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EFFECTS OF CANNABIS IN PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

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Abstract: INTRODUCTION Cannabis has gained attention as a potential therapeutic agent for Parkinson's disease and other movement disorders. Research highlights its role in managing motor symptoms such as tremor, rigidity, and bradykinesia, as well as non-motor symptoms like anxiety and sleep disturbances. The pharmacological properties of cannabinoids, including THC and CBD, suggest broad applicability due to their interaction with the endocannabinoid system. However, variability in patient responses and study methodologies has limited consensus on optimal therapeutic approaches. **OBJETIVE** To evaluate the efficacy, safety, and therapeutic potential of cannabis in the management of Parkinson's disease and other movement disorders, focusing on its impact on motor and non-motor symptoms and its potential neuroprotective effects. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Cannabinoids in Neurological Disorders" AND "Parkinson's Disease Therapy" OR "Movement Disorders Management" OR "Cannabis and Neuroprotection" OR "Non--Motor Symptom Treatment" in the last 5 years. **RESULTS AND DISCUSSION** Clinical and preclinical studies indicate that cannabis can mitigate levodopa-induced dyskinesias and improve overall quality of life in patients. Neuroprotective properties, such as reducing oxidative stress and neuroinflammation, have been demonstrated, suggesting potential benefits in slowing disease progression. Despite promising findings, safety concerns, including psychoactive side effects and dosing inconsistencies, underscore the need for further research. **CONCLUSION** Cannabis offers a novel approach to addressing unmet needs in movement disorder management. By integrating cannabinoids into comprehensive care models and addressing current regulatory and research challenges, cannabis-based therapies could significantly enhance treatment outcomes for these complex neurological conditions.

Keywords: Cannabis; Parkinson's Disease; Cannabinoids; Movement Disorders; Neuroprotection

INTRODUCTION

Cannabis has been employed for therapeutic purposes since antiquity, with its use documented in treating various conditions, including those affecting the nervous system[1]. Early accounts from civilizations such as Ancient China and India highlighted its role in alleviating pain and muscle spasms, underscoring the medicinal potential of cannabinoids[1]. The renewed scientific interest in cannabis-based therapies over the past few decades has paralleled advancements in our understanding of the endocannabinoid system, which governs several neurological processes[1]. Movement disorders are a heterogeneous group of conditions characterized by dysregulated motor activity resulting from abnormalities in the central nervous system[2]. This group includes Parkinson's disease (PD), dystonia, essential tremor, and Huntington's disease, each with distinct pathophysiological mechanisms but overlapping clinical manifestations[2]. These disorders impose significant functional limitations on affected individuals, often leading to reduced quality of life and heightened dependency[2].

Parkinson's disease, the second most common neurodegenerative disorder, affects approximately 1% of individuals over the age of 60 globally[3]. It is clinically defined by motor symptoms, including bradykinesia, rigidity, and resting tremor, often accompanied by a plethora of non-motor manifestations such as cognitive decline and sleep disturbances[3]. Despite the effectiveness of dopamine replacement therapies like levodopa, long-term use is

frequently associated with complications such as motor fluctuations and dyskinesias[3]. Other movement disorders present unique clinical challenges, with essential tremor being the most prevalent among them, affecting up to 4% of individuals aged 40 and above[4]. Dystonia, characterized by sustained muscle contractions leading to abnormal postures, and Huntington's disease, a hereditary condition with progressive neurodegeneration, also contribute significantly to the global burden of neurological diseases[4]. These conditions necessitate innovative therapeutic strategies beyond current pharmacological interventions[4].

The endocannabinoid system, integral to maintaining neurological homeostasis, comprises cannabinoid receptors (CB1 and CB2), endogenous ligands, and enzymes responsible for their metabolism[5]. CB1 receptors are predominantly expressed in the central nervous system, particularly in regions such as the basal ganglia, which are heavily implicated in motor control[5]. CB2 receptors, while primarily associated with immune modulation, have been identified in the brain, where they may play a role in neuroinflammation[5]. Phytocannabinoids, particularly Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), interact with the endocannabinoid system through distinct mechanisms[6]. THC acts as a partial agonist at CB1 receptors, influencing neurotransmitter release and motor control[6]. In contrast, CBD exhibits anti-inflammatory and neuroprotective properties, often mediated through non-cannabinoid receptor pathways, making it a promising candidate for managing neurological disorders[6].

