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Review Article

Chronic *Cannabis indica* exposure and neurodegenerative vulnerability: a review of observational evidence

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ABSTRACT

Neurodegenerative diseases are marked by the gradual loss of neurons due to factors such as protein toxicity, oxidative stress, and inflammation, resulting in declining cognitive and motor abilities. Alzheimer's disease (AD), Parkinson's disease (PD), and related dementias contribute significantly to global morbidity and mortality. Identifying modifiable risk factors is essential. This retrospective review synthesises available clinical and observational evidence exploring the association between chronic *Cannabis indica* exposure and neurodegenerative outcomes. A retrospective review of published observational studies and clinical records was conducted. Data sources included neurology and psychiatry case records and peer-reviewed literature reporting chronic *Cannabis indica* use and neurodegenerative outcomes. Primary outcomes were cognitive impairment, dementia syndromes, Parkinsonian features, and neuroimaging evidence of neurodegeneration. Chronic cannabis use was consistently associated with structural and functional brain alterations, particularly in CB1-rich regions such as the medial temporal cortex, orbitofrontal cortex, insula, and hippocampus. Neuroimaging studies reported reduced gray matter volume and altered white matter integrity, with functional connectivity changes. Evidence also suggests chronic exposure disrupts glutamatergic and GABAergic signaling and contributes to cognitive deficits in learning, executive function, memory, and attention. In dementia and Parkinson's cohorts, cannabis abuse was linked with increased emergency visits and higher pain burden. Observational evidence indicates a potential neurodegenerative vulnerability associated with chronic *Cannabis indica* use. Prospective longitudinal studies with standardized exposure metrics are required to clarify causality and inform public health policy.

Keywords: *Cannabis indica*, Neurodegenerative disorders, Chronic exposure, Cognitive decline, Retrospective review

INTRODUCTION

Neurodegenerative disorders involve the progressive loss of specific nerve cells, driven by factors like protein toxicity, oxidative damage, and inflammation, which result in the malfunction of neurons.[1] These disorders are an increasing global health issue, marked by ongoing neuronal loss, declining cognitive abilities, and motor problems. They encompass a range of neuropsychiatric diseases, including AD, multiple sclerosis (MS), PD, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and other neurological conditions.[2] Alzheimer's, Parkinson's, and related dementias make up a significant portion of illness and death globally. Therefore, identifying risk factors that can be modified is crucial for public health and clinical care.

Cannabis is one of the most widely used psychoactive substances globally. Delta-9 tetrahydrocannabinol (Δ9-THC) is the primary psychoactive constituent of cannabis, which is used annually by approximately 147 million individuals worldwide (2.5% prevalence).[3] Cannabinoids interact with the endocannabinoid system-implicated in neuroprotection, synaptic plasticity, and neuroinflammation and prolonged exposure to cannabis may disrupt neuronal homeostasis, especially in

susceptible individuals. Chronic recreational use of *Cannabis indica* is associated with different harmful effects on central nervous system and peripheral system including hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal/tendencies, psychotic symptoms and mood disorders and neurocognitive impairment.[4]

GLOBAL TRENDS AND BURDEN OF NEURODEGENERATIVE DISORDERS

Neurodegenerative diseases like Alzheimer's and Parkinson's are rising globally due to aging populations and potential long-term COVID-19 effects. The updated GBD 2021 data show significant increases in neurological burden, highlighting major medical, social, and economic challenges.[5] In 2021, 57 million people globally had dementia, with over 60% in low- and middle-income countries. Nearly 10 million new cases occur annually. Dementia has various causes, with AD accounting for 60-70% of cases.[6]

EPIDEMIOLOGY OF CANNABIS USE- GLOBAL PREVALENCE PATTERNS AND ADOLESCENT TRENDS

Recent data indicate a marked rise in recreational cannabis use among adolescents, with 2018 prevalence of 13.9% in 8th graders, 32.6% in 10th graders, and 43.6% in 12th graders.[7] Cannabis use prevalence varied widely across regions. In Europe (33 countries), rates ranged from 0.42% to 43.90%, highest in the Netherlands (2013) and lowest in Sweden (2016). In North and South America (15 countries), prevalence ranged from 1.40% to 38.12%, peaking in the United States in 2021. Oceania and Africa (18 countries) reported prevalence between 1.30% and 48.70%, highest in Australia (2004). Asia (16 countries) showed lower rates, ranging from 0.30% to 19.10%, with the lowest in Japan (2004) and highest in Israel (2017).[8]

