Cannabis use in multiple sclerosis

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Abbreviations

2-AG – 2- Aracchidonoyl Glycerol

5-HT1A – Serotonin 1A Receptor

Δ^9THC – Delta 9-Tetrahydrocannabinol

AC – adenylyl cyclase

AEA - Arachidonoyl Ethanolamide Anandamide

ARR - Annualized Relapse Rate

CB – Cannabinoid

CB1 – Cannabinoid Receptors type 1

CB2 – Cannabinoid Receptors type 2

CBC - Cannabichromene

CBD – Cannabinoids

CBDA – Cannabidiolic acid

CBG - Cannabigerol

CBGA – Cannabigerolic Acid

CBN – Cannabinol

CINV – Chemotherapy-Induced Nausea and Vomiting

CIS – Clinically Isolated Syndrome

CNS - Central Nervous System

COX - Cyclooxygenase

CSF – Cerebral Spinal Fluid

CYP450 – Cytochrome P450

DC - Dendritic Cells

DIS – Dissemination In Space

DIT – Dissemination In Time

DMT – Disease-Modifying Treatments

EAE - Experimental Autoimmune Encephalomyelitis

ECP002A - Δ^9- tetrahydrocannabinol

ECS – Endocannabinoid System

FAAH – Fatty Acid Amide Hydrolase

GPR55 – G Protein-coupled Receptor 55

HIV- Human Immunodeficiency Virus

IBD – Inflammatory Bowel Disease

IL – Interleukin

INF – Interferon

IM – Intramuscular

IV – Intravenously

LOX – Lipoxygenases

MAS – Modified Ashworth Scale

MC – Medical Cannabis

MMP3 - Matrix Metallopeptidase 3

MRI – Magnetic resonance imagining

MS – Multiple Sclerosis

NK. – Natural Killers cells

NRS – Numeric Rating Scale

NSAID – Non-Steroidal Anti-Inflammatory Drug

PC - Phytocannabinoids

PK – Pharmacokinetics

PNS – Peripheral Nervous System

PP – Primary Progressive

PPARγ – Peroxisome Proliferator-Activated Receptor- Gamma

PPMS – Primary Progressive Multiple Sclerosis

RA – Rheumatoid Arthritis

RIS – Radiologically Isolated Syndrome

RRMS – Relapsing-Remitting Multiple Sclerosis

SPAM - Secondary Progressive Multiple Sclerosis

THC - Tetrahydro-Cannabidiol

TNF - Tumor Necrosis Factor

TRPV1 – Transient Receptor Potential action cation channel subfamily V member 1

Vd – Volume of distribution

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Abstract

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Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) and part of the group of demyelinating diseases of the CNS. The main characteristics of MS are neurodegeneration, inflammation, and demyelination. There are three phenotypes of MS, each phenotype represents a stage in the disease progression, and each phenotype has its characteristics. However, those phenotypes usually overlap, and only in the retrospective patient history is it possible to know when there was a change in the phenotype. Therapy strategies for MS are to decrease the disease's biological activity, treat an acute attack of MS, and provide symptom relief through disease-modifying therapies and immunomodulation.

The analgesic effect of cannabis and its anti-inflammatory effect on the immune system and cannabis-based therapy are being investigated, and there is much interest in using cannabis as immunomodulation.

Several studies were done, and some are still ongoing in order to examine the use of Cannabis in MS-related spasticity and MS-related pain.

This thesis will provide an overview of current knowledge about cannabis treatment in MS.

Keywords: cannabis-based therapy, disease-modifying therapies, immunomodulation, multiple sclerosis

Sažetak

Naslov rada: Upotreba kanabisa u multiploj sklerozi

Autor: Inbal Kouzy

Multipla skleroza (MS) je autoimuna bolest središnjeg živčanog sustava (CNS) i dio je skupine demijelinizacijskih bolesti CNS-a. Glavne karakteristike MS-a su neurodegeneracija, upala i demijelinzacija. Postoje tri fenotipa MS-a, od kojih svaki fenotip predstavlja stadij u progresiji bolesti te svaki fenotip ima svoje karakteristike. Međutim, obično se ti fenotipovi preklapaju te je samo u retrospektivnoj anamnezi bolesnika moguće znati kada je došlo do promjene fenotipa. Današnje stategije terapije za MS su smanjenje biološke aktivnosti bolesti, liječnje akutnog napada MS-a i ublažavanje simptoma kroz terapiju koja modificira tijek bolest kao i simptomatsku terapiju.

