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THE IMPACT OF CHRONIC CANNABINOID USE AND DEPENDENCE ON OPIOID ANALGESIC TREATMENT – A SYSTEMATIC REVIEW AND PREDICTIVE ANALYSIS

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ABSTRACT

In recent years, there has been growing interest in cannabinoids as potential analgesics and alternatives to opioids. Cannabinoids, through modulation of the endocannabinoid system, affect nerve transmission, neuroplasticity, and inflammatory processes, and their action on CB1 and CB2 receptors is similar to the mechanisms of the opioid system, in particular μ, δ, and κ receptors. The aim of this study was to compare the mechanisms of action of cannabinoids and opioids, review studies on their combined use, and assess the impact of chronic cannabinoid use and dependence on the effectiveness of opioid-based pain treatment.

Analysis of the available data showed that moderate use of cannabinoids, especially preparations with a balanced THC and CBD content, can lead to an "opioid-sparing" effect, allowing opioid doses to be reduced without losing the analgesic effect. However, chronic use of cannabinoids, especially those with high THC content, is associated with the development of tolerance, mood disorders, desensitization of CB1 receptors, and disturbances in the co-regulation of μ receptors, which may lead to compensatory escalation of opioid treatment and the development of cross-addiction. In addition, partial clinical benefits have been observed in patients with neuropathic pain from the combination of cannabinoid and opioid therapy, while no clear analgesic effects have been observed in acute pain.

The proposed predictive model integrates molecular, clinical, and psychological aspects, indicating that the effectiveness of analgesic therapy depends on the duration of exposure to cannabinoids, the type of pain, and the individual predisposition of the patient. The authors point to the need for further research involving patients who are chronic users of cannabinoids or addicted to them and who are scheduled to be treated with opioids. The results of such analyses could form the basis for the development of clinical guidelines for integrated pain therapy that minimizes the risk of addiction and treatment failure.

KEYWORDS

Cannabinoids, Opioids, Chronic Pain, Acute Pain, Addiction

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Introduction

Pain is an unpleasant physical and emotional experience that poses a significant problem in modern medicine—it is estimated that 20% of people worldwide suffer from chronic pain [1]. Opioids are a popular group of drugs used to relieve pain, but their widespread use has led to a growing problem of addiction, which is why alternative or new ways of modifying treatment are being sought.

Cannabis sativa is a plant native to Asia, used in herbal medicine for many purposes, including as a pain reliever [1,2,3,4,5]; the plant is also known for its psychogenic properties. With the isolation of cannabinoids, substances that interact with the endocannabinoid system, this group of substances, as well as the dried plant itself, began to be used as a potential method of pain treatment.

In recent years, there has been a significant increase in the use of cannabinoids both in the general population and among patients suffering from chronic pain. Based on data from North American countries, it is estimated that up to 30% of people taking chronic opioids report concurrent use of cannabinoids, mainly to reduce opioid doses or limit side effects [1,2,4,6,7,8].

At the same time, there are increasing reports of cognitive impairment, tolerance, and addiction associated with long-term use of cannabis products [4]. Despite the relatively low risk of developing addiction after any exposure, which is 8.9% for cannabis products (compared to 22.7% for alcohol), reports from Europe and the US clearly indicate an increased frequency of addiction treatment for cannabis products [2,9].

Disorders related to cannabis use affect approximately 9–12% of users, with this percentage being higher among young people and those who use cannabis products for non-medical purposes [9]. The risk of developing dependence increases with the duration and intensity of use [4].

Some people who use cannabis products do so because they believe that "(cannabis) is a natural product" and is therefore considered safe [9]; this may suggest a lack of education, as indicated by research from Israel, where only 18% of respondents have knowledge about medical cannabis from their medical practitioner [4].

A specific group of patients are those suffering from chronic pain, which is often associated with co-occurring depression and anxiety disorders, which is associated with an increased risk of using opioids and cannabinoids. Gradual worsening of pain, desperation, and the development of tolerance will increase the chance of developing addiction [10].

