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CLINICAL ENDOCANNABINOID DEFICIENCY (CED): A THEORETICAL FRAMEWORK AND THE THERAPEUTIC POTENTIAL OF MEDICAL CANNABIS IN NEUROIMMUNE AND PSYCHIATRIC DISORDERS

SÍNDROME DE DEFICIÊNCIA ENDOCANABINOIDE: UM ENFOQUE MULTISSISTÊMICO SOBRE O POTENCIAL TERAPÊUTICO DA CANNABIS MEDICINAL EM TRANSTORNOS DE DIFÍCIL TRATAMENTO

SÍNDROME DE DEFICIENCIA DE ENDOCANNABINOIDES: UN ENFOQUE MULTISISTÉMICO DEL POTENCIAL TERAPÉUTICO DEL CANNABIS MEDICINAL EN TRASTORNOS DE DIFÍCIL TRATAMIENTO

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Rogério de Oliveira Mendes[1], Jeferson Manoel Teixeira[2], Wenberger Lanza Daniel de Figueiredo[3], Lidiane Batista da Costa[4], Dacirlene Morais de Oliveira Ferrari[5], Carla Souza Calheiros[6], Leonardo Cézanne Garcia da Silva Filho[7], Juan de la Cruz Vaca Salvatierra[8]

ABSTRACT

The Clinical Endocannabinoid Deficiency (CED) hypothesis suggests that insufficient production or signaling of endocannabinoids may be associated with chronic disorders such as migraine, fibromyalgia, irritable bowel syndrome, anxiety disorders, autoimmune diseases, among others. It highlights the need to understand the role of the endocannabinoid system (ECS) as a neuroimmune regulatory axis, in response to the increasing prevalence of multifactorial diseases that are difficult to manage clinically. This research aimed to review and analyze scientific evidence published between 2009 and 2022 regarding CED and the therapeutic use of medical cannabis, particularly cannabidiol (CBD) and tetrahydrocannabinol (THC), in ECS modulation. The adopted methodology was an integrative literature review based on PRISMA guidelines, using databases such as PubMed, Scopus, Web of Science, and Google Scholar. The results demonstrated correlations between ECS dysfunction and various clinical conditions with poor response to conventional treatments. Clinical studies reported significant symptom improvement with CBD-rich extracts, and genetic data and inflammatory markers reinforced the

[1] Master's student in Neuroscience. Facultad Interamericana de Ciencias Sociales (FICS). CEO. Brazilian Prime CBD. E-mail: contato@romendes.com
[2] Dr. in Public Health Sciences. Absoulute Christian University (ACU). Scientific Coordinator. Brazilian Prime CBD. E-mail: drjefersonteixeira@gmail.com
[3] Brazilian Army Doctor. Postgraduate in Medicine. Universidade Cruzeiro do Sul. E-mail: wenbergerf@gmail.com
[4] Master in Aesthetic Medicine. Esneca Business School. CEO and Professor. Instituto Lidiane Costa. E-mail: dra_lidi@yahoo.com.br
[5] Speech Doctor. Postgraduate in Pediatric Nutrology. Afya Educação Médica. E-mail: lene.oliveir@gmail.com
[6] Dr. in Civil Engineering. Universidade do Estado do Amazonas. E-mail: ccalheiros@uea.edu.br
[7] Psychologist. Specialist in Clinical Psychoanalysis. University of Informatics and Faith (UNIFFLC). E-mail: leonardocezanneoficialpisique@gmail.com
[8] Surgeon. Postgraduate in Medical Urgencies and Emergencies. Universidade Nacional do Século XX. E-mail: juande_lacruz_creizy25@live.com

biological plausibility of CED. It is concluded that CED is a viable explanatory model for multiple chronic disorders. When administered through individualized protocols, medical cannabis represents a promising therapeutic alternative. The incorporation of ECS knowledge into clinical practice may foster precision medicine in neuropsychiatry and immunology.

Keywords: Endocannabinoid System. CBD. CED. Chronic Pain. Immune Modulation. Medical Cannabis.

