. Adverse effects include neuropsychiatric, gastrointestinal, cardiovascular, and hepatic effects, affecting patient compliance and safety [126,127].

Table 2 summarizes the main adverse effects of Δ^9-THC, CBD, and their co-administration based on clinical trials and studies. These cannabinoids have demonstrated various therapeutic potentials, but their effects can vary significantly depending on dosage and individual response.

The adverse effects associated with CBD use (Figure 4) encompass a range of physiological responses observed across clinical studies.

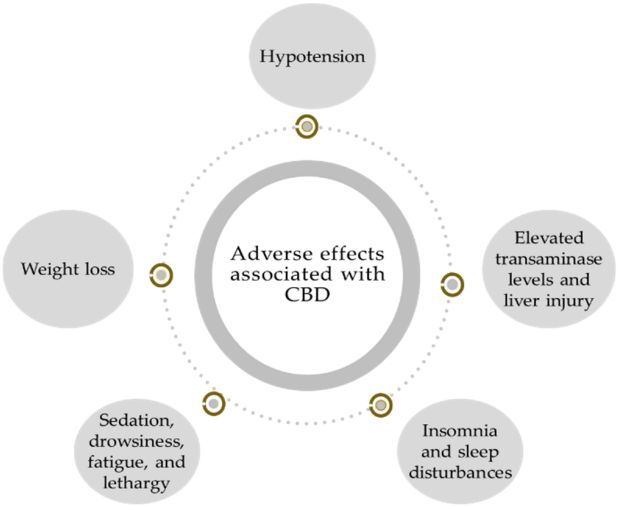

Figure 4. The most common adverse effects associated with CBD reported in clinical studies.

Table 2. Comparison of adverse events associated with Δ^9-THC, CBD, and their combined use.

Adverse Effects	Δ^9-THC		CBD		Δ^9-THC and CBD Co-Administration	
	Clinical Manifestations	**Use**	**Clinical Manifestations**	**Use**	**Clinical Manifestations**	**Use**
Neuropsychiatric	Psychosis, schizophrenia, depression, euphoria [120,123,126–130]	Clinical practice and/or trials [120,123,126–130] included patients with chronic pain, multiple sclerosis; exclusion of psychiatric history Recreational [120,129]: based on observational data; heterogeneous populations, often with psychiatric comorbidities	Sedation, drowsiness, fatigue [131–134]	Clinical practice and/or trials [131–134]: adults with epilepsy or anxiety; individuals with severe psychiatric disorders were excluded	CBD counteracts some neuropsychiatric side effects of Δ^9-THC; for instance, it reduces Δ^9-THC-induced anxiety and psychosis [120,122,135]	Clinical practice and/or trials [120,122,135] conducted in controlled settings in patients with refractory pain Recreational [120,122]
Cognitive	Memory deficits [134,136,137]	Clinical practice and/or trials [134,137]: patients with intact baseline cognitive function were included; exclusion of neurodegenerative diseases Recreational [136]: long-term cannabis users, including adolescents; limited cognitive assessments	Potential transient impairments in memory or attention, particularly at higher doses [133,138,139]	Clinical practice and/or trials: adults with stable cognitive profiles; no severe CNS disorders [133,138,139] Recreational [139]	CBD mitigates Δ^9-THC-related memory effects [122,139]	Clinical practice and/or trials: controlled environments; no severe cognitive impairments at baseline [122,139] Recreational [122,139]
Cardiovascular	Arrhythmias, including tachycardia and, less frequently, bradycardia, alongside ischemia-related conditions such as acute myocardial infarction, stroke, and acute coronary syndrome [140–145]	Clinical practice and/or trials [140,144,145] comprised patients with no baseline cardiovascular disease; controlled blood pressure Recreational [140–145]: mixed populations, including individuals with undiagnosed hypertension or arrhythmias	Hypotension without arrhythmias [145,146]	Clinical practice and/or trials [146] included adults with stable cardiovascular profiles; exclusion of high-risk patients (arrhythmia history) Recreational [145]	Limited evidence on combined cardiac impact [147,148]	Recreational [147,148]

