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Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: www.tandfonline.com/journals/ierr20

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To cite this article: Lucas Bibiano de Oliveira Souza, Juliana Paiva Gouvea Sicoli, Sara Teresinha Olalla Saad & Bruno Deltreggia Benites (2025) Modulation of the endocannabinoid system in chronic conditions: a potential therapeutic intervention yet to be explored in sickle cell disease, Expert Review of Hematology, 18:3, 215-224, DOI: 10.1080/17474086.2025.2471864

To link to this article: https://doi.org/10.1080/17474086.2025.2471864

Published online: 04 Mar 2025.

EXPERT REVIEW OF HEMATOLOGY
2025, VOL. 18, NO. 3, 215–224
https://doi.org/10.1080/17474086.2025.2471864

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REVIEW

Modulation of the endocannabinoid system in chronic conditions: a potential therapeutic intervention yet to be explored in sickle cell disease

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ABSTRACT

Introduction: Individuals living with Sickle Cell Disease (SCD) are subject to numerous chronic complications, including disabling chronic pain, often dependent on opioids and with important repercussions on the quality of life. The use of Medicinal Cannabis in this scenario may be a promising strategy for mitigating this impact.

Areas covered: This work compiles current knowledge regarding the endocannabinoid system in humans and the role of this system in various organic functions. Articles were retrieved through a comprehensive search of the PubMed NCBI database, covering relevant studies up to 2024. These data bring important speculations on the potential role of the use of medicinal cannabis in modulating SCD chronic complications, and the preliminary results of clinical trials carried out in this condition are discussed.

Expert opinion: The search for understanding the role of cannabis-derived products in the management of chronic complications of sickle cell disease could add resources to the serious challenge of dealing with the multiple aspects of the disease faced by patients. They range from the management of chronic pain itself to the risks of opioid dependence, in addition to other difficult scenarios, such as leg ulcers and chronic inflammation and its consequences.

ARTICLE HISTORY
Received 16 October 2024
Accepted 21 February 2025

KEYWORDS
Sickle cell disease; pain; chronic complications; endocannabinoid system; medical cannabis

1. Introduction

Sickle Cell Disease (SCD) is an umbrella term applied to a group of disorders that include Sickle Cell Anemia (HbSS), Sickle-Hemoglobin C Disease (HbSC), and Sickle/β-thalassemia (HbS/β-thal). These disorders are characterized by an inherited mutation on the gene that codifies hemoglobin subunits, in which glutamic acid is substituted by a valine amino acid at position 6 in the mature β-globin chain [1]. SCD affects over 250 million people worldwide with approximately 300 000 new cases each year with a burden that is both physiological and psychological and demands millions of dollars on health expenses annually worldwide [2]. The main manifestations of the disease are acute crises of disabling pain (named vaso-occlusive crises); however, many patients will also develop chronic pain, often becoming dependent on opioids and with major impacts on quality of life [3].

Since it was described in 1910 in Chicago by the physician James B. Herrick, many treatments for SCD have been tested; the most effective of them are hydroxyurea administration and erythrocyte transfusions; however, apart from hematopoietic stem cell transplantation and gene therapy, none of them are curative [4].

Over the past years with the discovery of the endocannabinoid system (ECS) and the advances in the understanding of the actions of ECS in human homeostasis, the use of Medical Cannabis has emerged as a potential adjunction or alternative to opioids in the case of debilitating pain. Furthermore, its systemic effects open up a range of possibilities in relation to preventing and treating common chronic complications in SCD patients. With that, the need to understand the possible relationships and overlaps between the pathophysiology of SCD and what is currently known about the expression and action of the endocannabinoid system arises [5].

Thus, this article discusses the present landscape of therapeutic possibilities for the medical use of cannabinoid molecules as agonists of the endocannabinoid system (ECS), particularly in the treatment of SCD chronic complications. To accomplish that, a literature search was carried out using the PubMed database, with articles published up to November/2024, using the following descriptors: 'sickle cell disease;' 'chronic pain;' 'endocannabinoid system;' 'medical cannabis,' together with the authors' clinical experience in managing these patients.

2. Sickle cell disease burden

SCD complications are a consequence of complex mechanisms arising from the mutation in one of the genes involved in the synthesis of the hemoglobin protein. Hemoglobin (Hb) is a tetrameric protein composed of four globin subunits; each globin is associated with a cofactor heme capable of transporting a molecule of oxygen. It comprises two α-globin

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Article highlights

- This paper delves into the endocannabinoid system (ECS) and its potential modulation as a novel therapeutic approach for addressing the chronic conditions associated with Sickle Cell Disease (SCD).
- It highlights the restricted effectiveness of current pain management strategies, such as opioid-based therapies, and their contribution to neuropsychiatric issues in SCD patients.
- The paper discusses initial evidence suggesting that cannabinoids may attenuate chronic pain, inflammation, and complications like acute chest syndrome (ACS) and vaso-occlusive crises (VOC).
- The initial research results reinforce the necessity of further investigation to substantiate the therapeutic potential of cannabinoids in SCD and outlines challenges and limitations in the field.

subunits and two β-globin subunits and a hereditary mutation that causes the substitution of a single nucleotide in the β-globin subunit results in the sickle Hb (HbS) [6].

The pathophysiology of SCD has not yet been completely elucidated, and as most of the affected individuals reside in low-income countries with limited resources, the data on the natural history of this disease and the impact of treatments are frequently uncertain and inadequately documented [4]. There are some common well-known burdens, related to chronic hemolysis, vasoocclusion, and inflammation: pain crises, tissue necrosis, acute chest syndrome, and leg ulcers – all important causes leading to hospitalization and morbimortality. Considering the chronic inflammation environment and the repetitive acute pain crises, another important feature of the SCD pathophysiology is the development of chronic pain syndromes, often refractory and dependent on opioids [7,8].

SCD crises often occur under circumstances of deoxygenation – that is, when the Hb is not bound to oxygen – such as in the microcirculation; in these circumstances, HbS molecules have a strong tendency to polymerize, causing the erythrocytes to assume a sickled shape, hence the name 'sickle cell disease.' [9]. Once rebounded to oxygen, the sickled erythrocytes can reassume their usual round and biconcave shape; however, numerous sickling/unsickling cycles can cause the erythrocytes to be permanently damaged, making them prone to early destruction (hemolysis) or adhesion to the endothelium, platelets, and neutrophils, leading to microvascular occlusion and tissue ischemia [10,11].

Alongside the process of hemolysis due to membrane damaging, there is the 'free-Hb scavenging effect,' in which free plasma Hb may reduce the circulating levels of nitric oxide (NO) by transforming it into nitrate (NO^{3-}) [12]. This is a particularly important cause of organ damage in the long term, as NO is the major endothelium-derived relaxing factor and responsible for vasomotor tone, and its reduced bioavailability may perpetuate micro vaso-occlusion and the ischemia-reperfusion injury [13].