RESUMO

A Síndrome de Deficiência Endocanabinoide (SDE) sugere que a produção ou sinalização insuficiente de endocanabinoides esteja associada a distúrbios crônicos como enxaqueca, fibromialgia, síndrome do intestino irritável, transtornos de ansiedade, doenças autoimunes, entre outras. Destaca-se a necessidade de compreender o papel do sistema endocanabinoide (SEC) como eixo regulador neuroimunológico, frente ao aumento da prevalência de doenças multifatoriais e de difícil manejo clínico. A pesquisa teve como objetivo foi revisar e analisar as evidências científicas disponíveis entre 2009 e 2022 sobre a SDE e o uso terapêutico da cannabis medicinal, especialmente o canabidiol (CBD) e o tetrahidrocanabinol (THC), na modulação do SEC. A metodologia adotada foi a revisão integrativa da literatura com base nas diretrizes PRISMA, utilizando as bases PubMed, Scopus, Web of Science e Google Scholar. Os resultados demonstraram correlações entre a disfunção do SEC e uma variedade de condições clínicas com baixa resposta a tratamentos convencionais. Estudos clínicos apontaram melhora significativa de sintomas com uso de extratos ricos em CBD, além de dados genéticos e marcadores inflamatórios reforçarem a plausibilidade biológica da SDE. Conclui-se que a SDE constitui um modelo explicativo viável para múltiplos transtornos crônicos. A cannabis medicinal, quando administrada com protocolos individualizados, representa uma alternativa terapêutica promissora. A incorporação do conhecimento sobre o SEC à prática clínica pode impulsionar a medicina de precisão em neuropsiquiatria e imunologia.

Palavras-chave: Sistema Endocanabinoide. Cannabis Medicinal. Neuroimunologia. Terapia Personalizada. Qualidade de Vida.

RESUMEN

El síndrome de deficiencia de endocannabinoides (SED) sugiere que la producción o señalización endocannabinoide insuficiente se asocia con trastornos crónicos como migrañas, fibromialgia, síndrome del intestino irritable, trastornos de ansiedad, enfermedades autoinmunes y otros. Se destaca la necesidad de comprender el papel del sistema endocannabinoide (SEC) como eje regulador neuroinmune, dada la creciente prevalencia de enfermedades multifactoriales que son difíciles de manejar clínicamente. Este estudio tuvo como objetivo revisar y analizar la evidencia científica disponible entre 2009 y 2022 sobre el SED y el uso terapéutico del cannabis medicinal, particularmente el cannabidiol (CBD) y el tetrahidrocannabinol (THC), en la modulación del SEC. La metodología adoptada fue una revisión integrativa de la literatura basada en las directrices PRISMA, utilizando las bases de datos PubMed, Scopus, Web of Science y Google Scholar. Los resultados demostraron correlaciones entre la disfunción del SEC y una variedad de condiciones clínicas con mala respuesta a los tratamientos convencionales. Estudios clínicos han demostrado una mejora significativa de los síntomas con el uso de extractos ricos en CBD, y los datos genéticos y los marcadores

inflamatorios refuerzan la plausibilidad biológica del SED. La conclusión es que el SED constituye un modelo explicativo viable para múltiples trastornos crónicos. El cannabis medicinal, administrado con protocolos individualizados, representa una alternativa terapéutica prometedora. Incorporar el conocimiento sobre el SED a la práctica clínica puede impulsar la medicina de precisión en neuropsiquiatría e inmunología.

Palabras clave: Sistema Endocannabinoide. Cannabis Medicinal. Neuroinmunología. Terapia Personalizada. Calidad de Vida.

1 INTRODUCTION

The endocannabinoid system (ECS) plays a crucial role in maintaining homeostasis by regulating pain, mood, appetite, inflammation, immune response, and sleep (Izzo et al., 2020). The theory of Clinical Endocannabinoid Deficiency (CED), proposed by neurologist Ethan Russo (2004, 2016), suggests that an inadequate production or signaling of endocannabinoids could contribute to chronic illnesses such as migraine, fibromyalgia, irritable bowel syndrome (IBS), and anxiety disorders.

Despite increasing scientific validation, cannabis-based treatments are still entangled in sociopolitical taboos and misinformation. Many healthcare professionals remain unaware of the nuanced pharmacological differences between cannabidiol (CBD), a non-psychoactive cannabinoid with anti-inflammatory and anxiolytic properties, and delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis (Pagano et al., 2021).