It is worth noting at this point that the tetrahydrocannabinol (THC) content, the main psychoactive substance in cannabis, has increased almost fourfold since the 1990s, which not only increases the risk of developing addiction but also increases the risk of developing psychotic disorders [5]. Adolescents and young adults are particularly vulnerable to the negative effects of daily use, such as reduced IQ, memory impairment, increased risk of developing schizophrenia [11], and changes in brain structure.

Methodology

This article was written as a compilation of available information on the impact of chronic use of various forms of cannabinoids on the effectiveness of opioid therapy for pain relief. Scientific studies evaluating this effectiveness have proven to be rare, so it was decided to focus this article on the physiological structure of the endocannabinoid system, the opioid system, their functions, and their interdependence, regardless of prior exposure to cannabinoids.

Therefore, this article includes articles on the structure of the endocannabinoid and opioid systems, the mechanism of addiction development and the role of the aforementioned systems, studies evaluating the effect of adding cannabinoid therapy to existing opioid therapy in the context of chronic and acute pain, and recommendations for the use of cannabinoids in pain management.

The source material was full-text scientific publications from peer-reviewed international journals and recommendations from recognized organizations. The analyzed literature included experimental studies, randomized clinical trials, observational studies, review articles, meta-analyses, and institutional documents on the mechanisms of action of cannabinoids and opioids and their use in pain management; the publications were from 2010–2025. The focus was mainly on publications from the last 5–7 years so that the data contained in this article would be as up-to-date as possible with current knowledge.

Studies on cannabinoids in non-pain-related diseases, case studies, editorial comments, conference abstracts, and articles covering the pediatric population not related to chronic pain were excluded from the analysis.

Data analysis process

The titles and abstracts of the publications were selected for their relevance to cannabinoid-opioid interactions. Studies that did not consider pain modulation, the CB1/CB2 receptor, or clinical outcomes of therapy were excluded.

For each study, the type of study, population, type of intervention (THC, CBD, plant extracts, endocannabinoids), nature of pain, measures used to assess the effect of cannabinoids on pain perception, observation time, and presence of long-term effects were evaluated.

In the case of preclinical studies, attention was paid to receptor expression, changes in neurotransmission, pain and addiction behaviors in animals.

The results of the studies were grouped thematically into five main areas of analysis: mechanisms of action of cannabinoids and opioids, receptor interactions, the effect of chronic cannabinoid use on the efficacy of opioids, psychological factors and the risk of addiction, and clinical effects.

This approach allowed for the comparison of results from studies with diverse methodologies, taking into account both the neurobiological basis of interactions and their therapeutic significance.

Although no formal assessment of systematic error risk or statistical meta-analysis was performed, the methodological quality assessment was based on the clarity of sample selection, transparency of the study protocol, use of validated pain analysis scales, length of observation, and transparency in demonstrating clinical and neurobiological results.

The use of narrative synthesis allowed for the inclusion of a wide range of studies, which is important in the context of the complex and still not fully understood interactions between the endocannabinoid and opioid systems and the lack of uniform clinical trial protocols involving cannabinoids.

Results

The endocannabinoid system (ECS)

The endocannabinoid system is a system that has a significant impact on the development of the nervous system and modifies its transmission, neuroplasticity, and inflammatory processes [12]. It mainly affects nerve tissue through CB1 and CB2 receptors [3], but in recent years, its effect on TRPV1 [13], GPR55, GPR119, and peroxisome proliferator-activated receptors (PPAR), which are also involved in the regulation of pain perception [14,15,16] by modifying the functioning of the endocannabinoid system [5].

Substances that interact with the endocannabinoid system can be divided into those of exogenous origin (THC; cannabidiol, CBD) and endogenous origin (anandamide, AEA; 2-Arachidonylglycerol, 2-AG) [9,12]. THC has an agonistic effect on CB1 and CB2 receptors, with a predominance on CB1, while CBD is mainly a CB2 receptor agonist and an inhibitor of cyclooxygenases [11,15,17], lipoxygenases, and may reduce the toxic effects of NMDA [15]; AEA moderately and continuously regulates neuron function, while 2-AG strongly regulates synaptic transmission at the moment of pain onset [9,14].