In fact, vaso-occlusive crises (VOC) are the most common acute complications of the disease, frequently leading to hospitalization. VOCs are generally described as sudden onset and excruciating pain, commonly in the lower back, joints, and extremities [6]. They can be precipitated by various factors such as changes in the weather, dehydration and infection, but often affect the patient with no prodrome whatsoever [3]. These pain crises tend to cease in a non-nociceptive state in most cases, but while adolescents and young adults often only experience these acute episodic nociceptive pains, many older adults develop chronic neuropathic and centralized pain. Both chronic and acute pain cause significant morbidity in SCD patients and produce a profoundly negative impact on patients' health-related quality of life (HRQL) [14].

Several cellular and molecular mechanisms have been postulated to explain the transition from acute pain episodes to a scenario of steady-state neuropathic chronic pain. Chronic neuropathic pain can be defined as long-lasting pain caused by a lesion or disease of the somatosensory nervous system, even after the primary cause is cured [15,16]. Although its mechanisms are not entirely clarified, the International Association for the Study of Pain (IASP) sets among the criteria utilized for the diagnostic of neuropathic pain the trigeminal neuralgia, peripheral nerve injury, painful polyneuropathy, postherpetic neuralgia, and painful radiculopathy [15]. The biological pathways through those include abnormal generation of neuronal action potentials, loss of endogenous pain control, development of new synaptic circuits, enhancement of the transmission of synaptic impulses, and neuroimmune interactions – which leads to nervous system sensitization [17].

Studies have shown that chronic pain and opioid-based management (which for most patients is not sufficiently efficient) has left the SCD population with a significant neuropsychiatric burden and worsened quality of life [18,19]. Osunkwo et al. have shown that a substantial proportion of patients reported that SCD caused a high negative impact on emotions (60%), school achievement (51%), and a reduction in work hours (53%); 41% reported that SCD also affected their family or social life [20].

As described above, both the neuromodulation caused by chronic pain and the lack of effective therapeutic options other than opioids attest to the fact that the current scheme of SCD treatment and pain management is insufficient in achieving a pain-free baseline for patients, nor does it prevent repercussions in other domains of life. In order to improve this scenario, one potential strategy is to look at the endocannabinoid system and its multiple components as a possible form of new treatment for the SCD burden [21]. Some multisystem complications of SCD can be seen in Figure 1 and will be discussed in detail throughout the article.

3. The endocannabinoid system (ECS)

The endocannabinoid system (ECS) has the primary function of maintaining homeostasis – that is, to maintain certain specific internal conditions of a given organism in a balanced state to keep it alive. Hence, the ECS has much influence across several vital functions, and despite acting mainly in the nervous and immune systems, ECS receptors are present in almost every cell of the human body [22,23]. The ECS is composed by a group of G protein-coupled receptors called Cannabinoid-receptor type 1 (CB1) and Cannabinoid-receptor type 2 (CB2) and endocannabinoids that are CB1/CB2 agonist molecules, of which N-arachidonoylethanolamide (Anandamide, AEA) and 2-arachidonoyl glycerol (2AG) are of

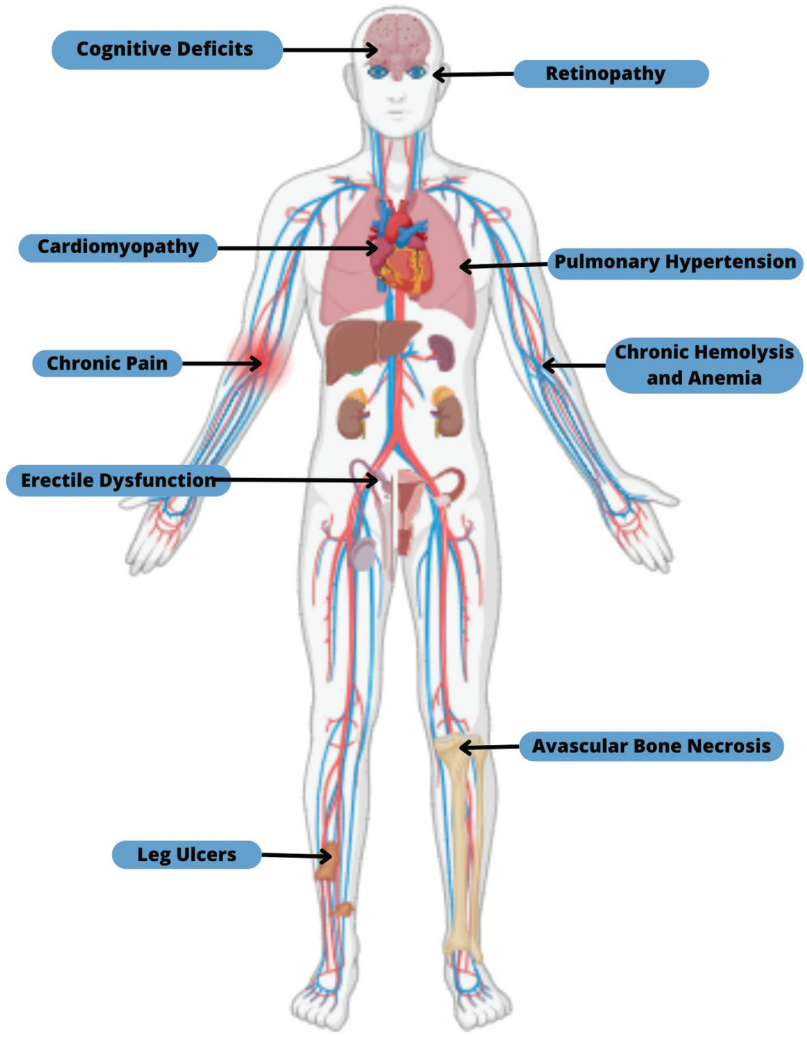

Figure 1. Chronic complications of sickle cell diseases reflect the systemic and multiorgan involvement of this group of pathologies.

cardinal importance, as well as by the enzymes responsible for the degradation of these ECS components [24].

CB1 is a receptor with many functions that may vary with its location. Although expressed throughout the whole body, it is significantly more present in the central and peripheral nervous system, where it is the most highly expressed G protein-coupled receptor [25]. The distribution of CB1 in the brain varies greatly, and although expressed mainly in neurons, CB1 is also expressed in astrocytes, oligodendrocytes, and microglia, where it has been shown to mediate synaptic transmission [26]. In the peripheral nervous system, CB1 is mostly expressed in sympathetic nerve terminals. Like many other G protein-coupled receptors, CB1 is predominantly expressed in the cell membrane but can further be found in intracellular regions, especially in non-neuronal cells [27,28].

CB2 is predominantly localized in immune cells, which is in line with its role in modulating immune response. Its expression is particularly high on lymph nodes and spleen when compared with immune cells in peripheral blood, of which expression also varies in different cell populations (B cells > NK cells > monocytes > neutrophils > CD8 T-cells > CD4 T-cells). CB2 is highly linked with the inflammatory response, often called the inflammatory cannabinoid receptor [29,30].