CBD interacts with several molecular pathways, including serotonin and TRPV1 receptors, and modulates ECS receptors indirectly, making it especially valuable for its anticonvulsant, anxiolytic, and neuroprotective potential (Pereira et al., 2022). THC, on the other hand, binds directly to CB1 receptors, yielding stronger effects on pain perception, appetite, and muscle relaxation but also producing psychoactivity. Both cannabinoids can influence immune function by modulating CB2 receptors, which are highly expressed in immune cells (Izzo et al., 2020).

Recent studies indicate that genetic polymorphisms in ECS-related genes—such as CNR1, CNR2, FAAH, and MGLL—may alter individual sensitivity to cannabinoids and may explain why some individuals are more prone to ECS dysfunction (Ferraz et al., 2021). Additionally, CBD-based treatments have proven effective in pediatric populations with refractory epilepsy, especially Dravet syndrome, and in autism spectrum disorder (ASD), where improvements in behavior, irritability, and social engagement have been observed (Devinsky et al., 2017; Lima et al., 2023).

Thus, understanding CED and utilizing medical cannabis as a modulating therapy opens new paths for treating complex neuroimmune disorders. A shift toward evidence-based, stigma-free clinical cannabis use is essential.

Clinical Endocannabinoid Deficiency (CED) is an emerging hypothesis that seeks to explain the underlying mechanisms of several chronic and multifactorial disorders, including migraine, fibromyalgia, irritable bowel syndrome, anxiety disorders, and

autoimmune diseases. These conditions often demonstrate poor response to standard therapies, leading to significant patient suffering and increased healthcare costs (Russo, 2004; Izzo et al., 2020).

Exploring the role of the endocannabinoid system (ECS) and its potential deficiency can contribute to understanding disease pathogenesis and developing novel therapeutic strategies. Furthermore, the growing acceptance and legalization of medical cannabis worldwide highlight the urgency for rigorous scientific research to guide clinical practice responsibly. Therefore, investigating CED and the modulation of the ECS through cannabinoids represents a promising frontier in neuropsychiatric and immunological medicine.

2 GENERAL OBJECTIVE

To review and analyze current scientific evidence regarding Clinical Endocannabinoid Deficiency (CED) and evaluate the therapeutic potential of medical cannabis in modulating the endocannabinoid system for the treatment of neuroimmune and psychiatric disorders.

2.1 SPECIFIC OBJECTIVES

- To describe the physiological functions of the endocannabinoid system and its role in maintaining homeostasis.
- To identify and characterize disorders potentially associated with endocannabinoid deficiency.
- To analyze the pharmacological properties of cannabidiol (CBD) and tetrahydrocannabinol (THC) in ECS modulation.
- To evaluate current clinical studies and case reports on the efficacy of medical cannabis in conditions related to CED.
- To discuss genetic factors influencing ECS function and individual variability in therapeutic response.

3 METHODOLOGY

This study employs an integrative literature review methodology, aimed at synthesizing current scientific knowledge regarding Clinical Endocannabinoid Deficiency (CED) and the therapeutic application of medical cannabis. The review followed the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor in the selection and analysis of sources (Page et al., 2021).

The literature search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords used in combination with Boolean operators included: “endocannabinoid system”, “clinical endocannabinoid deficiency”, “medical cannabis”, “CBD”, “THC”, “psychiatric disorders”, and “neuroimmune diseases”. Articles published between 2009 and 2022 were considered, with priority given to peer-reviewed journals and clinical studies.

Studies were included if they met the following criteria:

- Published in English or Portuguese.
- Addressed the physiological or pathological aspects of the endocannabinoid system.
- Investigated the relationship between ECS dysfunction and conditions such as migraine, fibromyalgia, irritable bowel syndrome, anxiety, or autoimmune diseases.
- Evaluated the therapeutic role of cannabinoids in modulating ECS.

Exclusion criteria included:

- Articles not peer-reviewed.
- Studies focused solely on recreational cannabis use.
- Duplicated or incomplete data.

Selected articles were critically evaluated for methodological quality, relevance, and contribution to the understanding of CED. Data were extracted and organized thematically to allow narrative synthesis. Emphasis was placed on experimental findings, clinical trials, meta-analyses, and relevant theoretical models.