CB1 receptors are located in the central nervous system, primarily in the cerebellum, hippocampus, basal ganglia, amygdala, cerebral cortex, and spinal cord. They exert their effect on the presynaptic part of the axon, but can also be observed intracellularly [5,14,15,18,19,20,21].

CB1 and CB2 receptors are negatively coupled to G protein, causing inhibition of adenylate cyclase activity. Activation of the CB1 receptor inhibits the release of excitatory neurotransmitters (glutamic acid, substance P and, to a lesser extent, acetylcholine, norepinephrine, serotonin, cholecystokinin, and D-aspartate) from the presynaptic membrane while stimulating the release of inhibitory neurotransmitters (GABA) and dopamine in the reward system [5,9,19,20]. Chronic stimulation of CB1 receptors may cause their internalization through the binding of G protein to β-arrestin [19].

CB2 receptors are found on the surface of microglia cells, astrocytes [14], spleen, thymus, T and B lymphocytes, macrophages, NK cells, monocytes, and neutrophils [14,15,18,19]. Activation of CB2 receptors modulates the inflammatory response by inhibiting the secretion of proinflammatory cytokines (TNF-α, IL-1β, IL-6) and interacting with serotonin receptors [5,9,14], which reduces the sensitivity of sensory neurons, mainly C fibers, to pain [18,21]. In the case of nervous tissue, CB2 activation inhibits the destruction of neurons by pro-inflammatory cytokines and reduces the permeability of the blood-brain barrier [19]. The use of highly selective CB2 agonists can cause immunosuppression.

As lipid compounds, cannabinoids bind to cholesterol, and higher cholesterol concentrations in the cell membrane may be associated with increased cannabinoid activity [22]. Cannabinoids also modify the action of the cell membrane – they increase its fluidity by reducing the percentage of cholesterol in it, which shifts the action potential threshold of the neuron in a negative direction [22,23].

Opioid system (OS)

The opioid system is responsible for regulating responses to pain and stress through μ, δ, and κ receptors, which are distributed in many structures, including the dorsal horns of the spinal cord, the brainstem, including the locus coeruleus, and the limbic structures, of which the most important from the perspective of this work is the nucleus accumbens [7,24,25,26].

μ receptors play a key role in the analgesic effects of opioids and in the development of addiction.

δ receptors modulate emotions during pain experiences and regulate interactions with the dopaminergic system [7,25].

κ receptors cause dysphoria by inhibiting dopamine secretion in the dopaminergic neurons of the reward system, which corresponds to negative emotional experiences when the addiction is not satisfied; the same effect on κ receptors is caused by the inflammatory process [7,10,25].

All three receptors are coupled to G protein, which has an inhibitory effect on adenylate cyclase, resulting in reduced neuron excitability. This inhibits the transmission of pain stimulus information from the brainstem to the prefrontal cortex [7,20,24].

In the case of chronic stimulation of opioid receptors, mainly the μ receptor, their internalization will occur; compensatorily, there will also be an increase in adenylate cyclase synthesis, which will increase the excitability of the nerve cell [7,20].

Receptor interactions between the ECS and OS

CB1 receptors of the endocannabinoid system and μ receptors of the opioid system have a similar structure [18] and are located on the same neurons in the same brain structures, including the dorsal horn of the spinal cord and the nucleus accumbens [7,26], which is part of the reward system. In this area, CB1 receptors and μ receptors are located inside neurons and in cells connected by synapses; in the caudate-putamen area, approximately 50% of neurons containing CB1 receptors also had μ receptors [7,20]. Additionally, CB1 receptors can form heterodimers with μ and δ receptors [7,25,27].

Chronic stimulation of either CB1 or μ receptors may increase the amount of available CB1–μ heterodimers in noradrenergic areas of the brain. Addicted patients with induced opioid craving who were given a CB1 receptor antagonist showed reduced withdrawal symptoms [7,27]; it is likely that withdrawal of chronically administered opioids causes internalization of the μ receptor from the cell membrane, allowing dimerization with the CB1 receptor.