Preclinical studies have consistently demonstrated the neuroprotective potential of cannabinoids in models of PD and other movement disorders[7]. These findings include the reduction of oxidative stress, attenuation of neuroinflammation, and mitigation of neuronal loss[7]. Such mechanisms may underpin the therapeutic effects observed in experimental settings, providing a rationale for clinical investigations[7]. Cannabinoids also exhibit significant anti-inflammatory effects, crucial in neurodegenerative disorders where chronic inflammation exacerbates neuronal damage[8]. By modulating glial cell activity and reducing the release of pro-inflammatory cytokines, cannabinoids may help to preserve neuronal integrity and function[8]. This anti-inflammatory property may hold particular relevance in the context of PD and Huntington's disease, where neuroinflammation is a key pathological feature[8].

The role of cannabinoids in promoting neuroplasticity has also garnered attention, as they may enhance the brain's ability to compensate for neuronal loss[9]. This process involves modulating synaptic transmission and fostering the release of neurotrophic factors, contributing to functional recovery in movement disorders[9]. These effects have been observed in both in vitro studies and animal models, suggesting potential translational applications[9]. Despite these promising findings, the clinical use of cannabis for neurological conditions faces significant regulatory and logistical challenges[10]. The legal status of cannabis varies widely across jurisdictions, complicating the standardization of formulations and dosages[10]. Additionally, the stigma associated with cannabis use and the lack of comprehensive clinical trials hinder its acceptance in mainstream medical practice[10].

Patient demand for cannabis-based therapies has grown, driven by anecdotal reports of symptom relief in movement disorders[11]. These reports often highlight improvements in both motor and non-motor symptoms, including tremors, rigidity, anxiety, and sleep quality[11]. However, such subjective findings underscore the need for robust clinical evidence to guide therapeutic decisions[11]. The interaction between cannabinoids and dopaminergic pathways adds another layer of complexity to their therapeutic potential[12]. Can-

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nabinoids modulate dopamine release and reuptake, influencing motor and cognitive functions[12]. Understanding these interactions is critical for optimizing cannabis use in managing movement disorders, particularly in combination with existing pharmacological treatments[12].

Lastly, the integration of cannabis into treatment paradigms for movement disorders demands a multidisciplinary approach, involving neurologists, pharmacologists, and regulatory bodies[13]. Addressing the gaps in knowledge through rigorous clinical trials and mechanistic studies will be essential to realizing the full potential of cannabinoids in these complex conditions[13]. Such efforts could pave the way for personalized therapeutic strategies that harness the benefits of cannabis while minimizing its risks[13].

OBJETIVES

To evaluate the efficacy, safety, and therapeutic potential of cannabis in the management of Parkinson's disease and other movement disorders, focusing on its impact on motor and non-motor symptoms and its potential neuroprotective effects.

SECUNDARY OBJETIVES

1. To analyze clinical trial data on the use of cannabinoids in Parkinson's disease.
2. To assess the role of cannabis in mitigating motor complications such as levodopa-induced dyskinesias.
3. To explore the efficacy of cannabinoids in treating non-motor symptoms such as anxiety and sleep disturbances.
4. To examine the neuroprotective properties of cannabinoids in preclinical and clinical contexts.
5. To evaluate the safety profile of cannabis-based therapies in patients with neurological disorders.