Table 2. *Cont.*

Adverse Effects	Δ^9-THC		CBD		Δ^9-THC and CBD Co-Administration	
	Clinical Manifestations	**Use**	**Clinical Manifestations**	**Use**	**Clinical Manifestations**	**Use**
Gastrointestinal (GI)	Cannabinoid hyperemesis syndrome [149–151]	Recreational [149–151] included chronic cannabis users; no exclusion criteria for pre-existing GI conditions	Diarrhea, appetite suppression [124,138,152]	Clinical practice and/or trials [124,138,152] incorporated adults with no baseline GI conditions; exclusion of malabsorption syndromes Recreational [124,152]	No established additive effects	
Hepatic	Rarely reported [153]	Clinical practice and/or trials [153] encompassed patients with normal liver function; exclusion of hepatotoxic drug use	Elevated transaminase levels, liver injury [138,153,154]	Clinical practice and/or trials [138,153,154]: adults without significant liver dysfunction were included; exclusion of concurrent hepatotoxic drugs	Requires monitoring in patients with hepatic conditions [124,153–155]	Clinical practice and/or trials [124,153–155]: combination use in stable patients; liver function monitoring Recreational [124,155]: no systematic exclusion of patients with liver conditions; observational data
Sleep-related events	Induce sleep latency, but has been associated with impaired long-term sleep quality and may exacerbate insomnia due to disruptions in sleep cycles [156,157]	Clinical practice and/or trials [156,157]: patients with a history of sleep disorders or risk of sleep pattern disruption were excluded; those with no baseline sleep issues were included	Improved sleep at high doses, insomnia at low doses [156,158]	Clinical practice and/or trials [156,158]: patients without sleep disorders were included	Potential normalization of sleep architecture [159]	Clinical practice and/or trials [159,160]: patients with a history of sleep disturbances were excluded

"Recreational" refers to effects observed in non-medical personal cannabis consumption, often linked to leisure activities or habitual social intake.

In a systematic review of the adverse effects of oral CBD, Souza et al. [154] examined the findings of randomized controlled trials published between 2020 and 2022. The study concluded that CBD has a generally favorable safety profile, with mild-to-moderate side effects including gastrointestinal symptoms (59.5%), somnolence (16.7%), loss of appetite (16.5%), and hypertransaminasemia (12.8%). Although uncommon, serious adverse effects have been documented, including elevated liver enzymes, seizures, and rash, particularly when CBD was used as an adjunct to anticonvulsant medications. While CBD is generally well-tolerated, the study highlighted the importance of monitoring its use, especially in combination with other drugs, due to the potential for drug interactions [154].

In line with these findings, oral CBD administration at doses between 10 and 20 mg/kg/day has been linked to weight loss, primarily due to appetite suppression and episodes of diarrhea. A systematic review of randomized trials found that a mean dose of 14 mg/kg/day predisposes individuals to these adverse effects, while no significant issues were observed at doses of 5 mg/kg/day [140]. Clinical trials have consistently reported diarrhea and appetite suppression as common side effects of CBD use [126].

Sedation, drowsiness, fatigue, and lethargy were observed in pediatric populations with uncontrolled epilepsy receiving CBD. For instance, in a study conducted by Hussain et al. (2015), 59% of children administered an average dose of 4.3 mg/kg/day over seven months exhibited these symptoms [133]. Similarly, Tzadok et al. (2016) identified these effects in 47% of children treated with oral CBD doses ranging from 1 to 20 mg/kg/day for six months) [134].

Building on the understanding of CBD's physiological effects, a recent meta-analysis delved into the potential adverse impacts of acute CBD use on cognitive and psychomotor performance. The findings emphasized a statistically significant increase in subjective sedation associated with CBD compared to the placebo, though no measurable impairments in objective cognitive or motor tasks were identified. In contrast, Δ^9-THC exhibited substantially greater adverse effects in these domains. While the study suggests that acute CBD use, even at high doses, is unlikely to compromise daily functioning or essential psychomotor abilities, the observed sedation underscores the importance of monitoring its effects, particularly in safety-sensitive activities [136].