In mice with neuropathic pain, increased expression of CB1–δ heterodimers was observed in the cerebral cortex, midbrain, hypothalamus, and spinal cord. Ligands that do not induce CB1 activity increased the activity of the δ subunit of the heterodimer, while the combination of agonists of both receptors at doses that would not be effective on their own was able to alleviate allodynia in the course of neuropathy. Neutral CB1 agonists have the ability to stimulate the μ and δ subunits of the heterodimer, with the μ receptor appearing to be more sensitive to this [27].

Depending on the duration of exposure to cannabinoids, their effect on the opioid system will vary – acute exposure increased the intracellular concentration of endogenous opioids, while chronic exposure to cannabinoids increased the precursors of endogenous opioids (prodynorphin, proenkephalin, and proopiomelanocortin). Potential sensitization of the locus coeruleus in response to stress in the form of attention deficit and anxiety disorders has been reported, which is likely due to modified μ receptor activity [28].

Review of available studies

The effect of cannabinoids on the efficacy of opioids

The effect of chronic use of medical marijuana and cannabinoids on the efficacy of opioid analgesia depends on the type of pain.

In some patients with neuropathic pain and chronic non-cancer pain, opioid requirements were reduced by 30–50%, but this was not accompanied by a reduction in pain. Nevertheless, patients reported an improvement in their quality of life [9,10,11,16,29,30]; the phenomenon of reducing the required dose of opioids when using cannabinoids is called the opioid-sparing effect and is particularly observed when using preparations containing THC and CBD in balanced proportions [3,9]. In patients with cancer pain who reported improved analgesia after administration of a THC/CBD mixture, the improvement in pain control lasted up to 2 years without the need to increase the doses of opioids previously used [18].

The mechanism potentially responsible for the reduction in opioids administered is likely to be an increase in the synthesis of endogenous opioids [21]; this translates directly into a reduction in hospitalizations and deaths caused by opioids, but there is no clear evidence to support this theory [11,26].

On the other hand, clinical studies cast doubt on the opioid-sparing effect, stating that its impact is negligible; this is particularly the case with cancer pain, where the use of cannabinoids only increases the risk of adverse effects such as nausea and vomiting [9,29,31,32]. In the same studies, patients suffering from chronic pain reported a 64–75% reduction in their opioid dose [9]. Previous exposure to cannabinoids and/or sensitization of opioid receptors may be the cause of these discrepancies, as this group of patients reported a better analgesic effect after a period of opioid dose reduction and the addition of cannabinoid treatment [33,34].

The discrepancies may be due to increased expression of the μ receptor protein, even though the tolerance developed to cannabinoids reduces the analgesic effect of morphine [20].

In order to perform their analgesic function, morphine, oxycodone, and fentanyl must first undergo hepatic metabolism—morphine by UGT2B7, oxycodone by CYP2D6 and UGT2B7, and fentanyl by CYP3A4 [35]. Cannabinoids, in this context THC and CBD, are inhibitors of CYP3A4, CYP3A5, and CYP2D6, among others; in addition, CBD is an inhibitor of UGT2B7 [13,15,35]. Despite the potentially reduced amount of the active metabolite, no reduction in analgesic effect is usually observed [35]. However, this may change due to the risk of hepatotoxicity when using CBD [5].

Risk of cross-addiction and compensatory addiction

It is possible to develop opioid dependence with chronic use of cannabinoids [11,32], but only 6% of young adults report starting to use cannabis products before alcohol or cigarettes [32]. People who report daily marijuana use are less likely to use opioids than those who use it occasionally [26].

Both cannabinoids and opioids affect the mesolimbic dopaminergic pathway by increasing dopaminergic activity in the ventral tegmental area and the nucleus accumbens [36,37]. Neurons in both areas contain opioid and cannabinoid receptors [17,37]. Dopamine concentration in the mesolimbic dopaminergic pathway is increased at the onset of addiction, but the number of available dopaminergic receptors will gradually decrease, resulting in a reduction in the volume of the nucleus accumbens, prefrontal cortex, and ventral tegmental area. A reduced number of connections between the ventral tegmental area and the prefrontal cortex is also observed. The same changes occur in patients with chronic pain and in states of reduced affect, such as depression and anxiety; this is caused by increased stimulation of κ receptors [10].