Anandamide (AEA) is an ethanol amide derivative of arachidonic acid that serves primarily to activate cannabinoids [31]. Anandamide effects are mediated by CB1 and CB2 and are involved in sleeping and eating patterns as well as pleasure enhancement and pain relief [32]. In fact, Uhelski et al. reported that the inhibition of Anandamide degradation enzymes can provide significant pain relief, since such an inhibition tends to result in a rise of anandamide local and serum levels, hence the pain relief [33].

The 2AG molecule is nowadays one of the most relevant monoacylglycerols and the most abundant molecule of the ECS. It is an agonist for the cannabinoid CB1 and CB2 receptors, known to be synthesized 'on demand' and produce innumerous (and probably yet to be discovered) effects on the brain [34]. 2AG plays a central role in the regulation of multiple neuroinflammatory processes in the brain [35]. Studies have generally shown a bidirectional effect of stress on endocannabinoid levels, with AEA levels decreasing and 2AG levels increasing compared to controls [35]. Although counterintuitive at first glance, one possible speculation is

that sustained stress may in fact significantly consume anandamide reserves, while at the same time exacerbating the inflammatory condition, forcing greater production of 2AG. A succinct model of the action of the molecules of the endocannabinoid system can be seen in Figure 2.

3.1. Hemopressin

It now appears that the endocannabinoid system components are not the only ones with therapeutic potential. In fact, the recently discovered hemopressin (Hp) seems to hold a lot of antinociceptive potential, especially for chronic and neuropathic pain patients [36]. The Hp molecule (PVNFKFLSH in rats and PVNFKLLSH in mice and humans) is a peptide fragment derived from the degradation of the α-chain of hemoglobin. It is an agonist to both receptors CB1 and CB2 of the ECS; extended fragments of hemopressin-like RVD-hemopressin, also known as pepcan-12, exhibit CB1 and CB2 receptor agonistic activity [37]. A study has successfully utilized Hp solution to obtain a long-lasting antinociceptive effect on murine models that had been subject to chronic constriction injury (CCI) of the sciatic nerve. This effect was shown to completely block signs of pain 14 days after CCI, supporting the idea that Hp induces true antinociception in this neuropathic pain model [38].

Recent studies have further expanded the understanding of hemopressins, particularly their diverse roles beyond antinociception. For instance, research highlights that variants like RVD-hemopressin (α) act as selective CB1 receptor agonists and influence a spectrum of physiological processes, including modulation of oxidative stress and apoptosis pathways. These properties make them promising candidates for addressing

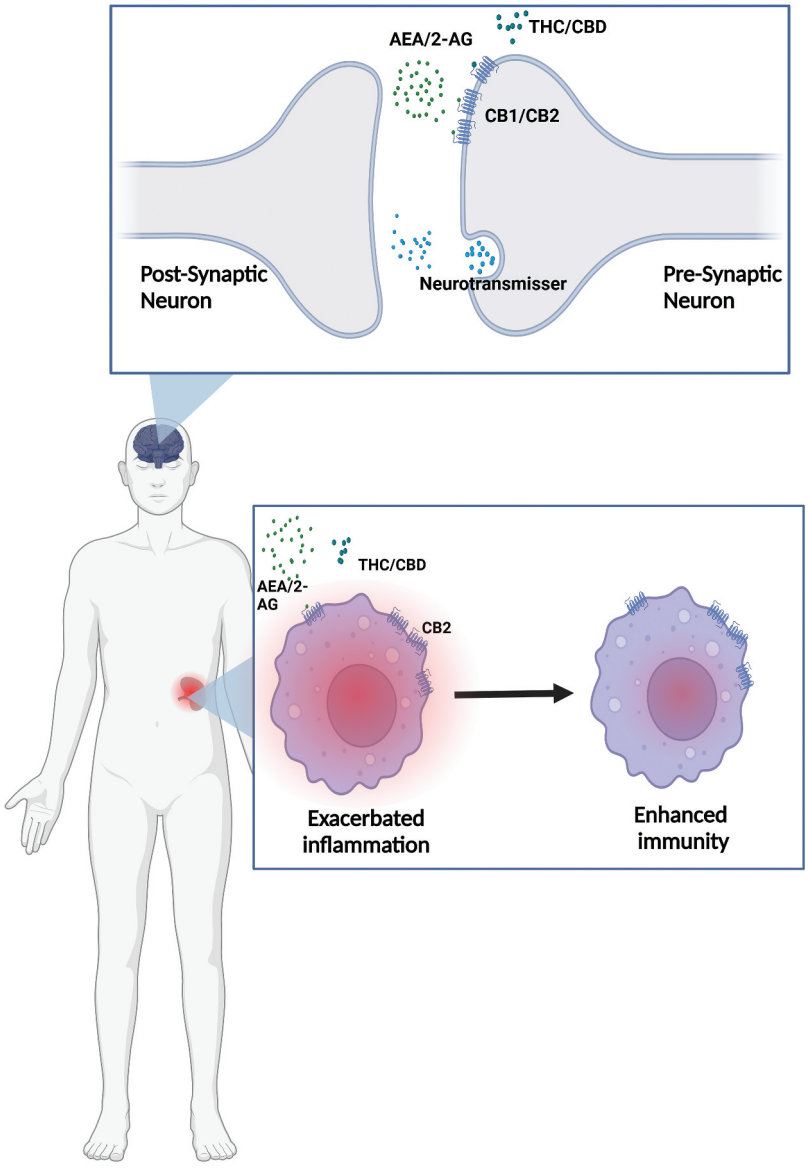

Figure 2. Two of the most significant ways the ECS may be targeted by cannabinoids: through modulation of neuronal synaptic conduction or through effects on components of the immune system.

neurodegenerative conditions like Alzheimer's disease, as they can ameliorate oxidative damage and support neuronal survival via pathways such as BDNF/TrkB/Akt [39].

Additionally, hemopressin peptides demonstrate the potential for cardiovascular applications by inhibiting angiotensin-converting enzyme 1 (ACE1), thereby offering a natural alternative for managing hypertension [40]. This multidimensional therapeutic capability underscores the growing interest in hemopressins as a class of bioactive peptides, which may serve as foundational molecules for innovative treatments targeting both pain and broader systemic disorders.

4. Medical cannabis

Cannabis is a genre of plant that has been used due to its therapeutic effects through millennia, especially *C. sativa* [41]. The use of cannabis has been largely prohibited in the occident during most of the last century, mainly due to a series of events highly related with the social structure of racism against Afro-American people in the American continent, a general moral panic, and the disagreement with the textile industry, which were highly dependent on cotton, against the large-scale production of hemp [42,43]. Despite this long-term prohibition, scientists have shown many important therapeutic effects of cannabis on diseases and syndromes such as Parkinson's disease [44], Tourette's syndrome [45], fibromyalgia pain [46], and cancer-related pain [47]. Nowadays, many countries are legalizing both the medicinal and recreational uses of Cannabis [48].

