

Recreational and Medicinal Cannabis Impact Assessment on Symptoms, Mental and Cognitive Functions in Patients With Multiple Sclerosis: A Short Review of the Literature

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Abstract

Nowadays there has been renewed interest in the therapeutic applications of medicinal cannabis, and people, particularly those with multiple sclerosis (MS), claim that it may have beneficial effects in their symptoms control. There is evidence (although inconsistent) supporting the use of cannabis or its derivatives for their therapeutic potential in treating MS symptoms. It is mentioned that, the use of medicinal cannabis can relieve patient-reported symptoms of spasticity, bladder disorders and pain (excluding central neuropathic pain). Currently available studies demonstrate no proof of a beneficial effect of cannabinoids on MS disease activity or disability progression. Also there was no obvious improvement in cerebellar disease, tremor or spasticity measured by tests administered by physicians. Additionally, it is not yet clear if medicinal cannabis has immunosuppressant or neuroprotective properties in MS and its safety needs to be re-evaluated, regarding the subsequent cognitive deficits and neuropsychiatric symptoms, which were found more often in users than non-users patients with MS.

The aim of this short review is to redefine medicinal cannabis influence on MS symptoms, its potential side effects and long-term prognosis, taking into account data derived through reviewing and searching Pubmed. Also evidence was searched regarding any possible provocative or causative effect of cannabis in the MS pathogenesis, the cannabis impact in the appearance of subsequent cognitive deficits or dementia and whether potentially protective action in their progression later ensues.

Future research with randomized controlled studies is necessary, in order to determine the efficacy and the safety of medicinal cannabis. The risks and benefits of its therapeutic use should be weighed and considered carefully in elderly or particularly sensitive patients. That's because patients with psychosis or pre-existing cognitive dysfunction, may have increased susceptibility to cannabinoids' toxicities. Neuropsychological testing should be used before and during long term monitoring of patients, to prevent neuropsychiatric complications from overcoming the benefit of improving body symptoms.

Abbreviations

CBD: cannabidiol

CBMEs: cannabis-based medicinal extracts

CNS: central nervous system

MS: multiple sclerosis

THC: tetrahydrocannabinol

Introduction

Cannabinoids have a long history of consumption for recreational and medical reasons. The primary active constituent of the hemp plant *cannabis sativa* is delta 9-tetrahydrocannabinol (delta 9-THC). Cannabis is the most widely used illicit drug worldwide, while it is estimated that 4% of the global population uses cannabis and 10% of them develop daily use pattern. The recent legalization of medical and recreational use in several countries and the introduction of a legal cannabis industry is going to increase cannabis use [1,2].

Epidemiological and clinical researches have established that cannabis use can produce adverse effects on cognitive function and mental health [3]. Other experimental, placebo controlled studies have repeatedly confirmed that single doses of cannabis can cause a dose dependent reduction in performance. This was evaluated by using specific tests for measuring motor function, memory, attention and impulse control. The zenith of performance impairment was during the first hour after smoking, the decline 2-4 hrs after cannabis use, while there was still distinct presence at serum levels 2-5ng/ml of Δ 9-tetrahydrocannabinol (THC) [4-9]. Recreational cannabis differs from medical cannabis in that, it has a higher concentration of tetrahydrocannabinol (THC). THC is the psychoactive component (may produce anxiety, dysphoria, cognitive impairment or psychosis) and has dependency potential. Medical cannabis has higher levels of cannabidiol (CBD) which is non-intoxicating with anti-inflammatory, analgesic, and antipsychotic properties [10].

There is some evidence (although inconsistent) that the use of medicinal cannabis can relieve patient-reported symptoms of spasticity, bladder disorders and pain (excluding central neuropathic pain). Currently available studies demonstrate no proof of a beneficial effect of cannabinoids on MS disease activity or disability progression. Also there was no obvious improvement in cerebellar disease, tremor or spasticity measured by tests administered by physicians. Additionally, it is not yet clear if medicinal cannabis has immunosuppressant or neuroprotective properties in MS and its safety needs to be re-evaluated, regarding the subsequent cognitive deficits and neuropsychiatric symptoms, which were found more often in users than non-users patients with MS [11-18].