Elevated transaminase levels and potential liver injury remain significant concerns with CBD use. Watkins et al. (2021) observed alanine aminotransferase levels surpassing the upper normal limit (ULN) in 44% of healthy adults receiving up to 1500 mg/day of CBD, with levels reaching five times the ULN in 31% of participants [156]. Similarly, a clinical trial involving Dravet syndrome patients treated with Epidiolex® (CBD doses of 10 and 20 mg/kg/day) reported transaminase elevations exceeding three times the ULN in 3% and 13% of patients, respectively, particularly when combined with sodium valproate [139]. A systematic review and meta-analysis [153] further highlighted the increased likelihood of liver enzyme elevations (odds ratio = 5.85, 95% confidence interval: 3.84–8.92, $p < 0.001$) and drug-induced liver injury (odds ratio = 4.82, 95% confidence interval: 2.46–9.45, $p < 0.001$) associated with CBD compared to a placebo. Elevated liver enzymes were reported in 7.4% of participants, while drug-induced liver injury occurred in 2.96%, with high doses ($\geq$1000 mg/day or $\geq$20 mg/kg/day) and the concomitant use of antiepileptic drugs like valproate identified as significant risk factors. Importantly, no severe liver injuries were documented. These insights emphasize the need for caution when combining CBD with hepatotoxic medications such as antiepileptics, paracetamol, and certain antibiotics, especially in individuals with pre-existing liver conditions [126,155].

Sleep disorders, including insomnia, have a complex relationship with CBD dose. Maddison et al. (2022) demonstrated that a 160 mg dose of CBD increased sleep duration in individuals with sleep disorders, while lower doses (40 and 80 mg) showed no improve-

ment [158]. Sleep disturbances may also stem from interactions with drugs like tricyclic antidepressants, dopaminergic agonists, and β-blockers. An adjustment of CBD dosage or intervals may help reduce these effects, although sedative pharmacotherapy is not recommended due to the risk of excessive sedation and potential adverse interactions [126,161].

Hypotension is another reported effect, particularly in hypertensive individuals. Kumric et al. (2023) found that CBD doses ranging from 225 to 450 mg reduced serum catestatin levels, a neuroendocrine marker linked to hypertension, over a 5-week period, with no change in the placebo group [148]. The hypotensive effects of CBD are particularly pronounced in elderly individuals and those on antihypertensive therapies, necessitating careful monitoring during treatment [162].

These findings highlight the importance of dose optimization, patient-specific considerations, and close monitoring during CBD therapy to ensure efficacy while mitigating risks.

Regarding the adverse effects of Δ^9-THC (Figure 5), they have been extensively documented, particularly in relation to psychiatric conditions such as psychosis and schizophrenia. Newman-Taylor et al. (2021) conducted a clinical trial involving 20 participants (15 receiving 15 mg of Δ^9-THC orally and five receiving a placebo), which found that acute Δ^9-THC intoxication heightened psychotic experiences linked to cognitive fusion [128]. Furthermore, a systematic review by Patel et al. (2020) [129] confirmed a dose–response relationship between Δ^9-THC use and psychosis, with frequent users showing a fourfold increased risk [130,163]. Chronic use of Δ^9-THC may also worsen schizophrenia symptoms by interfering with cannabinoid receptors, cortical development, and addiction mechanisms [164,165].

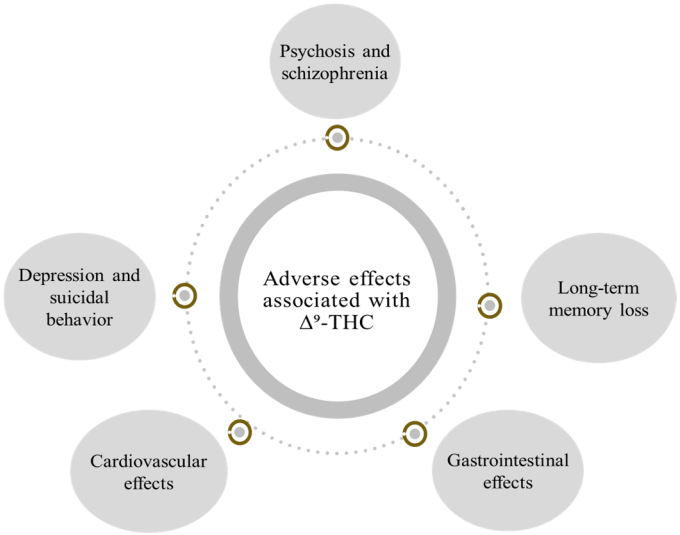

Figure 5. Adverse effects associated with Δ^9-THC.