C. sativa concentrates multiple substances of importance and among them are the phytocannabinoids such as Δ9–tetrahydrocannabinol (THC) and cannabidiol (CBD), which are lipid molecules that can be found throughout the whole plant and are particularly abundant on the unfertilized female flowers [49]. Both molecules affect mammals' brains and produce a complex number of interactions, mainly with the CB1 and CB2 not only in the endocannabinoid system but also cardiovascular and neural systems [50]. In this review, we will focus on the most pharmacologically relevant and well-known phytocannabinoids, THC and CBD.

THC was the first phytocannabinoid to be discovered and studied (1964), and it has been the main research object for scientists who tried to better understand Cannabis pharmacological features in the human body [51]. THC is the most influential psychoactive molecule in *C. sativa*, producing most of the neuropsychiatric effects cannabis is known for. In the past, most of the treatments using cannabis derivatives would use only THC to obtain an antinociceptive response – this approach has been proved not to be the most efficient, since the dose of THC necessary to obtain significant analgesia tends to be too intense for most patients due to THC psychotropic effects [52,53].

Cannabidiol (CBD), a lipid molecule that is a primary component in the cannabis plant, is well known for its therapeutic effects and, unlike THC, presents no psychotropic effects, and studies indicate that CBD produces dose-dependent, but not dose-proportional peak concentrations [54]. Generally considered to be safe for human use, CBD presents a safe pharmaceutical profile and limited side effects. Although few, there are preeminent studies that show CBD efficacy in the treatment of general chronic pain and in the improvement of HRQL in patients who suffer from chronic pain [55–57].

The treatment of medical cannabis is often made with a mix of different phytocannabinoids, sometime called 'full-spectrum products,' to obtain what is called the 'entourage effect' which is obtained by one cannabinoid molecule enhancing the general efficacy and/or tolerability; this effect is attributed to synergy between cannabinoids and other components in the cannabis plant [58]. One example of the entourage effect lies in the significant reduction of the THC psychotropic effects when paired with a given dose of CBD [57].

It is important to delineate that there are many different forms of cannabis products, each with its own therapeutic value. Among those forms, it is especially important to understand the benefits and risks of smoking and vaporization of the Cannabis plant material as well as the oral use of CBD plus THC mixed in oil, butter, or gelatin [52].

Smoking the Cannabis plant is, despite being illicit in many countries, the most common use, though not the safest, commonly sought for patients on their own and without proper medical attention. Patients commonly relate to some levels of pain relief shortly after smoking, but this technique usually does not provide long-lasting pain relief. Another way of utilizing the Cannabis plant through breathing is the vaporization method, a slightly different technique that significantly reduces the proportion of toxic residues inhaled if compared to smoking [59].

Apart from the raw plant material, there is the possibility of utilizing only purified CBD and/or THC. They are usually prescribed together; most of the studies utilizing cannabinoids to treat pain have chosen to utilize THC and CBD oil or an enriched gelatin to be orally consumed or, in some cases, topical application [60].

5. Targeting the endocannabinoid system for specific SCD complications

In the case of SCD patients, current strategies for the management of debilitating pain rely essentially on opioids, which can cause both tolerance and dependence. In this setting, the *C. sativa* compounds might represent an important advance in care, especially when considering its systemic action, potent pain relief, and good overall tolerability [61,62]. In the following topics, potential applications of its use in different complications of SCD are discussed.

5.1. Acute, chronic, and neuropathic pain

When compared to the use of opioids, medical Cannabis benefits include a low risk of developing dependence and/or resistance, and significantly smaller damage to the liver and kidneys [63–65]. A recent consensus recommendation on the use of medical cannabis states that it may be considered for patients experiencing neuropathic, inflammatory,

nociplastic, and mixed pain [66]. Furthermore, one meta-analysis on the efficacy of cannabis-based medicines in the treatment of chronic and neuropathic pain has shown that THC/CBD interventions provided a significant improvement in pain intensity and estimated they were highly likely to provide up to 50% reduction in pain [67].

In a qualitative investigation, Aron et al. prospected the effect of medical cannabis certification on hospital use by SCD patients. The study enrolled 36 SCD patients with cannabis certification and found no significant reductions in the hospital use by those patients, although 44% of the patients chose to be recertified, presumably choosing to continue with the medical cannabis treatment. The study concluded that these data might indicate that patients had perceived some improvement in their HRQF; however, due to the small sample size, those benefits could not be analytically perceived [68].

Another important study has shown that among 798, 313 hospitalizations for VOC in the United States, 0.08% of the patients have reported to use marijuana regularly and those had lower proportions of Acute Chest Syndrome (ACS) – a severe lung-related complication – compared with those who did not use marijuana; marijuana users were also usually hospitalized later than non-users. This study showed no differences in mortality rate and length of stay in the two groups, but the significant reduction in ACS and age of hospitalization indicates that medical cannabis may help in daily pain management [69].

A recent systematic review intended to specifically determine whether cannabis can be used for pain relief in SCD patients was faced with conflicting results. One of the findings is that the number of clinical trials that specifically addressed the issue of pain in this population remains scarce and, despite pointing toward benefits, no definitive conclusions can be drawn at this stage. The perspective is that more robust recommendations may emerge with new clinical trials designed specifically to observe objective outcomes, such as a better understanding of the effect on long-term pain and the possible reduction in the need to seek emergency services and for the use of opioids [70].

CBD has recently received approval from regulatory agencies in the United States, Europe, India, and Brazil for use as an adjunctive therapy in cases of refractory epilepsies, such as Dravet syndrome, Lennox Gastaut syndrome, and Tuberous sclerosis [71]. It is interesting to consider that the anticonvulsant activity of CBD occurs through several mechanisms that go beyond the coupling to CB1/CB2 receptors. The action of CBD on TRPV (Transient receptor potential vanilloid-1) channels has been demonstrated, leading to desensitization and reduced neuronal excitability; its action through GPR-55 (G-protein coupled receptor-55) receptors also regulates neuronal excitability and inflammation, and it also has an antagonistic action on 5HT1A (5-hydroxytryptamine receptor 1), increasing the availability of inhibitory neurotransmitters while decreasing excitatory ones, leading to lower overall neuronal excitability [72]. We can speculate that these mechanisms may also help in pain control and attenuating the progression of chronic pain, similar to what occurs with other centrally acting drugs, such as gabapentin and pregabalin.

5.2. Immunity and inflammation

.Considering the chronic inflammation environment associated with SCD, modulating the immune system in a continuous manner may be crucial to improve patients' outcomes, such as reducing VOC frequencies and chronic pain, and preventing end organ damage. There are studies demonstrating immune-regulatory properties for Cannabis and that modulating the ECS, especially CB2 - using phytocannabinoids – can provide significant improvement in highly debilitating auto-immune diseases such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease [73].

Evidence gathered from recent studies supports the idea of modulating CB2 and reducing inflammation, such as those of Sido et al., that used an *in vivo* model to show that the production of 2-AG by activated B- and T-cells modulates inflammation, and Dotsay et al. demonstrated that transient administration of CB2 antagonists during immunization heightened the intensity of antigen-specific antibody responses [74,75].