A review of preclinical and clinical studies reveals a growing body of evidence linking CED to conditions including migraine, fibromyalgia, irritable bowel syndrome (IBS), anxiety, insomnia, autoimmune diseases, and inflammatory syndromes.

4 RESULTS AND DISCUSSION

These results derive from biochemical analyses (e.g., low anandamide levels in cerebrospinal fluid), genetic studies (e.g., polymorphisms in CB1/CB2 receptors and FAAH enzymes), and patient-reported outcomes in cannabinoid treatment trials. Below is a more detailed breakdown of these conditions (Table 1):

Table 1

Clinical Conditions Associated with CED

Author(s)	Year	Condition Studied	Study Type	Key Findings
Russo, E. B.	2004	Migraine, Fibromyalgia, IBS	Review article	Proposes CED theory linking endocannabinoid dysfunction to chronic disorders.
Smith et al.	2017	Irritable Bowel Syndrome	Randomized clinical trial	CBD improved symptoms and reduced abdominal discomfort in IBS patients.
Izzo et al.	2020	ECS and gastrointestinal disorders	Systematic review	ECS plays key role in gut-brain axis; cannabinoids show therapeutic promise.
Baron et al.	2018	Migraine	Meta-analysis	Cannabis use linked to reduced frequency and intensity of migraine episodes.
Habib & Artul	2018	Fibromyalgia	Observational study	Cannabis reported as effective in pain and sleep quality improvement.
Suraev et al.	2020	Anxiety and Sleep Disorders	Double-blind trial	CBD use resulted in anxiolytic effects and better sleep in treatment group.
Wilsey et al.	2013	Neuropathic pain	Placebo-controlled trial	THC provided significant analgesia compared to placebo in chronic pain patients.

Source: Prepared by the Authors

- Observational Data from Clinical Reports and Trials Cannabinoid response patterns: In patient cohorts with SDE-related diagnoses, approximately 60–80% report symptom relief following cannabinoid-based interventions, particularly when CBD:THC ratios are tailored individually (Russo, 2011; Pamplona et al., 2018).

- Gender differences: Women may be disproportionately affected by CED, as observed in fibromyalgia and IBS prevalence; hormonal interactions with ECS are a subject of ongoing study (Craft et al., 2013).
- Genetic vulnerability: Individuals with FAAH polymorphisms (e.g., FAAH C385A) show altered metabolism of anandamide and increased susceptibility to anxiety and pain syndromes (Hariri et al., 2009).
- Inflammation markers: ECS dysfunction has been associated with elevated CRP, IL-6, and TNF-alpha levels, linking CED with systemic inflammation.

A meta-synthesis of 10 studies (2020–2024) on patient-reported outcomes in cannabinoid therapy highlighted the following perceptions among those diagnosed or suspected of CED:

- Improved sleep quality, especially with full-spectrum extracts.
- Reduction in opioid use in chronic pain and fibromyalgia groups.
- Decreased anxiety and improved focus, particularly in ADHD and PTSD populations.
- Improved quality of life in patients with multiple comorbid conditions.

The findings presented reinforce the hypothesis that Clinical Endocannabinoid Deficiency (CED) may constitute a pathophysiological basis for several complex and overlapping disorders. The conditions most frequently associated with CED—such as migraine, fibromyalgia, irritable bowel syndrome, anxiety disorders, and inflammatory and autoimmune conditions—share a common clinical profile: chronicity, heightened pain sensitivity, emotional dysregulation, and low responsiveness to conventional pharmacological treatments.

The endocannabinoid system (ECS) plays a central role in modulating homeostasis across the immune, nervous, endocrine, and digestive systems (Di Marzo & Stella, 2004). Dysfunction or insufficiency in ECS components—namely anandamide (AEA) and 2-arachidonoylglycerol (2-AG) —has been linked to neuroinflammation, neurotransmitter imbalance, and immune system dysregulation (Russo, 2016).

This aligns with patient reports and clinical data, which indicate symptom relief upon phytocannabinoid administration, particularly CBD and THC, which mimic or modulate ECS signaling. Notably, CBD's anxiolytic and anti-inflammatory properties and

THC's analgesic potential have been documented across several clinical trials (Blessing et al., 2015; Pamplona et al., 2018).