Istražuje se analgetski učinak kanabisa i njegov protuupalni učinak na imunološki sustavi te terapija na bazi kanabisa, a postoji veliki interes za korištenje kanabisa kao imunomodulacijske terapije.

Provedeno je nekoliko studija, a neke su još u tijeku sa ciljem utvrđivanja upotrebe kanabisa u spastičnosti povezanoj s MS-om i boli povezanoj s MS-om.

Ovaj diplomski rad pružit će pregled trenutnih spoznaja o liječenju kanabisom kod multiple skleroze.

Ključne riječi: terapija kanabisom, terapije koje modificiraju tijek bolesti, imunomodulacija, multipla skleroza

Introduction:

Cannabis is a generic name for plants belonging to the genus cannabis, and it is also a bioactive preparation. Cannabis plants contain more than 400 metabolites, and many of those metabolites have bioactive effects. The two primary active metabolites of the cannabis plants are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [(1)]. THC has psychoactive effects, while CBD is a non-intoxicating metabolite with anti-inflammatory, analgesic, and anti-psychotic effects [(2)].

Cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) are the cannabinoid receptors, transmembrane G protein-coupled receptors. Those receptors are scattered in the central and peripheral nervous systems and the immune system. The CB1 receptor is found more abundantly in the central nervous system (CNS), especially around the pain signaling control area; CB1 receptors can also be found in the peripheral nervous system (PNS). Activation of the CB1 receptor causes a decrease in neurotransmitter release, affecting the nociceptive pathways. In the immune cells, we can find mainly CB2 receptors and, to a lesser degree, CB1 receptors, which explains some of the anti-inflammatory characteristics of cannabinoids [(3)].

The immune cells express both CB1 and CB2 receptors; those receptors' activation by endocannabinoids plays a role in immune homeostasis and control. Some studies examined the role of endocannabinoids on the immune cells. Those studies showed that endocannabinoids affect cytokines production by the immune cells, accounting for their anti-inflammatory characteristic [(4)].

Animal studies found that the deletion of the CB2 gene leads to exacerbation in the inflammatory effect [(5)]. Due to the cannabis immunomodulatory effect, cannabis-based treatment for autoimmune, inflammatory, tumors, and other conditions that involve the immune system. are being investigated [(6)].

One of the diseases that cannabis-based therapy is being examined for, is multiple sclerosis (MS). MS is an autoimmune, inflammatory demyelinated disease of the CNS. The main characteristics of MS are inflammation, demyelination, axonal loss, and neurodegeneration. MS primarily affects young women [(7,8)]. The main symptoms of MS are motor symptoms such as spinal cord syndrome, optic neuritis, cognitive impairment, and brainstem or cerebellar syndrome [(8)]. The non-motor symptoms include pain, muscle spasms, headaches, fatigue, and depression. The MS symptoms depend on the location of the lesions within the CNS [(9)]. The initial presentation of MS is called clinically isolated syndrome (CIS), and it usually can be optic neuritis, incomplete myelitis, or brainstem syndrome [(10)].

The aim of this thesis is to present current knowledge about the potential use of cannabis as an immunomodulator drug in the treatment of MS and as a drug for symptoms-related MS treatment.

Literature review

1. Cannabis background:

Four species of the cannabis plant exist Cannabis Sativa, which is the predominant form and the most commonly used, Cannabis Indica, Cannabis Ruderalis, and Cannabis Afghanica [11]. Cannabis or cannabis Sativa is an old cultivated plant which origins in central and south Asia. Cannabis has been used as a material in medicines and food for thousands of years [12].

The cannabis plant contains around 545 natural compounds that are different in their chemical structures, and those natural compounds of cannabis are known as cannabinoids (CB). The present-day history of medical cannabis use started in the 19th century when William Brooke O'Shaughnessy, was an Irish medical doctor with interest in chemistry and toxicology, used cannabis for analgesia, inflammation, and seizures [13]. O'Shaughnessy studied medicine at the University of Edinburg and later moved to Calcutta; he is famous for setting the foundation of fluid therapy during the Cholera epidemic. In 1839 O'Shaughnessy published the results of his observations on cannabis; he noted that the effects of cannabis depended on "resinous secretion" that was absent in European hemp [14,15].

Medical Cannabis (MC) is the usage of either the cannabis plant itself or Cannabis extract for medical use. The usage of cannabis in medicine has been growing lately, despite its potential to create physical and mental addiction. Around 124 million people worldwide use Cannabis per year [9,12,16].