The study by Chandy et al. (2024) reinforces these findings, emphasizing that the chronic use of Δ^9-THC may elevate the risk of psychosis and schizophrenia, particularly in individuals with a predisposition to mental health disorders [122]. The review suggests that Δ^9-THC exacerbates psychiatric conditions by altering brain function, neurotransmitter systems, and cannabinoid receptor activity. This suggests that individuals vulnerable to psychiatric issues may experience a heightened risk of triggering or worsening symptoms from chronic Δ^9-THC use.

Studies consistently show a strong association between cannabis use, particularly Δ^9-THC, and an increased risk of depression and suicidality. The umbrella review by Shamabadi et al. (2023) [166] highlights the association between cannabis use and a higher risk of suicidality, emphasizing that cannabis and Δ^9-THC may exacerbate mental health

conditions. Similarly, research by Hinckley et al. (2023) underscores the relationship between cannabis use and depression severity, as well as suicidality, particularly among adolescents [167]. Gobbi et al. (2019) reviewed 11 studies involving 23,317 participants and also found a significant correlation between cannabis use in adolescence and subsequent depression and suicidal tendencies in adulthood, even after periods of abstinence [131].

Cardiovascular events (CVEs) may occur due to the activation of the sympathetic nervous system, with inhibition of the parasympathetic nervous system, leading to changes in heart rate and blood pressure, platelet activation, endothelial dysfunction, and oxidative stress. High doses of Δ^9-THC can also directly stimulate the parasympathetic nervous system, resulting in bradycardia and hypotension. In contrast, CBD may offer protective cardiovascular effects by reducing heart rate and blood pressure, enhancing vasodilation, and decreasing inflammation and vascular permeability [147]. However, Δ^9-THC itself has been linked to an increased risk of CVEs, including stroke and acute coronary syndrome, which could be attributed to mechanisms like reversible cerebral vasoconstriction, pro-coagulant activity, arrhythmia, and ischemia [142,144]. A review by Jouanjus et al. (2017) of 81 cases revealed that Δ^9-THC can elevate heart rates and potentially induce coagulopathies [142]. Further studies have also associated cannabis use with myocardial infarction through CB_1 and CB_2 receptor activation on platelets, promoting endothelial dysfunction [145,168].

The chronic use of Δ^9-THC has been increasingly associated with gastrointestinal disturbances, particularly through the activation of the CB_1 receptor, which disrupts motility and can lead to cannabinoid hyperemesis syndrome (CHS). This condition, characterized by recurrent nausea, vomiting, and abdominal pain, is common among chronic cannabis users. A study by Venkatesan et al. (2019) found that 68% of 271 patients with CHS were daily cannabis users, with many using cannabis for over a year before symptoms emerged [151]. Hasler et al. (2024) elaborated on how long-term cannabis use contributes to these gastrointestinal issues, particularly by highlighting the role of Δ^9-THC in altering gut motility [153]. Evidence suggests that cannabis compounds, especially Δ^9-THC, can affect the enteric nervous system, which regulates gastrointestinal function. The activation of CB_1 receptors on gut neurons can slow down motility, disrupt normal peristalsis, and potentially contribute to the cyclic nature of CHS, where individuals experience repeated cycles of symptoms. Additionally, prolonged use of cannabis may sensitize the gastrointestinal system, making it more prone to hyperactivity or dysfunction, leading to the onset of CHS after long periods of use.

Long-term memory loss is another concern, particularly when exposure occurs during adolescence. Felice et al. (2023) demonstrated hippocampal anomalies and glutamatergic dysregulation, leading to memory deficits and anxiety behaviors [138]. Murray et al. (2022) confirmed these results in a trial with 24 participants, showing that doses of 7.5 mg and 15 mg of Δ^9-THC reduced memory capacity by altering neurophysiological processes [139].