Association of Cannabis Use to Cognitive Function in MS Patients: Neuropathological Features, Clinical Impact and Long Term Prognosis

Data depicted from epidemiological and clinical studies established that cannabis use can produce adverse effects on cognitive function and mental health. Single doses of cannabis was found to cause a dose dependent/time related (time after smoking period) reduction in performance, as assessed with neuropsychological tests measuring memory (short-term memory impairment), attention, impulse control and motor function [4-9,19].

Other studies depicted the acute and chronic impacts of cannabinoids on human cognition, including impaired encoding, storage, manipulation and retrieval mechanisms. Verbal learning, memory, attention and some executive functions were also impaired. Recurrent exposures have shown permanent ill-effects on memory, behavior, attention, and executive function, especially when cannabis use started early in life [20-22]. Beside cognitive deficits, vulnerable individuals were found more prone to develop psychotic reactions, and emotional dependence with consequent social and psychological dysfunction [23,24].

Although some studies depicted that, there was little evidence to connect mild cognitive impairment in chronic cannabis users to drug-induced neuropathology [25], others [26] provided new evidence of exposure-related structural abnormalities in the hippocampus and amygdala in long-term heavy cannabis users, reflecting long term harmful effects on brain tissue and mental health. Furthermore, changes were found in brain maturation and intellectual function, with decrease in intelligence quotient in chronic users, and possible permanence in users early in life [26,27].

The recreational use of cannabis during adolescence, where there is development of myelination, formation of white matter tracts and neural connections, can cause deleterious effects to the brain by disturbing white matter connectivity. As it is known, cannabinoid receptors are distributed throughout the central nervous system and are part of the cannabinoid system, which participates in memory procession and also in neuroprotection [28]. The neurodegeneration findings were more prominent in: frontal lobes, fornix, hippocampus, frontal-limbic connections, corpus callosum, and commissural fibers. Cognitive deficits and impulsivity could be attributed to alterations of frontal lobe white matter. Attention, decision making, inhibition and executive control deficits could be a result of impairment in cingulo-fronto-parietal cognitive attention network [29,30].

The diverse neurophysiological properties of cannabis are described in a study, referring to possible influences on: membranes of neurons, synaptic vesicles and neurotransmitters (increase in central cholinergic activity, a moderate increase in catecholaminergic activity and effects on the GABA and serotonin systems) [31].

The toxicity of marijuana was underestimated for a long time, since findings revealed that, delta 9-THC induced cell death with shrinkage of neurons and DNA fragmentation in the hippocampus. Cannabinoids were found to increase the activity of dopaminergic neurons in the ventral tegmental area-mesolimbic pathway [32]. A recent study revealed that dopamine neuronal loss of ventral tegmental area (VTA) dopaminergic neurons at pre-plaque stages contributes to memory and reward dysfunction in a model of Alzheimer's disease [33].

Impairments in behavior and cognition were linked to prenatal exposure and thought to be result of alterations in endocannabinoid signaling pathways, with weakening of fetal neuronal architecture. This assumption was made, because THC binding to cannabinoid-1 receptors during gestation alters central dopamine and opioid neurotransmitter system development, while this could also increase vulnerability to future drug abuse [34].

It is estimated that cognitive dysfunction affects 40% to 60% of patients with MS [35]. Many studies provide evidence that the prolonged use of inhaled or ingested street cannabis in patients with MS is associated with impaired mentation and cognitive impairment in comparison to not users. Especially working memory, information processing speed, and executive function difficulties were affected. A recent study confirmed the lasting effects of adolescent cannabis use in cognition, which appears to be more pronounced even than those observed in alcohol abuse [36-40]. Neuropathological studies confirmed the association between cannabis use, more widespread cognitive impairment and structural brain changes in MS patients, referring also to tissue volume in subcortical, medial temporal, and prefrontal regions [41]. On the other hand, depicted data from another study indicated that no significant cognitive decline occurs after relatively short-term, controlled, pharmaceutical use administration of cannabis-based medicinal extracts (CBMEs) [42].

