


## Chapter 8

# Neurobiology of Cannabinoids and Medical Cannabis in Therapeutic Intervention for Multiple Sclerosis: Understanding the Molecular Mechanisms of Action

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### ABSTRACT

*Cannabinoids, either phytocannabinoids or synthetic derivatives of medical cannabis, exhibit a variety of potential pharmacotherapeutic effects by acting on the endocannabinoid system, through interactions with the cannabinoid receptors (CB1, CB2, and other receptors). Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that causes spasticity, neuropathic pain, urinary bladder dysfunction, and sleep disturbance. Treatment with cannabinoids decreases the severity of disease in animal models of experimental autoimmune-Theiler's virus-induced-encephalomyelitis or toxic demyelination. CBD anti-inflammatory effects decrease CNS inflammatory infiltrates, microglial activation, and cytokines IFN- $\gamma$ , IL-1 $\beta$ , IL-17, or TNF- $\alpha$ , whereas  $\Delta$ 9-THC reduces spasticity. Add-on*

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*treatment with cannabinoids (Nabiximols, Sativex, equimolar concentration of THC:CBD) have demonstrated potential in alleviating the symptoms of patients with MS. This chapter reviews the evidence-based therapeutic effects of cannabinoids and their mechanisms of action relevant to MS.*

## **INTRODUCTION**

### **Multiple Sclerosis**

Multiple Sclerosis (MS) is an immune-mediated demyelinating disease in which the immune system attacks the myelin sheath and damages the central nervous system (CNS), forming MS lesions, plaque, or scars. MS lesions can occur anywhere in the CNS, including the spinal cord, gray matter, optic nerves, and periventricular areas (Hagemeyer et al., 2012). The demyelination damages the motor nerve fibers and causes inflammation, metabolic imbalance, and severe impairment of nerve signal transmission between the brain and spinal cord as a result of irreversible axonal degeneration (Alizadeh et al., 2015). Neurological symptoms usually develop following conduction blockage within the fibers. Such pathogenesis causes heterogenic symptoms, including spasticity, muscle spasms, oculomotor abnormalities, optic neuritis, tremors, neuropathic pain, diplopia, neurogenic bladder, gait problems, paresthesia, and cognitive dysfunction (Allegri et al., 2011). Spasticity and neuropathic pain are frequent symptoms of MS that reduce the quality of life of MS patients. Spasticity causes the stiffness of the muscles (or contracture), muscle spasms, and nociceptive pain. Spasticity, a form of elevated muscular tone, is a common (affecting 60–84%) and severe MS symptom that worsens with disease progression. Contractures in muscles, tendons, and joints, which can worsen limb posture, mobility, and function, may evolve as adaptive traits (Hugos & Cameron, 2019). Lesions of the somatosensory system slow down spinal somatosensory conduction, causing balance deficits and neuropathic pain. During the course of the disease and the broad clinical spectrum, the signs and symptoms of MS are unpredictable and highly variable. A French neurologist, Jean-Martin Charcot, was the first to characterize MS as a distinct nosological entity (Joy & Johnston Jr., 2001). Described as *la sclérose en plaques* in 1868, Charcot uses the anatomopathological and clinicopathological features of presentation in person to diagnose MS having disseminated grayish and reddish patches of varying sizes in both the brain and spinal cord. In MS, irreversible axonal and myelin loss is related to clinical impairment.

### **Disease Course and Diseases Burden of MS**

Relapsing-remitting multiple sclerosis (RRMS), which causes flare-ups of inflammatory demyelination in the CNS along with an acute worsening of neurological activities and existing symptoms, affects patients in the majority of MS cases (roughly 85 percent) (Goldenberg, 2012). RRMS could be either active (showing evidence of new relapses), non-active (no disease activity), worsening (increased disability), or stable (no increasing disability). During relapsing MS, the axonal loss is frequent (Cree et al., 2021). The edema associated with new MS lesions is a major factor in neurological relapses because it blocks conduction potentials. Nearly 60–70% of RRMS patients progress to SPMS within 20–25 years, which is characterized by progressive neurological impairment after an initial relapsing–remitting course (Barzegar et al., 2021). Furthermore, ~10% of MS have a disease course that includes a persistent deterioration in neurological function without recovery, which is categorized as progressive relapsing MS (PRMS)

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