As for SCD specifically, there are no studies that have focused on modulating inflammation via medical cannabis, but the initial evidence of pain reduction, as well as the lower chances of ACS and VOC, suggests that it might reduce chronic inflammation; nonetheless, further studies are needed [68,69,71].

Apart from the chronic inflamed environment, as SCD patients are further burdened with ischemic spleen atrophy and subsequent poor immune response to infections, it is interesting to consider the possibility of the ECS acting, through the CB2, as an adaptive immune system enhancer. The evidence on this matter, however, remains scarce and contradictory, as endocannabinoids, such as 2-AG, have been shown to preferentially induce the chemotaxis of unstimulated naïve B cells [76]., though exocannabinoids have been shown to induce the apoptosis of B lymphocytes via CB2 mechanisms, in *in vivo* mouse studies [77].

5.3. Leg ulcers

Limb ulcers are one of the possible complications of sickle cell disease, often appearing unpredictably and difficult to heal, eventually progressing to osteomyelitis and amputations. Their occurrence appears to be associated with chronic hemolysis, in which nitric oxide is consumed to metabolize free hemoglobin; nitric oxide scavenging then leads to endothelial damage and impaired local vasodilation [78,79].

When it comes specifically to the leg ulcers associated with SCD, Maida et al. have demonstrated interesting results on the topical use of cannabis-based medicines showing wound closing trends in up to 90% of 33 complex patients with refractory non-healing wounds of over 6 months of duration [80]. This study is in line with others that demonstrate that topical use of cannabis may be efficient for the treatment of inflammatory skin diseases and even ulcers caused by other diseases such as calciphylaxis [81,82].

6. Neuropsychiatric burden

Medical cannabis may have a significant impact on the mental health of SCD patients and help patients who struggle with the neuropsychiatric burden of the diseases such as anxiety and depression. There are studies demonstrating that patients with different psychiatric disorders often report significant improvement in the clinical symptoms of anxiety and depression, when utilizing cannabinoids [83].

In a recent systematic review, García-Gutiérrez et al. have shown that multiple double-blind randomized placebo-controlled studies have demonstrated the efficiency and effectiveness of CBD as an anxiolytic and antidepressant. Some of those studies have used THC to potentialize these desirable effects, but this approach heightens the risks of substance abuse as a collateral effect of this treatment. Despite preeminent results, those studies did not include many participants, and the CBD multifactorial molecular profile, acting on more than 65 targets, complicates the comprehension of the metabolic pathways involved. Safety has not been totally granted, which supports the need for larger studies on the theme, especially for SCD patients who have their own many pathophysiological pathways to elucidate [84].

There has been a particular interest in understanding how the use of medical cannabis could mitigate the impact of opioid dependence, especially considering the opioid crisis in some countries such as the USA [85,86]. In fact, there are surveys showing that the implementation of laws permitting broader cannabis access, including implementation of medical dispensaries, was associated with lower rates of opioid-related deaths in the US from 2002 to 2020 [87].

7. Harmful effects of cannabis for SCD patients?

Although presenting multiple possible medical properties, as with any other important medication, potential risks must be considered. This is especially the case when used without proper medical orientation, as demonstrated by Miodownik et al.: the use of medical cannabis by SCD patients was related with more frequent pain crisis and especially with the chance of developing avascular necrosis [88]. A systematic review by Singh et al. showed that, in some cases, the use of medical cannabis could worsen the patients' pain and offered little to no help compared to opioids or hydroxyurea usage [72]. The main considerations pointing to this lack of benefit, or potential risks would be the fact that many patients seek the use of cannabis outside of the medical monitoring and prescription context and lack adequate follow-up, which may interfere with the efficacy of results. As such, it is clear that further research is necessary to ascertain the safety and efficacy of such treatments [61].

8. Clinical trials specifically in SCD patients

There are still three important clinical trials to mention regarding the use of medical cannabis in SCD patients. 'Dronabinol for Pain and Inflammation in Adults Living with Sickle Cell Disease [NCT03978156]' was conducted at the Yale University and sadly terminated without results due to the COVID-19 outbreak, and the newest of them is still at the recruiting phase: 'Cannabinoids for the Reduction of Inflammation and Sickle Cell Related Pain (CRISP) [NCT05519111].'

Recently, the results of another clinical trial evaluating vaporized cannabis for chronic pain associated with SCD showed that, compared to placebo, this method did not significantly reduce pain and associated symptoms, except interference in mood. However, an important criticism to this study is the fact that the intervention with vaporized cannabis was tested for only 5 days, which may have prevented the observation of more consistent results – in addition to this route leading to a more ephemeral effect than the oral route, for example [89].

9. Conclusion

The management of complications of SCD is a major medical challenge, especially in relation to its chronic repercussions, such as chronic debilitating and opioid-dependent pain, leg ulcers, and associated neuropsychiatric conditions. Given the restriction of possibilities in the current therapeutic arsenal, the use of cannabis-based drugs can be a promising strategy, similar to what has been observed in numerous other pathological conditions. Considering the complex pathophysiology of SCD and the wide organic distribution of the elements of the endocannabinoid system, this review strived to present insights regarding the numerous potentially beneficial applications; nevertheless, more clinical studies are crucial in this specific population, in order to obtain more definitive answers regarding the safety and efficacy of its use in this group of patients.

10. Expert opinion

Managing chronic complications of SCD is a major challenge in the multidisciplinary care for these patients, especially in the case of chronic pain. In addition to the impact of the painful sensation itself for this group of individuals this complication takes on even greater dimensions, such as the issue of opioid dependence and its consequences, the need for frequent visits to the emergency room, loss of work days, and higher rates of anxiety and depression – all of which considerably reduce quality of life. This is a particularly relevant issue nowadays, as the more recent advances in the treatment of these diseases, such as the use of hydroxyurea, vaccinations, antibiotics, and optimized use of blood transfusions, have considerably increased the survival rate of these patients. Although very exciting, it also means that patients will have time to deal with the emergence of other disabling chronic complications and comorbidities. This paradigm shift also reveals the fact that we still do not fully know how to deal with the complications and comorbidities emerging in adulthood and older age. In this sense, the search for safer and more effective strategies is urgent, and medicinal cannabis could represent an important element to fill this gap.

There are still few clinical trials evaluating cannabis products in the population of patients with SCD, but the results observed in other inflammatory and degenerative pathologies point to a potential that still needs to be

further evaluated. Several issues remain to be better clarified, such as the best route of administration in each context, safety (especially considering the frequent use of multiple concomitant medications), and what is the effect for each specific complication – from chronic pain itself to neuropsychiatric disorders, inflammation, and limb ulcers, among others. The current availability of different molecules, isolated or in combination (and in this case, in varying proportions), when considered from the perspective of numerous complications of the same disease, attests to how there is still a long way to go in terms of research until a better definition of the best regimen for each patient phenotype.