Chronic pain, sleep disorders, and stress are referred to as a triad of symptoms associated with a poorer prognosis for pain treatment [6,20], because disorders of the cortico-mesolimbic system in the form of hypodopaminergia can cause its persistent stimulation, resulting in pain and dysphoria [32], which in turn will prompt the search for ways to relieve pain, such as stimulants [10]. The lack of μ-receptor stimulation also seems to be responsible for the negative effects of withdrawal syndrome, as studies in mice with inactivated μ-receptors, which were suddenly withdrawn after chronic THC administration, showed weaker withdrawal syndrome effects [25].

It has been shown that THC administration for more than 5 days increases the expression of prodynorphin, proenkephalin, and proopiomelanocortin genes in the central nervous system [20].

CBD behaves differently, appearing to reduce withdrawal symptoms, including in opioid-dependent individuals [2,9]. This is due to CBD's ability to regulate the impaired function of the mesolimbic dopaminergic pathway resulting from addiction [2,26], while CBD also has a low risk of developing dependence due to its weak agonistic effect on CB1 receptors [9]. Mixtures of THC and CBD in ratios of 1:1 or 1:4 may reduce the psychogenic effect of THC while maintaining its analgesic effect [9,14].

Discussion

Translation into clinical practice

Chronic pain is defined as pain lasting longer than 3 months [32].

The use of cannabinoids in cancer pain was associated with a slight improvement, but compared to placebo, it was associated with a higher risk of side effects. Higher doses of dronabinol, a CB1 and CB2 agonist, provided a better analgesic effect, but lower doses were associated with better tolerance of the preparation and helped to reduce the dose of opioids [9,11,15,38]. The most common reason for prescribing medical marijuana was the patient's psychological comfort [15].

It can be assumed that cannabinoids make pain easier to bear, but do not change its intensity [10].

Neuropathic pain is a common component of chronic pain, often accompanied by allodynia and hyperalgesia [20]. Nerve damage, which is the etiology of neuropathic pain, causes sensitization of CB2 receptors in the dorsal nerve ganglia, which is why the neuromodulatory effect of cannabinoids may be helpful in treatment [8,9,14].

Analgesia with THC was not altered by additional activation of μ, κ, or δ receptors, but THC administration alone was associated with increased concentrations of dynorphin B, an agonist of κ and δ receptors. A decrease in μ receptor expression in the spinal cord was observed, with no change in κ and δ receptor expression [20].

Administration of a 1:1 mixture of THC/CBD in cancer patients suffering from neuropathic pain had a weak analgesic effect, with the strongest effect occurring between weeks 14 and 26 of treatment, and the therapy becoming less effective after 39 weeks [15]. Despite being weak, the result was significant, as the chance of reducing pain by 30% was doubled with a simultaneous reduction in opioid consumption by 64% [5]; moreover, a long-term improvement in patients' quality of life was achieved [15]. The use of a simultaneous CB1 and CB2 receptor agonist reduced allodynia without the development of tolerance [39], which may be related to the "entourage effect," i.e., the synergistic effect of a mixture of different cannabinoids [13,16,30,32].

Worse results in pain management are observed in patients with neuropathic pain caused by trauma or surgery – in this group, changes in efficacy vary from day to day and remain inconclusive [21,40].

In the case of acute pain, the use of cannabinoids before or after surgery to relieve postoperative pain had no effect or may even have intensified pain sensations; analgesia in musculoskeletal pain also appears to be poor [12,14,21].

Psychological and behavioral aspects

In stressful situations, the noradrenergic system is involved – stimulation of the locus coeruleus, medial prefrontal cortex, nucleus accumbens, and solitary tract nucleus sensitizes their CB1 receptors even when they are desensitized due to chronic cannabinoid use [7].

People with chronic pain, in whom anxiety caused moderate to severe pain, tended to be more prone to using stimulants, including cannabis products. In the face of the body's desensitization to cannabis products, their use may escalate, so a basic understanding of anxiety-induced pain may be crucial for effective pain management [4].