During the 1920s, a negative campaign about cannabis use started in the US. Later, cannabis was classified as a narcotic drug, and a stigma about cannabis users occurred. The change in view about cannabis occurred between 1980 and the 1990s, with the use of cannabis as an antiemetic in oncology and HIV patients [16–18].

2. The pharmacology of cannabis

Out of the many chemical compounds of the cannabis plants, only 100 are naturally occurring phytocannabinoids (PCs), and those are divided into ten different subclasses. So far, the two subclasses that have gotten the most scientific attention are CBD and Δ^9-THC. PCs are primarily produced and secreted by glandular protuberances in the leaves and stems of cannabis plants. Gaoni and Mecholam first isolated both CBD and Δ9-THC in the 1960s [12].

When CB bind to their cannabinoid receptors, they modify neurotransmitter release in the brain. The primary psychoactive substance in the cannabis plant is THC. THC concentration in the cannabis plant fluctuates, usually around 1-24%. The primary non-psychotropic CB in cannabis plants is CBD. CBD concentration in cannabis plants is usually less than 1% [19].

All CB have structural resemblance consisting of resorcinol, an A- ring, and terpenoid moiety, a C-ring. Cannabigerolic acid (CBGA) is the biosynthetic starting point for most CB and is the direct precursor of both THC and CBD. Oxidative cyclization of CBGA forms a link between C-1 and C-6 of the prenyl unit, which results in CBD formation [16].

THC molecule is a 21- carbon terpenoid. It is yellow-colored, highly viscous oil, lipophilic, with low vapor pressure. It has two stereocenters with levorotatory trans stereoisomer. Both

THC and cannabidiolic acid (CBDA) formation occur due to the cyclization of CBGA via a cationic intermediate [16].

CBD was discovered by Adams et al. in 1940, but the structure of CBD was entirely found during the 1960s by Melchoulam et al. Until now, the mechanism of CBD action is not fully known [13].

2.1 Pharmacokinetics of cannabinoids

Pharmacokinetics of any drug, so cannabinoids too, consists of absorption, distribution, metabolism, and excretion. The pharmacokinetics of MC depends on the formulation given and the route of administration [20]. In 2018, Millar et al. systematically reviewed CBD pharmacokinetics (PK). They concluded that the data we have about CBD PK is limited, conflicting, and requires accurate studies [21].

2.1.1 Absorption of cannabinoids

The administration of CB via inhalation or intravenously (IV) has a similar PK to the inhalation of both CBD and THC; the peak plasma concentration is reached within 3 to10 minutes, with higher maximum concentrations than oral preparations. THC bioavailability after inhalation ranges from 10% to 35% compared to inhaled CBD, with an average systemic bioavailability of 31%. CBD and THC are highly lipophilic and have poor bioavailability [20,22].

When administrating cannabis via smoking, it is essential to estimate the dose to assess the absorption of cannabinoids. Additional uncontrolled factors in assessing the absorption of cannabinoids are the source of the plant material, the cigarette's composition, and the efficiency of smoking by the subject itself. According to The United States National Institute of Drug Abuse (NIDA), 20% to 37% of THC is delivered in mainstream smokers with pyrolytic destruction of 23% o 30% and sidestream losses of 40% to 50%. The results seem similar for smoked CBD and cannabinol (CBN), except that the plasma level of CBN seems twice as variable as the other cannabinoids [23].

The absorption of THC by inhalation is very rapid in comparison to the absorption of THC via the IV route [23]. After inhalation of THC, it can be detected in the plasma for at least one day after a single dose and 13 days in chronic users [24]. There is no difference in the plasma half-life of heavy and light users [25].

Absorption of oral THC is 90% to 95% after a single dose. Psychomotor effects occur faster with smoking THC than with taking THC via the oral route. A pilot study shows that rectal THC has twice as bioavailability as the oral form; this is associated with lower absorption and higher first-pass metabolism of the oral route [23].

2.1.2 Distribution of cannabinoids

The distribution of CB is rapid into well-vascularized organs such as the brain. The distribution can be affected by the body mass, body composition, and conditions that influence the permeability of the blood tissue barriers. Chronic use of CB can lead to their accumulation in the adipose tissue. CBD and THC have a high volume of distribution (Vd) [20].

THC distribution begins rapidly after absorption [23]. Approximately 97% of THC and its metabolites bind to plasma proteins. THC is primarily bound to low-density lipoproteins, and up to 10% is found in red blood cells (RBC) [26]. THC is lipid-soluble, and this characteristic causes a large volume of distribution, which is approximately 10 L/Kg, with the highest

concentrations found in adipose tissue and the heart. THC can cross the blood-brain barrier (BBB). Regarding the concern about the consequences of the long persistence of THC in fatty tissue, there is no evidence that THC residues stay in the brain. The THC release from fatty tissue is slow, so the collected levels are low. It is essential to mention that with chronic usage, THC will accumulate [23].