In addition to the main issue of pain affecting these patients, a point of potential interest would be the possible immunomodulatory effects of the use of medicinal cannabis in this group of diseases. An important part of the pathophysiology of this condition is the chronic inflammatory environment derived from repetitive episodes of ischemia and reperfusion, as well as the effects of chronic hemolysis and its consequences. In addition to being responsible for many chronic manifestations of the disease, this inflammatory milieu is accompanied, paradoxically, by relative immunosuppression, as a result of changes in the polarization of immune system cells, associated with functional asplenia. Therefore, considering the effects previously demonstrated, mainly in relation to CB2 receptors in immune cells, the use of cannabis derivatives could reshape the immune system toward a less inflammatory situation though more effective in relation to the response to pathogens – such as neutrophil chemotaxis, macrophage polarization, and antibody production by lymphocytes.

Therefore, this field remains open to experimentation and speculation, with the possibility of important discoveries in the coming years that could greatly improve the care of these patients. For this adequate continuation, access barriers must be broken, including the prejudice associated with cannabis and the restrictive laws that are, still to this date, imposed in several countries, which may impact the development of clinical trials and patients' access to these new therapeutic possibilities. This change of scenario will certainly need to involve the evolution of education and the responsible dissemination of adequate information free from ideological bias, both for patients and the care team.

Another point that should be discussed is the high cost of these formulations, especially when it comes to countries with more restricted socioeconomic conditions – precisely where the largest proportion of patients with Sickle Cell Disease live. In this sense, an interesting topic for investigation would be the potential impact of cannabis use in reducing other unfavorable outcomes – such as days of hospitalization, use of other medications, and loss of productive days. If cost-effectiveness is proven, these results could support government and public health actions to facilitate access to these new medications and their integration into care guidelines.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Williams TN, Thein SL. Sickle cell anemia and its phenotypes. Annu Rev Genom Hum Genet [Internet]. (2018;19(1):113–147. doi: 10.1146/annurev-genom-083117-021320
2. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN, Osrin D. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10(7):e1001484. doi: 10.1371/journal.pmed.1001484
3. Darbari DS, Sheehan VA, Ballas SK. The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management. Eur J Haematol. 2020 Sep;105(3):237–246.
4. Serjeant GR. The natural history of sickle cell disease. Cold Spring Harb Perspect Med. 2010 Oct 1;3(10):a011783.
5. Lowe H, Toyang N, Steele B, Bryant J, Ngwa W. The endocannabinoid system: a potential target for the treatment of various diseases. Int J Mol Sci MDPI. 2021;22(17):9472. doi: 10.3390/ijms22179472
   • **This paper offers a exploration of the endocannabinoid system's role in disease regulation, highlighting its potential as a therapeutic target for conditions ranging from neurological disorders to inflammatory diseases, making it a good addition for those interested in innovative treatment approaches.**
6. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. Am J Hematol. 2005;79(1):17–25. doi: 10.1002/ajh.20336
7. Piccin A, Murphy C, Eakins E, et al. Insight into the complex pathophysiology of sickle cell anaemia and possible treatment. Eur J Haematol. 2019 Apr;102(4):319–330.
8. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin a novel mechanism of human disease [Internet.
9. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nat Rev Dis Primers. 2018 Mar 15;4:18010.
   • **This comprehensive review provides an in-depth analysis of sickle cell disease, covering its pathophysiology, clinical manifestations, and emerging therapeutic strategies, making it a valuable resource for both researchers and clinicians.**
10. Roumenina LT, Chadebech P, Bodivit G, et al. Complement activation in sickle cell disease: dependence on cell density, hemolysis and modulation by hydroxyurea therapy. Am J Hematol. 2020;95(5):456–464. doi: 10.1002/ajh.25742
11. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J Clin Investigation Am Soc For Clin Investigation. 2017;127(3):750–760. doi: 10.1172/JCI89741
12. Reiter CD, Gladwin MT. An emerging role for nitric oxide in sickle cell disease vascular homeostasis and therapy. Curr Opin Hematol. 2003;10(2):99–107. doi: 10.1097/00062752-200303000-00001
13. Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med dezembro de. 2002;8(12):1383–1389. doi: 10.1038/nm1202-799