PHARMACOKINETICS, ENDOCANNABINOID SIGNALLING, AND NEUROSTRUCTURAL SEQUELAE OF CANNABIS EXPOSURE

Cannabis indica, commonly referred to as marijuana, weed, pot, or ganja, is the most widely used illicit recreational substance globally. Smoking a 500-1,000 mg cannabis cigarette delivers approximately 0.2-4.4 mg THC, of which ~1% reaches the brain (2-44 µg), within the pharmacologically active range of 2-22 mg.[4] After inhalation, THC rapidly achieves high plasma levels and, due to lipid solubility, distributes widely with a prolonged half-life. THC undergoes hydroxylation to form the psychoactive metabolite 11-hydroxy-Δ9-tetrahydrocannabinol, which is further oxidized to the inactive 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH), a key diagnostic marker.[9] Cannabinoids act via the endocannabinoid system (ECS) of our body, which maintains homeostasis by regulating metabolism, intercellular communication, appetite, memory, immunity, and pain through two types of receptors of ECS namely CB1 and CB2 receptors.[11]

In vivo studies demonstrate dose-dependent THC toxicity and structural brain alterations, predominantly in CB1-rich regions including cerebellum, hippocampus, amygdala, prefrontal cortex, and striatum.[4] Multiple studies indicate that *Cannabis indica* consumption via inhalation and combustion is associated with an increased risk of cerebral infarction.[12] A recent evidence demonstrates a significant reduction in gray matter within CB1 receptor–enriched regions i.e. medial temporal cortex, temporal pole, para-hippocampal gyrus, insula, and orbitofrontal cortex-in regular cannabis smokers compared with occasional cannabis users; these regions subserve motivation, emotion, and affective processing.[13]

This retrospective review summarizes few clinical and observational studies on chronic *Cannabis indica* abuse and neurodegenerative disorders. Emerging evidence suggests that long-term cannabis abuse may increase the risk of neurodegeneration. These findings highlight the need for further research on cannabis-related neurological effects and the development of effective prevention strategies.

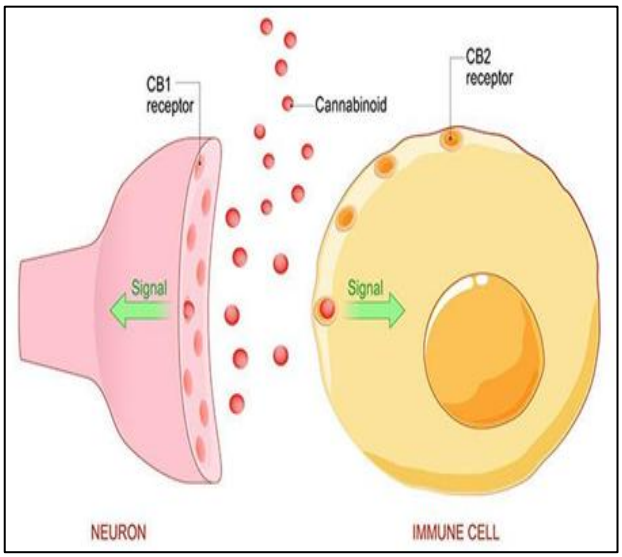

Figure 1: Endocannabinoid system.[10]

METHODS AND MATERIALS USED FOR STUDY

Study design

A retrospective review design was adopted, encompassing previously published observational studies.

Data sources

Data were obtained from neurology and psychiatry medical records and from peer-reviewed literature along with various articles reporting chronic *Cannabis indica* exposure and neurodegenerative outcomes.

Outcome measures

Primary outcomes included cognitive impairment, dementia syndromes, Parkinsonian motor features, and neuroimaging evidence of neurodegeneration.