2.1.3 Metabolism of cannabinoids

Cannabinoid metabolism occurs primarily in the liver, with different metabolites predominance when using different routes of administration [23].

THC metabolism is complex and involves allylic oxidation, epoxidation, decarboxylation, and conjugation [23]. THC metabolism is primarily hepatic metabolism via cytochrome p450, the leading site of hydroxylation is carbon 11, which CYP 2CP catalyzes. CYP 2CP is the enzyme suspected to influence drug interactions [20,23]. 11-hydroxy-THC and 11-nor-9-carboxy-THC are the primary initial metabolites of THC. Most of the metabolites of THC are polar and acidic. The metabolite 11-hydroxy-THC is rapidly formed by hepatic microsomal oxidase action, and its plasma levels parallel the duration of observable drug action. THC and its metabolite 11-hydroxy are primary phase 1 product [23]. Also, due to lipophilic characteristics, THC can cross the placenta and be excreted in human breast milk [20,22].

The primary metabolism of CBD is also via hepatic metabolism. The primary enzymes in CBD metabolism are CYP2C19 and CYP3A4. CBD is hydroxylated to a 7-hydroxy cannabinoid, which goes through further hepatic metabolism followed by fecal and urinary exertion of CBD metabolites [20].

2.1.4 Excretion of cannabinoids

Both THC and CBD have a long elimination half-life [20,22].

Inhaled THC and its metabolites are eliminated via feces which account for 65%, and urine which accounts for 20%. In the urine, the metabolites are mainly acidic, while that eliminated by feces can be acidic or neutral [23]. The primary acid metabolite of THC is the psychoactive 11-nor-9-carboxy-THC, which is excreted in the urine [27]. 11-nor-9-carboxy-THC is usually the most monitored cannabinoid in forensic analysis of body fluids [28].

After an oral dose of the drug, THC and its biotransformation products are eliminated by feces and urine, with biliary excretion being the primary route of elimination [23].

2.2 The possibility of cannabinoids interactions

Until this day, there is not enough information about dose-response and drug-to-drug interaction [29]. Potential pharmacokinetic interactions exist between CBD and THC, and other drugs. Those interactions can occur via inhibition or induction of enzymes (for example, during hepatic metabolism), transporters, and pharmacodynamic drug-drug interactions [20].

One of the known interactions is the interaction between cannabis and tobacco smoking. Both of them induce the CYP1A2 enzyme. It is also known that the induction is additive when they are smoked together. This interaction might be significant for patients taking it with other drugs metabolized by CYP1A2 enzymes [20].

Inhibition of p-glycoprotein-mediated drug transport by CBD was shown in an in-vitro study. This study shows how CBD can affect the absorption and disposition of other coadministered drugs [30].

It is also known that coadministration of rifampicin, a drug used for tuberculosis treatment, which is a CYP3A4 inducer, causes a decrease in the peak plasma concentration of CBD and that coadministration of ketoconazole, an antifungal drug, which is a CY3A4 enzyme inhibitor, almost double the peak plasma drug concentration [31].

Another in-vitro study showed that CBD could potently inhibit the CYP2C19 enzyme [20].

2.3 Pharmacodynamic of cannabinoids

Most of the phytocannabinoid effects are mediated by agonist or antagonist interaction at specific receptor sites. The cannabinoid receptors and their endogenous ligand form the endogenous cannabinoid system or the endocannabinoid system (ECS). Some phytocannabinoids and their synthetic derivatives effects are non-receptor mediated, such as their effect on the immune system, neuroprotective effects in ischemia and hypoxia, and some of their effects on the circulation [22].

THC antiemetic effects are in part non-receptor-mediated. That is one of the reasons for using THC as an antiemetic in children and adults undergoing chemotherapy [22].

Cannabis causes sedation. There are significant pharmacodynamic interactions when using cannabis with other CNS depressant drugs. The use of cannabis is associated with pathological and behavioral toxicities [20].

THC causes a dose-dependent performance impairment, cardiac toxicity, and tachycardia, increasing anxiety. Some reports show that coadministration of CBD with THC reduces THC's adverse psychotropic and cardiovascular effects. CBD's adverse effects are associated with fatigue and somnolence [20,22].

The contraindications for CB therapy use are psychiatric, cardiovascular, renal, or hepatic diseases [20].