14. Vilela RQB, Cavalcante JC, Cavalcante BF, Araújo DL, de M LM, Nunes FAT. Quality of life of individuals with sickle cell disease followed at referral centers in Alagoas, Brazil. Rev Bras Hematol Hemoter. 2012;34(6):442–446. doi: 10.5581/1516-8484.20120110
15. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain Lippincott Williams And Wilkins. 2019;160(1):38–44. doi: 10.1097/j.pain.0000000000001363
    - **This paper provides a crucial update on the classification of chronic neuropathic pain within the ICD-11 framework, offering a standardized approach that enhances diagnosis, research, and treatment strategies for clinicians and pain specialists, this could be a particularly good reading for those starting to better understand the study of chronic pain.**
16. Campos RMP, Aguiar AFL, Paes-Colli Y, et al. Cannabinoid therapeutics in chronic neuropathic pain: from animal research to human treatment. Front Physiol. 2021 Nov 30;12:785176.
17. Karafin MS, Singavi A, Hussain J, et al. Predictive factors of daily opioid use and quality of life in adults with sickle cell disease. Hematology. 2018;23(10):856–863. doi: 10.1080/10245332.2018.1479997
18. Carroll CP, Lanzkron S, C H Jr, et al. Chronic opioid therapy and central sensitization in sickle cell disease. Am J Prev Med. 2016). Aron 51(1 Suppl 1):S69–77. doi: 10.1016/j.amepre.2016.02.012
19. Orhurhu MS, Chu R, Claus L, et al. Neuropathic pain and sickle cell disease: a review of pharmacologic management. Curr Pain Headache Rep. 2020 Jul 24;24(9):52.
20. Osunkwo I, Andemariam B, Minniti CP, et al. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: results from the international sickle cell world assessment survey (SWAY). Am J Hematol. 2021;96(4):404–417. doi: 10.1002/ajh.26063
21. de Melo Reis RA, Isaac AR, Freitas HR, et al. Quality of life and a surveillant Endocannabinoid system. In: Frontiers in neuroscience. Vol. 15. Frontiers Media S.A.; 2021.
22. Hillard CJ. Stress regulates endocannabinoid-CB1 receptor signaling. Semin Immunol. 2014 Oct;26(5):380–8.
23. Joshi N, Onaivi ES. Endocannabinoid system components: overview and tissue distribution. Em: advances in experimental medicine and biology. Adv Exp Med Biol. 2019;1162:1–12.
24. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci MDPI AG. 2018;19.
25. Kano M, Ohno-Shosaku T, Hashimotodani Y, Uchigashima M, Watanabe M. Endocannabinoid-mediated control of synaptic transmission. Physiol Rev. 2009;89(1):309–380. doi: 10.1152/physrev.00019.2008
26. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005;(168):299–325.
27. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci MDPI AG. 2018;19(3):833. doi: 10.3390/ijms19030833
28. Mulpuri Y, Marty VN, Munier JJ, et al. Synthetic peripherally-restricted cannabinoid suppresses chemotherapy-induced peripheral neuropathy pain symptoms by CB1 receptor activation. Neuropharmacology. 2018;139:85–97. doi: 10.1016/j.neuropharm.2018.07.002
29. Simard M, Rakotoarivelo V, Di Marzo V, Flamand N. Expression and functions of the CB2 receptor in human leukocytes. Front Pharmacol. 2022 Feb 22;13:826400.
30. Kiran S, Rakib A, Moore BM, Singh UP. Cannabinoid receptor 2 (CB2) inverse agonist SMM-189 induces expression of endogenous CB2 and protein kinase a that differentially modulates the immune response and suppresses experimental colitis. Pharmaceutics. 2022 Apr 26;14(5):936.
31. Mock ED, Gagestein B, van der Stelt M. Anandamide and other N-acylethanolamines: a class of signaling lipids with therapeutic opportunities. Prog Lipid Res. 2023 Jan;89:101194.
32. Biringer RG. The rise and fall of anandamide: processes that control synthesis, degradation, and storage. Mol Cell Biochem. 2021 Jul;476(7):2753–2775.
33. Uhelski ML, Gupta K, Simone DA. Sensitization of C-fiber nociceptors in mice with sickle cell disease is decreased by local inhibition of anandamide hydrolysis. Pain. 2017;158(9):1711–1722. doi: 10.1097/j.pain.0000000000000966
34. Baggelaar MP, Maccarrone M, van der Stelt M. 2-arachidonoylglycerol: a signaling lipid with manifold actions in the brain. Prog Lipid Res. 2018 Jul;71:1–17.
35. Gaetani S, Dipasquale P, Romano A, et al. Chapter 5 the endocannabinoid system as a target for novel anxiolytic and antidepressant drugs. Int Rev Neurobiol. 2009;85:57–72.
36. Heimann AS, Dale CS, Guimarães FS, et al. Hemopressin as a breakthrough for the cannabinoid field. Neuropharmacology. 2021 Feb 1;183:108406.
    - **This article presents insights into hemopressin, a peptide with cannabinoid-modulating properties that could be of great future importance, shedding light on its potential to influence cannabinoid receptor activity and paving the way for novel therapeutic applications in pain management and neuropsychiatric disorders.**
37. Castro LM, Cavalcanti DMLP, Araujo CB, et al. Peptidomic analysis of the neurolysin-knockout mouse brain. J Proteomics. 2014;111:238–248.
38. Toniolo EF, Maique ET, Ferreira WA, et al. Hemopressin, an inverse agonist of cannabinoid receptors, inhibits neuropathic pain in rats. Pept (NY). 2014;56:125–131. doi: 10.1016/j.peptides.2014.03.016
39. Zhang R, He X, Cheng J, et al. (m) rvd-hemopressin (α) ameliorated oxidative stress, apoptosis and damage to the BDNF/TrkB/Akt pathway induced by scopolamine in HT22 cells. Neurotox Res. 2023;41(6):627–637. doi: 10.1007/s12640-023-00677-w
40. Antony P, Baby B, Rahma A, et al. Molecular insights into the inhibition of angiotensin-converting enzyme 1 by hemopressin peptides. Sci Rep. 2024;14(1). doi: 10.1038/s41598-024-78893-3
41. Ren M, Tang Z, Wu X, et al. A N T H R O P O L O G Y the origins of cannabis smoking: chemical residue evidence from the first millennium BCE in the pamirs [internet]. Sci Adv. 2019;5(6). doi: 10.1126/sciadv.aaw1391
42. Cody Bachelor DL. Smoke signals: cannabis moral panics in the United States [Thesis]. School of Sociology and Social Work, University of Tasmania; 2006.
43. Solomon R. Racism and its effect on cannabis research. Cannabis Cannabinoid. 2020;5(1):2–5. doi: 10.1089/can.2019.0063
44. Yenilmez F, Fründt O, Hidding U, Buhmann C. Cannabis in Parkinson's disease: the patients' view. J Parkinsons Dis. 2021;11(1):309–321. doi: 10.3233/JPD-202260
45. Szejko N, Saramak K, Lombroso A, Müller-Vahl KR. Cannabis-based medicine in treatment of patients with Gilles de la Tourette syndrome. Neurologia i Neurochirurgia Polska Via Medica. 2022;56(1):28–38. doi: 10.5603/PJNNS.a2021.0081
46. Khurshid H, Qureshi IA, Jahan N, et al. A systematic review of fibromyalgia and recent advancements in treatment: Is medicinal cannabis a new hope? Cureus. 2021. doi: 10.7759/cureus.17332
47. Byars T, Theisen E, Bolton DL. Using cannabis to treat cancer-related pain. Semin Oncol Nurs. 2022 Jun;35(3):300–309.
48. Fraguas-Sánchez AI, Torres-Suárez AI. Medical use of cannabinoids. Drugs. 2018 Nov;78(16):1665–1703.
49. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. P & T a Peer-Reviewed J For Formulary Manag. 2017;42(3):180–188. doi: 10.1371/journal.pone.0089566
50. Ligresti A, De PL, Di MV. Pleiotropic physiological and pathological roles through complex pharmacology. Physiol Rev [Internet];2016;96(4):1593–1659. doi: 10.1152/physrev.00002.2016
51. Crocq MA. History of cannabis and the endocannabinoid system. Dialogues Clin Neurosci. 2020;22(3):223–228. doi: 10.31887/DCNS.2020.22.3/mcrocq
52. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol [Internet]. 2011;163(7):1344–1364. doi: 10.1111/j.1476-5381.2011.01238.x
53. Abraham AD, Leung EJY, Wong BA, et al. Orally consumed cannabinoids provide long-lasting relief of allodynia in a mouse model of