METHODS

This is a narrative review, in which the main aspects of cannabis in the management of Parkinson's disease and other movement disorders, focusing on its impact on motor and non-motor symptoms and its potential neuroprotective effects in recent years were analyzed. The beginning of the study was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Cannabinoids in Neurological Disorders" AND "Parkinson's Disease Therapy" OR "Movement Disorders Management" OR "Cannabis and Neuroprotection" OR "Non-Motor Symptom Treatment" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case--control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

RESULTS AND DISCUSSION

The efficacy of cannabis in the management of Parkinson's disease (PD) has been extensively evaluated, with varying outcomes depending on the study design, patient characteristics, and cannabinoid formulations used[13]. Clinical trials have demonstrated a range of benefits, including reductions in tremor, rigidity, and bradykinesia, although inconsistencies in study methodologies complicate direct comparisons[13]. For example, a randomized controlled trial assessing cannabidiol (CBD) in PD patients highlighted significant improvements in motor symptom scores, particu-

larly in those with levodopa-induced dyskinesias[13]. However, other studies have reported negligible differences between cannabinoid treatments and placebo, underscoring the need for more standardized protocols[14].

One of the most promising areas of research involves the use of cannabis to mitigate motor complications arising from dopaminergic therapies[14]. Levodopa-induced dyskinesias (LID), which are among the most challenging complications in advanced PD, have shown responsiveness to cannabinoid treatment[14]. In a double-blind study, patients treated with a THC/CBD combination reported reduced dyskinesia severity scores, with minimal adverse effects[14]. This reduction is believed to result from the modulation of striatal excitability, an effect mediated by CB1 receptor activation[15]. However, variability in individual responses to cannabinoids highlights the complexity of their pharmacodynamics and the need for tailored treatment approaches[15]. Cannabis's role in treating non-motor symptoms such as anxiety, depression, and sleep disturbances is also of significant interest[15]. Non-motor symptoms often severely impact the quality of life in PD patients and are frequently inadequately managed with conventional therapies[15]. Cannabidiol, known for its anxiolytic and sedative properties, has demonstrated potential in reducing anxiety scores and improving sleep patterns in patients with movement disorders[16]. Notably, open-label studies have reported enhanced sleep efficiency and reduced nighttime awakenings among PD patients using CBD oil, though larger trials are needed to confirm these findings[16].

The neuroprotective properties of cannabinoids are another area of exploration, particularly their potential to slow disease progression in PD[16]. Preclinical studies have consistently shown that cannabinoids reduce oxidative stress and neuroinflammation, two key contributors to dopaminergic neuron loss[16]. In rodent models of PD, treatment with CBD significantly preserved motor function and dopaminergic cell viability, suggesting a role for cannabinoids in modifying disease pathology[17]. However, translating these findings into clinical practice requires long-term studies assessing the impact of cannabinoids on neurodegeneration in human patients[17]. Essential tremor, another prevalent movement disorder, has also been investigated as a potential target for cannabinoid therapies[17]. Patients with essential tremor have reported reductions in tremor amplitude and improved motor steadiness following cannabis use, though these findings are largely anecdotal or derived from small observational studies[17]. A recent pilot trial evaluating the effects of oral cannabis extracts on essential tremor demonstrated promising results, with participants experiencing significant reductions in symptom severity[18]. The mechanisms underlying these effects likely involve CB1 receptor-mediated modulation of cerebellar activity, although further research is needed to elucidate this relationship[18].

Cannabis-based treatments for dystonia have shown mixed results, with some studies reporting significant symptom relief and others showing limited efficacy[18]. Dystonia, characterized by abnormal muscle contractions and postures, is thought to benefit from the muscle relaxant properties of cannabinoids[18]. A small randomized trial involving patients with focal dystonia demonstrated improvements in spasm frequency and intensity following THC treatment, though adverse effects such as sedation and dizziness were noted in a subset of participants[19]. These findings underscore the importance of balancing efficacy with tolerability in cannabinoid therapies[19]. Huntington's disease, a neurodegenerative disorder with a strong inflammatory component, has emerged as a potential indication for cannabinoid use[19]. Clinical trials assessing THC/CBD formulations in Huntington's patients have reported modest impro-

vements in motor symptoms such as chorea, as well as enhancements in cognitive and psychiatric domains[19]. These effects are believed to stem from the anti-inflammatory and neuroprotective actions of cannabinoids, which may mitigate neuronal damage and promote synaptic stability[20]. However, the small sample sizes and short durations of these studies limit the generalizability of their findings[20].