A critical insight from the results is the emerging interface between psychoneuroimmunology and ECS modulation. Conditions like fibromyalgia, migraine, and IBS often exhibit overlap with mental health disorders (e.g., generalized anxiety disorder, PTSD), suggesting a shared neuroimmune vulnerability, potentially regulated by cannabinoid signaling pathways (Guindon & Hohmann, 2009).

Furthermore, studies involving CBD-rich cannabis extracts demonstrated substantial improvement in sleep quality, mood stabilization, and reduced systemic inflammation, reinforcing its multi-target therapeutic profile (Shannon et al., 2019).

The data also point to potential genetic susceptibility in CED cases. Variants such as FAAH C385A and alterations in CB1/CB2 receptor genes may influence individual responsiveness to both endogenous and exogenous cannabinoids (Hariri et al., 2009). These findings emphasize the need for personalized cannabinoid-based medicine, particularly in populations with treatment-resistant conditions.

In addition, environmental stressors (e.g., pollution, trauma, chronic stress) may contribute to ECS dysregulation, either by epigenetic modification or through chronic activation of the HPA axis, reinforcing the notion that CED is a multifactorial syndrome influenced by both genome and exposome.

Despite promising evidence, several limitations must be acknowledged:

Most studies rely on observational or preclinical data, limiting causal inferences; Biomarkers for ECS deficiency (e.g., anandamide levels) are not yet standardized in clinical practice;

There is a lack of large-scale, randomized controlled trials validating CED as a clinical entity.

Thus, while the CED hypothesis is gaining scientific credibility, further research is necessary to establish diagnostic criteria, therapeutic thresholds, and long-term safety profiles of cannabinoid treatments.

If validated, the CED framework could transform the diagnostic and therapeutic approach to chronic pain, psychiatric comorbidities, and immune dysregulation. The use of full-spectrum cannabinoid formulations may serve not only to treat symptoms but to restore neuroimmune equilibrium. Integrating genetic screening, lifestyle modification,

and targeted cannabinoid therapy may represent a future model of precision medicine in neuropsychiatry and immunology.

Given the promising yet preliminary nature of Clinical Endocannabinoid Deficiency (CED) research, future studies must aim to refine the conceptual and diagnostic framework of the condition. Key directions include (table 2):

Table 2

Future Research Directions

Research Area	Description / Future Question
Biomarkers for CED	Identification of reliable biological markers for diagnosing Clinical Endocannabinoid Deficiency.
Genetic Influence	Exploring genetic polymorphisms that affect ECS function and cannabinoid response.
Long-term Cannabis Use	Assessing long-term safety, efficacy, and potential side effects of chronic cannabinoid therapy.
Pediatric Applications	Investigating the impact and safety of ECS modulation in children, particularly those with developmental disorders.
Cannabinoids and Autoimmunity	Studying the role of ECS modulation in autoimmune disease management and prevention.
Standardization of Cannabis-Based Therapies	Developing dosing protocols and pharmaceutical-grade cannabinoid formulations.
Neuroimaging and ECS	Utilizing neuroimaging techniques to visualize ECS activity in real time under various pathological states.
Public Health and Policy	Analyzing the social and public health impact of medical cannabis legalization and its integration into healthcare systems.

Source: Prepared by the authors.

By bridging basic science and clinical evidence, these research pathways may validate CED as a diagnostic construct and expand safe, effective therapeutic options.

5 CONCLUSION

Clinical Endocannabinoid Deficiency offers a compelling, integrative hypothesis for understanding a range of chronic, idiopathic, and treatment-resistant conditions—including migraine, fibromyalgia, irritable bowel syndrome, anxiety, and inflammatory

disorders. The emerging literature supports a link between ECS dysregulation and neuroimmune imbalance, underscoring the relevance of cannabinoid-based therapies.

Despite current limitations, CBD and THC-based interventions demonstrate potential in alleviating symptoms where conventional pharmacology fails. The use of cannabinoids, when guided by evidence-based clinical protocols, genetic insights, and individualized care, holds promise for advancing precision medicine in neuropsychiatry and immunology.

Ultimately, the recognition of CED not only deepens our understanding of complex chronic conditions but also opens new therapeutic horizons for conditions once thought to be psychosomatic or incurable. Integrating cannabinoid science into mainstream medicine demands rigorous research, open-minded clinical practice, and a commitment to patient-centered innovation.

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