chronic neuropathic pain. Neuropsychopharmacol. 2011;45 (7):1105–1114. doi: 10.1038/s41386-019-0585-3
54. Sales AJ, Fogaça MV, Ag S, et al. Cannabidiol induces rapid and sustained antidepressant-like effects through increased BDNF signaling and synaptogenesis in the prefrontal cortex. Mol Neurobiol. 2019;56(2):1070–1081. doi: 10.1007/s12035-018-1143-4
55. Britch SC, Babalonis S, Walsh SL. Cannabidiol: pharmacology and therapeutic targets. Psycho-Pharmacology. 2021;238(1):9–28. doi: 10.1007/s00213-020-05712-8
56. Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. Postgrad Med. 2020;132 (1):56–61. doi: 10.1080/00325481.2019.1685298
57. Fisher E, Eccleston C, Degenhardt L, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a protocol for an overview of systematic reviews and a systematic review of randomised controlled trials. Pain Rep. 2019 Apr 30;4(3):e741.
58. Anand U, Pacchetti B, Anand P, Sodergren MH. Cannabis-based medicines and pain: a review of potential synergistic and entourage effects. Pain Manag. 2021 Apr;11(4):395–403.
59. Cohen K, Weizman A, Weinstein A. Positive and negative effects of cannabis and cannabinoids on health. Clin Pharmacol Ther. 2019 May;105(5):1139–1147.
60. Farokhnia M, McDiarmid GR, Newmeyer MN, et al. Effects of oral, smoked, and vaporized cannabis on endocrine pathways related to appetite and metabolism: a randomized, double-blind, placebo-controlled, human laboratory study. Transl Psychiatry. 2020;10(1). doi: 10.1038/s41398-020-0756-3
61. Meffert BN, Morabito DM, Mosich MK, Loflin MJ, Sottile J, Heinz AJ. Navigating blind in the green rush: clinical considerations and harm reduction practices for cannabis. Curr Drug Res Rev. 2018;11(1):3–11. doi: 10.2174/2589977511666181109153958
62. Argueta DA, Aich A, Muqolli F, et al. Considerations for cannabis use to treat pain in sickle cell disease. J Clin Med MDPI. 2020;9 (12):3902–3920. doi: 10.3390/jcm9123902
63. Porter B, St Marie B, Milavetz G, Herr K. Cannabidiol (CBD) use by older adults for acute and chronic pain. J Gerontological Nurs Slack Incorporated. 2021;47(7):6–15. doi: 10.3928/00989134-20210610-02
64. Atici S, Cinel I, Cinel L, Doruk N, Eskandari G, Oral U. Liver and kidney toxicity in chronic use of opioids: an experimental long term treatment model § [Internet]. Vol. J Biosci. 2005;30(2):245–252. doi: 10.1007/BF02703705
65. Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based Pain medication: patient self-report. Cannabis Cannabinoid Res. 2017;2(1):160–166. doi: 10.1089/can.2017.0012
66. Bhaskar A, Bell A, Boivin M, et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified delphi process. J Cannabis Res. 2021;3 (1). doi: 10.1186/s42238-021-00073-1
67. Aviram J. Efficacy of cannabis-based medicines for PainManagement: a systematic review and MetaAnalysis of randomized controlled trials. Pain Physician. 2017;6(20;6):E755–E796. doi: 10.36076/ppj.20.5.E755
68. Aron JA, Healy EW, Robinson JRM, Blinderman CD. Effects of medical cannabis certification on hospital use by individuals with sickle cell disease. Cannabis Cannabinoid Res. 2022;9(2):629–634. doi: 10.1089/can.2022.0136
69. Sama S, Tandon V, Kethireddy N, Boddu P. Effect of marijuana smoking among adult sickle cell patients on trends in sickle cell crisis hospitalizations and acute chest syndrome: a nationwide inpatient assessment. Blood. 2019;134(Supplement_1):4850–4850. doi: 10.1182/blood-2019-122179
70. Paulsingh CN, Mohamed MB, Elhaj MS, et al. The efficacy of marijuana use for pain relief in adults with sickle cell disease: a systematic review. Cureus. 2022. doi: 10.7759/cureus.24962
71. Lattanzi S, Brigo F, Trinka E, et al. Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis. Drugs. 2018;78 (17):1791–1804. doi: 10.1007/s40265-018-0992-5
72. Singh A, Madaan P, Bansal D. Update on Cannabidiol in Drug-Resistant Epilepsy. Indian J Pediatr. 2025;92(1):61–69. doi: 10.1007/s12098-024-05337-1
73. Almogi-Hazan O, Or R. Cannabis, the endocannabinoid system and immunity—the journey from the bedside to the bench and back. Int J Mol Sci MDPI AG. 2020;21(12):1–17. doi: 10.3390/ijms21124448
74. Dotsey E, Ushach I, Pone E, et al. Transient cannabinoid receptor 2 blockade during immunization heightens intensity and breadth of antigen-specific antibody responses in young and aged mice. Sci Rep. 2017;7(1). doi: 10.1038/srep42584
75. Sido JM, Nagarkatti PS, Nagarkatti M. Production of endocannabinoids by activated T cells and B cells modulates inflammation associated with delayed-type hypersensitivity. Eur J Immunol. 2016;46(6):1472–9.
76. Tanikawa T, Kurohane K, Imai Y. Induction of preferential chemotaxis of unstimulated B-lymphocytes by 2-arachidonoylglycerol in immunized mice. Microbiol Immunol. 2007;51(10):1013–1019. doi: 10.1111/j.1348-0421.2007.tb03985.x
77. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology. 2010;215(8):598–605. doi: 10.1016/j.imbio.2009.04.001
78. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J Clin Invest. 2017;127 (3):750–760. doi: 10.1172/JCI89741
79. Sahu T, Verma HK, Ganguly S, et al. But neglected: a comprehensive review of leg ulcers in sickle cell disease. Adv Skin Wound Care. 2021;34(8):423–431. doi: 10.1097/01.ASW.0000755924.12513.40
80. Maida V, Shi RB, Fazzari FGT, Zomparelli LM. A new treatment paradigm for sickle cell disease leg ulcers: topical cannabis-based medicines. Exp Dermatol. 2021 Feb;30(2):291–293.
81. Martins AM, Gomes AL, Boas IV, Marto J, Ribeiro HM. Cannabis-based products for the treatment of skin inflammatory diseases: a timely review. Pharmaceuticals MDPI. 2022;15(2):210. doi: 10.3390/ph15020210
82. Makhakhe L. Topical cannabidiol (CBD) in skin pathology - A comprehensive review and prospects for new therapeutic opportunities. S Afr Fam Pract. 2022 May 30;64(1):e1–e4.
83. Hill KP, Gold MS, Nemeroff CB, et al. Risks and benefits of cannabis and cannabinoids in psychiatry. Am J Psychiatry Am Psychiatric Assoc. 2022;179(2):98–109. doi: 10.1176/appi.ajp.2021.21030320
84. García-Gutiérrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J. Cannabidiol: a potential new alternative for the treatment of anxiety, depression, and psychotic disorders. Biomolecules. 2020;10(11):1575. doi: 10.3390/biom10111575
85. Silver J, Pavano C, Bellas N, et al. Cannabis use is associated with decreased opioid prescription fulfillment following single level anterior cervical discectomy and fusion (ACDF). N Am Spine Soc J. 2023 May 3;14:100226.
86. Silver J, Ford BT, Pavano CJ, et al. Cannabis use is associated with fewer filled opioid prescriptions after treatment of proximal humerus fractures. Orthopedics. 2024 May-Jun;47(3):147–151.
87. Castillo-Carniglia A, Rivera-Aguirre A, Santaella-Tenorio J, et al. Changes in opioid and benzodiazepine poisoning deaths after cannabis legalization in the US: a county-level analysis, 2002–2020. Epidemiology. 2023;34(4):467–475. doi: 10.1097/EDE.0000000000001609
88. Miodownik H, Curtis SA, Olivia Ogu U, et al. Frequent health care utilisation and avascular necrosis are associated with cannabis use in adults with sickle cell disease. Br J Haematol. 2022 Mar;196(5):e41–e44.
89. Abrams DI, Couey P, Dixit N, et al. Effect of inhaled cannabis for pain in adults with sickle cell disease. JAMA Netw Open. 2020;3(7):e2010874. doi: 10.1001/jamanetworkopen.2020.10874