These findings emphasize the varied and potentially severe adverse effects of Δ^9-THC use, underscoring the importance of careful consideration in therapeutic applications and public health contexts.

The co-administration of Δ^9-THC and CBD has garnered attention for its potential to mitigate some of the adverse effects of Δ^9-THC while enhancing therapeutic outcomes. One of the key benefits of combining these two cannabinoids is that CBD can counteract some of the neuropsychiatric and cognitive side effects of Δ^9-THC, such as anxiety, psychosis, and cognitive impairments. Studies have shown that CBD can reduce these negative effects, potentially making cannabis therapy more tolerable for certain patients [122,123,137,141,169].

However, the effects of CBD in combination with Δ^9-THC are dose-dependent and vary significantly depending on the ratio between the two cannabinoids, a factor that lacks

standardization across studies. This variability makes it challenging to predict the exact outcome of co-administration [123,124,137].

Moreover, caution is advised when combining Δ^9-THC and CBD due to potential cardiovascular considerations [149,150]. For instance, the two cannabinoids may have additive hypotensive effects, which could lead to unwanted drops in blood pressure. Additionally, there may be alterations in liver enzyme activity, which could affect drug metabolism and safety. As such, patients using Δ^9-THC and CBD together should be closely monitored for these effects [146,156,157].

To optimize therapeutic effects while minimizing adverse outcomes, several recommendations have been proposed. First, standardizing cannabinoid ratios is essential to achieve consistent therapeutic benefits while reducing risks [123,136]. Second, regular monitoring of hepatic function and cardiovascular health is critical for patients undergoing cannabis-based therapies, ensuring an early detection of any potential complications [125,157]. Finally, dosing strategies should be tailored to individual patient needs, taking into account factors such as pre-existing medical conditions and other medications that may interact with cannabinoids [140,148].

6.2. Drug Interactions

As mentioned above, the phytocannabinoids Δ^9-THC and CBD can act as inhibitors of some enzymes, such as cytochrome P450, which predisposes them to interactions with other drugs, especially those that are metabolized by the CYP3A4 isoenzymes, CYP2C9, CYP2C19, CYP2D6, and carboxylesterase 1 (CES1). Also, drugs that bind extensively to plasma proteins (such as warfarin) and that have narrow therapeutic indices (such as anticoagulants and immunosuppressants) must be carefully monitored when used concomitantly with Δ^9-THC or CBD. Furthermore, in vitro studies have shown that CBD and Δ^9-THC interact with efflux transporters of the ATP binding cassette (ABC) family, namely P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp) [170,171], and they may therefore affect the pharmacokinetics of drugs that are substrates of these transporters [119]. Potential interactions between these phytocannabinoids and some common drugs are discussed below.

Warfarin, an anticoagulant drug, is administered as a racemic mixture of R- and S-stereoisomers, with S-warfarin being metabolized predominantly by the CYP2C9 isoenzyme, while the R- stereoisomer is metabolized via CYP3A4 [172]. As previously mentioned, Δ^9-THC and CBD act as inhibitors of CYP2C9 and CYP3A4 and as such can affect the metabolism of warfarin, increasing its plasma levels and consequently the risk of bleeding during treatment [172–174].

Statins reduce endogenous cholesterol synthesis by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The reduction in intracellular cholesterol concentration leads to an upregulation of the expression of low-density lipoprotein (LDL) receptors on the surface of hepatocytes, which increases the hepatic uptake of LDL cholesterol and subsequently decreases blood levels of this lipoprotein [175]. Both CBD and Δ^9-THC bind to lipoproteins, mainly LDL, which means that the free fractions of these cannabinoids in plasma are low. CBD-LDL and THC-LDL can reach the intracellular space of the hepatocyte through the LDL receptor located in the membrane, just like cholesterol. When cannabinoids are co-administered with statins, there is an increase in plasma clearance of the former since statins, by reducing LDL-cholesterol, will increase the free fraction of CBD and Δ^9-THC. Furthermore, there is a direct proportionality between the increase in LDL receptors in the liver and the biotransformation of phytocannabinoids. Both factors can lead to a decrease in plasma concentrations of free and total CBD and Δ^9-THC. Therefore, cannabinoids may be less effective in patients

taking statins [119]. In addition, some statins are metabolized by CYP3A4 and are P-gp substrates [176]. Thus, xenobiotics that inhibit CYP3A4 and/or P-gp, such as CBD, may increase the plasma concentration of these statins, increasing the risk of adverse effects such as myopathy and/or rhabdomyolysis [119].