Association of Cannabis Use to Induction and Progression of Multiple Sclerosis

The recreational smoking of cannabis has become widespread, including adolescents. Cannabis contains a class of compounds known as phytocannabinoids that include cannabidiol (CBD) and $\Delta(9)$ -tetrahydrocannabinol (THC). Recreational cannabis differs from medical cannabis in that it has a higher concentration of tetrahydrocannabinol (THC) which is the major psychoactive component, has dependency potential, but also exhibits immunosuppressive activity. Medical cannabis has higher levels of cannabidiol (CBD) with no psychotropic action, but modulating properties on immune function and greater therapeutic value.

It is known that, the endocannabinoid system is composed of two receptors, CB1 and CB2, and different endogenous ligands. CB1 receptors and ligands are found in the brain and also in immune and other peripheral tissues. Conversely, CB2 receptors and ligands are found especially in the immune cells in the periphery. Accumulative evidence has shown that cannabinoids could modulate a variety of immune cell functions in humans and also could modulate T helper cell development, chemotaxis, and tumor development. Cannabinoids seems to interfere with brain-immune axis and presumably immune deficiency. In addition,

in a murine model of MS, cannabidiol was found for first time, to attenuate experimental, autoimmune encephalomyelitis model of MS, through induction of myeloid-derived suppressor cells [43,44].

There are accumulating data regarding the impact of CBD and THC on immune-competent cells within the CNS in relation to susceptibility to infection. The migratory capability of microglia toward sites of microbial invasion was found to be inhibited by THC. Furthermore, exposure to these substances early in life was found to alter potentially the cardinal immune response of the CNS to specific microbial agents in adult life [45]. Previous studies revealed also that, cannabis and other exogenous cannabinoids could alter the immune function and decrease the host resistance to microbial infections in experimental animal models and *in vitro*. It was supposed that, the disturbed homeostatic immune balance was due to direct exposure to high concentrations of cannabinoids (membrane perturbation in lung), or presumably by perturbing the balance of T helper (Th1 pro-inflammatory versus Th2 anti-inflammatory cytokines) [46].

Researchers revealed the important role of the endocannabinoid system in the control of a variety of gastrointestinal functions, inflammation and gut permeability, and dynamic interactions with gut microbiota [47]. Recent studies have suggested that alterations in the gut microbiota (dysbiosis), are associated with MS, while gut microbiota differs in patients with MS from the healthy population. This is supported by a recent study in which, fecal microbiota transplantation was associated with 10 years of stability in a patient with secondary progressive multiple sclerosis (SPMS). It seems that, gut microbiota may act as a pathogenic environmental risk factor, while the recent discovery of the central nervous system lymphatic system may call for a reassessment of basic assumptions in neuroimmunology and sheds new light on the aetiology of neuroinflammatory and neurodegenerative diseases associated with immune system dysfunction [48-55].

There is the hypothesis that MS patients lead a riskier premorbid lifestyle, which endanger and expose them to a variety of hostile environmental agents with a possible role in MS pathogenesis. If we combine the aforementioned data, we could support that cannabis users may be more susceptible to the development of MS pathology, due either to the immunosuppressive activity of cannabis or the social and psychological dysfunction and impulsivity that enhances the riskier attitude [56]. This is confirmed by conducted studies, which delineate possible co-factors in MS pathogenesis associated with onset, relapses or progression in multiple sclerosis, such as: lower exposure to sunlight and/or lower serum vitamin D levels, cigarette smoking, Epstein-Barr virus (particularly infectious mononucleosis during adolescence), human herpes virus 6 (HHV-6), upper respiratory tract infections and obesity during adolescence [57,58].

The interaction between genetic predisposition and environmental factors are of great significance in the pathogenesis and development of autoimmune diseases, such as MS. As human mucosal cavities are the most frequent sites that interact with the exterior environment, cannabis and other exogenous cannabinoids could play a crucial role in the regulation of immune system, through interfering with gastrointestinal inflammation, gut permeability and dynamic interactions with gut microbiota. Growing evidence has shown that gut dysbiosis through influencing the expression level of Toll-like receptors (TLRs) of antigen presenting cells, and contributing to Th17/Treg imbalance, is closely related to autoimmune diseases [29,34,59,60].