Data analysis

Findings were analyzed descriptively, emphasizing patterns of association rather than causal inference.

DISCUSSION

Neurodegenerative disorders are increasing worldwide, alongside a parallel rise in recreational cannabis use, particularly among adolescents and young adults. This trend has raised important concerns regarding the potential long-term neurocognitive and neurodegenerative effects of chronic cannabis exposure.

Chronic *Cannabis indica* exposure has been linked to structural and functional brain changes in observational studies, particularly in regions rich in CB1 receptors. Regular users show reduced gray matter volume in the medial temporal cortex, temporal pole, para-hippocampal gyrus, insula, and orbitofrontal cortex. Cannabis abuse in patients with neurological and cerebrovascular disorders is consistently associated with higher rates of emergency healthcare utilization and greater pain burden across conditions including neuropathy, MS, stroke, and dementia subtypes.[14] Acute THC dose-dependently alters glutamatergic signalling, increasing subcortical glutamate/glutamine (Glx) in humans, while CBD similarly affects subcortical Glx but reduces Glx in the anterior cingulate cortex. Baseline Glx moderates these effects. In chronic cannabis users, magnetic resonance spectroscopy studies show 10-15% reductions in glutamate metabolites in cognitive regions, with possible concurrent GABA decreases.[15]

Scott et al conducted a comprehensive meta-analysis demonstrating that cannabis use in adolescents and young adults is associated with small-to-moderate impairments across multiple neurocognitive domains. The largest deficits were observed in learning (d= -0.33) and executive functions, including abstraction/shifting (d=-0.30), with additional impairments in processing speed, memory, working memory, inhibition, and attention (d≈ -0.21 to -0.26).[16]

In a study of 48 marijuana users and 62 matched controls, structural MRI showed reduced orbitofrontal cortex (OFC) volume in users, while functional MRI revealed increased OFC network connectivity. Diffusion tensor imaging studies showed dynamic changes in white matter integrity over time. Early stages were associated with increased fractional anisotropy and improved integrity of the forceps minor, possibly reflecting adaptive or compensatory neural responses. However, with prolonged use, these measures gradually declined, suggesting progressive disruption and degeneration of white matter microstructure.[17]