The impact of cannabinoids on neurotransmitter systems is multifaceted, extending beyond dopaminergic modulation to include effects on serotonin, glutamate, and GABA pathways[20]. These interactions contribute to the broad spectrum of cannabis's therapeutic potential in movement disorders, addressing both motor and non-motor symptoms[20]. For instance, the inhibition of glutamate release by CB1 receptor activation may reduce excitotoxicity in the basal ganglia, a mechanism implicated in both PD and Huntington's disease[21]. Similarly, the enhancement of serotonergic signaling by CBD may underlie its anxiolytic and antidepressant effects, which are critical for improving overall patient well-being[21]. Safety and tolerability remain significant considerations in the clinical use of cannabis for neurological conditions[21]. While adverse effects such as sedation, dizziness, and cognitive impairment are commonly reported with THC-rich formulations, CBD-dominant therapies exhibit a more favorable safety profile[21]. Importantly, the risk of developing tolerance or dependency appears to be lower with cannabinoids compared to traditional pharmacological agents, though this aspect warrants further study[22]. Establishing standardized dosing regimens and monitoring protocols will be essential for optimizing the risk-benefit ratio of cannabis-based treatments[22].

Real-world evidence from observational studies has provided valuable insights into patient-reported outcomes with cannabis use[22]. Many patients describe significant improvements in quality of life, with reductions in symptom burden and enhanced functional capacity[22]. However, the reliance on subjective measures in these studies highlights the need for more objective, clinically validated endpoints to guide therapeutic decision-making[23]. Additionally, disparities in access to cannabis-based therapies across regions underscore the importance of addressing regulatory and logistical barriers[23].

CONCLUSION

The therapeutic potential of cannabis in Parkinson's disease and other movement disorders represents a promising frontier in neurology. Emerging evidence from both preclinical and clinical studies highlights its ability to address motor and non-motor symptoms, mitigate complications such as levodopa-induced dyskinesias, and possibly offer neuroprotective benefits. Despite these advancements, the heterogeneity in study methodologies, patient populations, and cannabinoid formulations necessitates further standardization and rigorous clinical trials to establish its efficacy and safety. Cannabinoids such as THC and CBD have demonstrated distinct pharmacological profiles, each contributing uniquely to symptom management. While THC's interaction with CB1 receptors offers relief for motor symptoms, CBD's anxiolytic and anti-inflammatory properties hold promise for addressing non-motor symptoms and improving overall quality of life. The challenge remains to identify optimal formulations and dosing strategies that maximize therapeutic benefits while minimizing psychoactive effects and other adverse outcomes.

One of the most compelling aspects of cannabis therapy is its potential to modify disease progression through neuroprotective mechanisms. By reducing oxidative stress and neuroinflammation, cannabinoids may slow neuronal degeneration, particularly in Parkinson's disease and Huntington's disease.

However, translating these preclinical findings into clinical practice requires longitudinal studies with robust methodologies to confirm these effects in human populations. The integration of cannabis into treatment regimens for movement disorders must be approached with caution. Regulatory, ethical, and logistical challenges continue to impede widespread adoption, and the lack of standardized products complicates clinical decision-making. Moreover, patient education and monitoring are critical to ensure safe and effective use, particularly given the variability in individual responses to cannabinoids.

As interest in cannabis-based therapies grows, it is imperative to address disparities in access and conduct large-scale clinical trials to refine treatment protocols. Collaborative efforts between clinicians, researchers, and policymakers will be essential in overcoming existing barriers and establishing cannabis as a viable option in the management of movement disorders. In summary, cannabis offers a novel and multifaceted approach to treating Parkinson's disease and other movement disorders, addressing unmet needs in both symptom management and disease modification. While challenges remain, the growing body of evidence underscores its potential to enhance patient outcomes and transform the landscape of neurological therapeutics.

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