Concerning the anti-inflammatory and immunologic effects of cannabinoids in MS, studies in animal models did not confirmed disease-modifying effects and no overall effect on the progression of MS in the

progressive phase. Only in a recent study was depicted that, cannabidiol treatment may ameliorate experimental autoimmune encephalomyelitis model of MS, through induction of immunosuppressive myeloid-derived suppressor cells [16,18,43].

Materials and Methods

In order to serve the aim of this short review, regarding recreational and medicinal cannabis impact assessment on symptoms, mental and cognitive functions in patients with MS, we took into account data derived through reviewing and searching Pubmed. Evidence was depicted from epidemiological studies, clinical studies and reviews in order to estimate medicinal cannabis influence on MS symptoms, its potential side effects and long-term prognosis. We also searched if there is any potential provocative or causative effect of cannabis in the MS pathogenesis, any possible impact in the appearance of subsequent cognitive deficits or dementia and whether potentially protective action in their progression later ensues.

Discussion

MS is a chronic debilitating autoimmune disease and the relatively recent and popular administration of cannabis-based medicinal extracts or cannabis use for their therapeutic properties, although promising needs thorough investigation. Beside the existing evidence - although inconsistent - that the use of medicinal cannabis can relieve patient-reported symptoms, currently available studies demonstrate no proof of a beneficial effect of cannabinoids on MS disease activity or disability progression. Additionally, the immunosuppressant or neuroprotective properties and safety of medicinal cannabis in MS patients needs to be re-evaluated regarding the subsequent, possible acute and/or chronic impact on cognitive function and mental health. The latter is supported by neuropathological and radiological evidence of the aforementioned studies. The administration of cannabis-based medicinal extracts seems to be more promising in diminishing the underlying neuroinflammation in MS patients, with less impact on cognitive functions.

Growing evidence suggests that, cannabis use by children, adolescents or young adults can result in abnormal neural development and long-term neurological deficits, while there is direct correlation between repeated, young-age cannabis exposure and white matter changes in the brain. We must take into account also that, the induction of gut dysbiosis triggers the development of spontaneous experimental autoimmune encephalomyelitis (EAE) during adolescence and early young adulthood, and that there is an increase in immunological tolerance with aging which suppresses disease onset after late young adulthood in mice. Therefore, the emerging danger for multifactorial MS pathogenesis in young, cannabis users needs not to be underestimated.

In near future randomized, controlled studies will define more precisely the association of cannabis use to induction and progression of MS, any possible therapeutic or aggravating element and any possible interaction of cannabis with other commonly used MS drugs. Additional studies are needed to investigate the cumulative, long term, hazardous impact in the brain of young, cannabis users either from abnormal neural development and long-term neurological deficits as direct effect of cannabis use or the emerging neuroinflammation from gut dysbiosis and other environmental agents.

Conclusions

Although the administration of cannabis-based medicinal extracts seems to be more promising, with less impact on cognitive functions than recreational use of cannabis, this needs more proof evidence. Future research is needed to depict and assess the medicinal cannabis impact on symptoms, on mental or cognitive functions and the long-term prognosis in patients with MS.

Some issues which need further evaluation include: the more favorable dosage and route of medicinal cannabis administration (smoking, edibles, drops, oromucosal spray, etc.), the possible immunosuppressant or neuroprotective properties of long-term cannabis use and any possible interaction of cannabis with other commonly used MS drugs.

The risks and benefits of medicinal cannabis use should be weighed and considered carefully in elderly or particularly sensitive patients. That's because patients with psychosis or pre-existing cognitive dysfunction, may have increased susceptibility to cannabinoids' toxicities. Neuropsychological testing should be used before and during long term monitoring of patients, to prevent neuropsychiatric complications from overcoming the benefit of improving body symptoms.

Educational programs for young people should be implemented to emphasize the potential risks of recreational cannabis use, especially those referring to intellectual decline and increased incidence of psychotic attacks. Physicians should always provide guidance to pregnant women and inform them that, prenatal exposure is linked not only to growth restriction, but to neurobehavioral and cognitive impairments of their children later in life, with increased also vulnerability to future drug abuse.

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Conflicts of Interests

Authors report no conflicts of interest.

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