Given that CBD can be used as a complementary therapy to other antiepileptic drugs and that CYP enzymes are involved in the metabolism of these drugs, metabolic overlap may occur. However, there are still few data on the interactions of CBD with other antiepileptic drugs, and the studies found in the literature [177–179] focus on the effect of CBD on the plasma concentrations of other antiepileptic drugs, but information on the effect of other antiepileptic drugs on plasma CBD levels is lacking.

6.3. Long-Term Usage

The use of cannabis for the treatment of chronic pain has shown mixed results, particularly with long-term use. Halman et al. (2024) investigated the efficacy of cannabinoid-based medications for the treatment of pain, mental health, and sleep disorders over a 12-month period and found significant benefits, particularly within the first 6 months. Patients reported reduced pain severity, improved mental health (particularly anxiety and depression), better sleep quality, and reduced reliance on other medications, improving overall quality of life. However, the therapeutic effects, particularly for pain and medication reduction, waned after six months, possibly due to receptor desensitization or disease progression. While improvements in mental health and sleep were sustained, some patients experienced a decline in perceived benefits [180]. These findings are consistent with other studies that have shown an initial efficacy of medical cannabis but an overall mild-to-modest long-term improvement in pain and associated symptoms over 12 months [181,182]. In contrast, a real-world analysis of the efficacy and safety of oral medical cannabis in 3961 cannabis-naive patients demonstrated a rapid and significant improvement in all measured patient and clinically reported validated outcomes that were maintained for over two years [183]. Although short-term benefits are evident for many patients, the long-term efficacy of cannabis in managing chronic pain remains inconclusive. While some patients report consistent improvements, others may not experience the same benefits or may even experience adverse effects, underscoring the complexity of the mechanisms by which cannabis relieves pain and regulates emotional states.

The variability in responses to cannabis use for chronic pain may be closely related to its role in modulating anxiety, stress, and depression. Chronic pain is often associated with psychological conditions that amplify pain perception, such as anxiety and stress, which activate the hypothalamic–pituitary–adrenal (HPA) axis and increase cortisol release. Chronic pain is influenced by pain-related fears and cognitive distortions, integrating neural, psychological, and physiological mechanisms in brain regions (e.g., amygdala, hippocampus, and prefrontal cortex) associated with stress and pain modulation. Acute stress exacerbates threat memory encoding, further perpetuating the fear-avoidance cycle in chronic pain [184]. The endocannabinoid system plays a critical role in modulating stress response, anxiety, and associated behaviors through the regulation of two key endocannabinoids, AEA and 2-AG. AEA constrains stress responses via CB_1 receptor signaling, but its FAAH-mediated reduction promotes excitatory glutamate release in the hypothalamus and amygdala and disinhibits stress pathways in the prefrontal cortex, heightening stress susceptibility, anxiety, and glucocorticoid levels. Conversely, stress-induced glucocorticoid feedback enhances 2-AG synthesis and CB_1 activation, which can restore stress resilience [185].

7. Conclusions

The studies presented in this review indicate that phytocannabinoids have the potential to modulate pain perception and effectively reduce inflammation, offering a valuable alternative to traditional painkillers. For many patients, especially those who have not found relief from conventional treatments or who face unwanted adverse effects, medical cannabis represents a real hope for a more comfortable and functional life.

Therefore, as we move forward, it is imperative to take an integrated, multidisciplinary approach to chronic pain management that includes medical cannabis as part of a comprehensive therapeutic arsenal. This requires not only more research and robust scientific evidence but also a review of clinical policies and practices to ensure fair and safe access to this plant for those who could benefit from it.

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