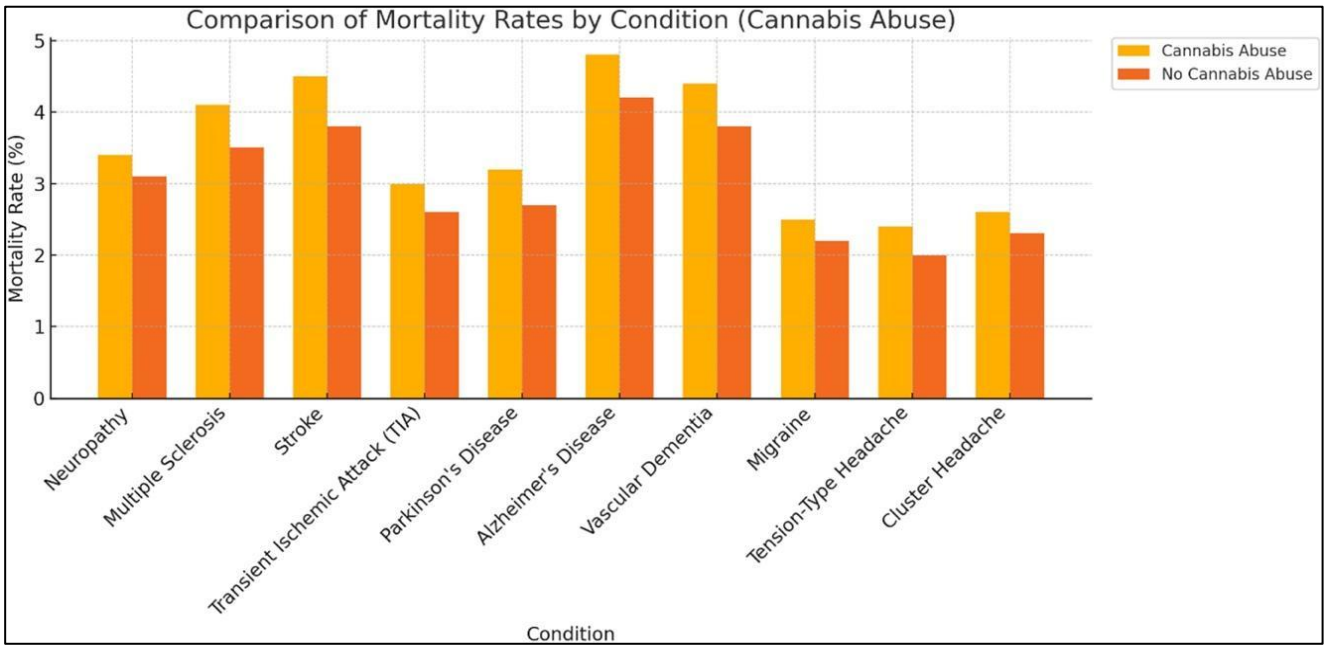

Figure 2: Graphical representation of mortality occurrence is slightly elevated in cannabis-abusing patients.[14]

Another study reveals that THC and CBD influence memory, with effects modulated by factors such as dose, tolerance, timing, and route of administration. Cannabis use is linked to acute impairments in memory, attention, and executive function, along with sustained deficits in verbal memory in middle-aged adults, whereas such persistent effects are not consistently observed in younger populations.[15]

In a study of adolescents and young adults reviewing acute and chronic cannabis effects, chronic use was associated with altered glutamatergic and GABAergic functioning in neurocognitive regions, potentially increasing neuropsychiatric risk.[18]

In a cohort study following data was found.[14] In PD, mortality was 3.2% in cannabis abuse versus 2.7% in non-users (RD -0.005; 95% CI -0.011-0.001; p=0.145; RR 0.844; OR 0.832). Pain incidence was higher with cannabis abuse (13.9% vs 9.7%; RD -0.042; 95% CI -0.051- -0.033; p<0.001; RR 0.698; OR 0.675). In AD, emergency visits occurred in 29.8% of patients with cannabis abuse versus 22.1% without (RD -0.077; 95% CI -0.086 to -0.068; z -15.84; p<0.001; RR 0.741; OR 0.705). Mortality was 4.8% versus 4.2% (RD -0.006; 95% CI -0.015 to 0.003; p=0.165; RR 0.875; OR 0.862). Pain incidence was 18.7% versus 13.5% (RD -0.052; 95% CI -0.061 to -0.043; p<0.001; RR 0.722; OR 0.695). In vascular dementia, emergency visits occurred in 28.4% with cannabis abuse versus 21.5% without (RD -0.069; 95% CI -0.078- -0.060; p<0.001; RR 0.757; OR 0.722). Mortality was 4.4% versus 3.8% (RD -0.006; p=0.145; RR 0.864; OR 0.853). Pain incidence was 16.9% versus 12.5% (RD -0.044; p<0.001; RR 0.740; OR 0.713). Stroke recurrence was 1.6% versus 1.2% (RD -0.004; p=0.216; RR 0.788; OR 0.777).

This retrospective review highlights consistent associations between chronic *Cannabis indica* exposure and structural brain alterations in CB1-rich regions, including the medial temporal cortex, orbitofrontal cortex, and insula. Evidence indicates chronic cannabis exposure is associated with neurostructural and neurochemical degeneration along with cognitive alterations, particularly in young users. This highlights the need for targeted prevention, longitudinal research, and informed public health strategies.

CONCLUSION

Despite rapid changes in cannabis legality, availability, and potency over the past decade, rigorous public health research is deficit. This review synthesizes available observational evidence linking chronic *Cannabis indica* exposure with structural and functional brain alterations. Consistent findings of reduced gray matter volume, altered white matter integrity, and changes in functional connectivity suggest a potential neurodegenerative vulnerability associated with prolonged cannabis use. Well-designed longitudinal studies are needed to better understand the long-term effects of chronic cannabis use. Standardized assessment of cannabis exposure and careful control of confounding factors are essential to determine whether cannabis acts as an independent risk factor for neurodegenerative disorders.

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