In the context of stress, CBD exhibits anxiolytic effects by modulating 5-HT1A receptors, thereby alleviating anxiety [3] and dysregulated dopaminergic mesolimbic system function [2].

THC, due to its psychogenic properties, may increase the incidence of mental disorders [18], so caution should be exercised with high doses that may exacerbate anxiety; low and medium doses of THC, on the other hand, may reduce stress [6].

Conclusions and directions for further research

Based on the literature review, it can be predicted that the effect of chronic cannabinoid use on the effectiveness of opioid analgesia is complex and depends on a number of biological and behavioral factors. Patients who chronically use preparations with a high tetrahydrocannabinol (THC) content may experience reduced opioid analgesia efficacy, which may result from increased internalization of CB1 and μ receptors and an increased number of CB1–μ heterodimers in the brain structures responsible for pain perception and reward sensation. This results in receptor desensitization and the need for higher doses of opioids to achieve a comparable analgesic effect.

On the other hand, if the ratio of THC to cannabidiol (CBD) is 1:1 or 1:4, it may have an opioid-sparing effect, allowing for lower daily doses of opioids without compromising pain control. Although this does not always translate into a significant reduction in pain intensity on the NRS scale, an improvement in patients' quality of life and a reduction in the frequency of adverse effects associated with opioid therapy have been observed.

It is also predicted that chronic exposure to high doses of THC may exacerbate anxiety and depressive disorders and lead to sleep disturbances, which secondarily impair the effectiveness of pain treatment by increasing pain perception. In this context, cannabidiol has a protective effect – it can alleviate opioid withdrawal symptoms and reduce the risk of relapse by stabilizing the dopaminergic function of the mesolimbic pathway.

It is expected that differences in therapeutic response will also depend on the pain phenotype – patients with neuropathic and non-cancer pain may benefit most from the use of cannabinoids, while in the case of cancer or postoperative pain, this effect will be limited or clinically insignificant. High doses of THC may even intensify postoperative pain by increasing the sensitivity of pain receptors.

It is difficult to clearly determine the impact of chronic use of cannabis-derived preparations on the effectiveness of de novo opioid therapy in pain management. Due to the fact that the cannabinoid content in dried cannabis, which is the more common choice among addicts, is variable, the doses required to ensure satisfactory pain control may be either higher or lower than standard doses. The most significant limitation of this article is the lack of research on the response to analgesic treatment with opioids. The entire study had to be based on studies in which cannabinoid therapy was secondary to opioid therapy, not to mention the lack of data on previous exposure to cannabinoids; for this reason, this study is a collection of available data on the interaction between cannabinoids and opioids and should therefore be treated as a hypothesis rather than an unequivocal statement.

At the clinical level, the inclusion of opioid therapy in addicted patients does not seem to be an obstacle to pain treatment in most cases, and the opioid dose required for effective analgesia is likely to be lower on average. It is reasonable to include monitoring of the mental state of patients using cannabinoids in routine clinical practice, including screening for signs of addiction, especially in patients with a history of substance abuse. Pain relief will be associated with a fairly good quality of life in this group of patients, as long as other symptoms are not excessively burdensome.

In light of the growing use of cannabinoids in both the general population and clinical practice, it is necessary to develop consistent and evidence-based guidelines for their use in pain therapy. The current state of knowledge indicates a need for prospective, multicenter clinical trials involving patients who are chronic users of cannabinoids and who are undergoing de novo opioid therapy. These studies should take into account differences in pain phenotypes (neuropathic, non-cancer, cancer, postoperative) and precisely define the patient's experience with cannabis products and how they are used.

At the systemic level, it is desirable to develop interdisciplinary standards of care involving collaboration between specialists in anesthesiology, neurology, psychiatry, and clinical pharmacology in order to better understand the interactions between these two groups of substances. It is also recommended to develop educational programs for physicians and patients on the safe use of cannabinoids, side effects, and their interactions with opioids. This approach provides a foundation for the development of precision medicine in pain management and may contribute to improving the safety and efficacy of complex therapies involving cannabinoids, opioids, and, potentially, other pain treatments.

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