2.4 Cannabis receptors

Cannabinoid receptors CB1 and CB2 were discovered during the 90s of the last century. Both receptors inhibit G-protein coupled receptors; they are negatively coupled to adenylyl cyclase (AC). Also, both receptors have different distributions in the body region [11].

CB1 receptors are mainly found in the CNS, with the highest density in basal ganglia, hippocampus, and cerebellum, where they are localized in the presynaptic membrane. The CB1 receptors are also found on peripheral organs such as endocrine glands, heart, spleen, urinary, and gastrointestinal tracts. In contrast to CB1 receptors, CB2 receptors are found in the PNS, mainly in immune cells [11,22].

CB1 receptor activation produces the effect of cannabis on the psyche and the circulation, while CB2 receptor activation does not produce marijuana-like effects [22].

CB have different affinities to CB1 and CB2 receptors; they can act as selective agonists or antagonists. Δ9- THC has almost equal affinity at CB1 and CB2 receptors but has higher efficacy to CB1 receptors, with lower efficacy to CB2 receptors, where it can act as a partial agonist, agonist, or antagonist [22].

Some preclinical and clinical observations show that interactions with the cannabinoid receptors CB1 and CB2 alter the molecular pathways responsible for disease development.

This is one reason why CB are a candidate for use in autoimmune diseases. In specificity, CBD which lacks psychotropic effects [13,32].

CBD modulates receptors in CNS, such as the CB1 receptor, which acts as a negative allosteric modulator. CB2, peroxisome proliferator-activated receptor gamma (PPARγ), serotonin 1A receptor (5-HT1A), transient receptor potential cation channel subfamily V member 1 (TRPV1), and G protein-coupled receptor 55 (GPR55) [13].

Even though CBD acts as a weak agonist on CB2 receptors, it is shown that activation of the CB2 receptor provides anti-inflammatory and anti-oxidative effects. Also, CBD may act as an inverse agonist, which explains its anti-inflammatory properties inhibiting immune cell migration [13].

In vivo assays shows that some of the CBD's biological activity can be blocked by pharmacological inhibition of the PPARγ, a nuclear receptor; this shows that some of the CBD metabolites have activity on the PPARγ [13,33]. Also, it was shown that CBD action on TRPV1 causes analgesic effects, and the action of CBD on the 5HT1A receptor help in relieving anxiety [13,34]. CBD acts as a functional antagonist on GPR55, explaining CBD's anticonvulsant activity [13].

2.5 Endocannabinoid system

ECS is a family of endogenous lipid molecules, and arachidonoylethanolamide, also known as anandamide (AEA) and 2- arachidonylglycerol (2-AG) are the most important ones among them. The endocannabinoids are released from the cells upon a stimulus, and then they are rapidly deactivated by the cell uptake mechanism [20].

The body's endocannabinoid levels are regulated by enzymes, such as fatty acid amide hydrolase (FAAH), which metabolizes AEA, and monoacylglycerol lipase (MAGL), which metabolize 2-AG [13].

ECS alterations are seen frequently in neurological diseases. Animal models show that genetic and pharmacological changes in the ECS system have a significant role in developing neurodegenerative disorders and demyelinating diseases [13,35].

3. Cannabis effect on the immune system

Endocannabinoids can be found on cells of the immune system such as basophils, lymphocytes, macrophages, monocytes, and dendritic cells. Endocannabinoids are enzymatically produced and released from the immune cells according to their need. The functional activity of the immune system can be changed due to both CBD and CBN. In general, cannabis and the active CB act as an immune-modulating substance by affecting the immune cells, such as T-cells, B-cells, monocytes, and microglia leading to a decrease in pro-inflammatory cytokine production with an increase in anti-inflammatory cytokines production [36].

Cannabigerol (CBG) is a natural phytocannabinoid that acts as an AEA reuptake inhibitor, but it has anti-inflammatory action when combined with CBD. It causes a reduction of tumor necrosis factor (TNF) expression, and it up-regulates the levels of cytokines such as interleukin (IL)-10 and IL-37. CBN causes inhibition of cyclooxygenase (COX), lipoxygenases (LOX), and CYP450, while Cannabichromene (CBC) is a CB2 antagonist. The main effects of CB receptor binding on the immune system are a decrease in activation of the immune system and

the migration of the immune cells due to apoptosis induction, inhibition of mobilization of immune cells, and suppression of transcription factors and cytokine release [12].

The highest amount of CB1 and CB2 expression in immune cells is in the B-cells. It was shown that CB could decrease antibody production. CB regulates T-cell proliferation by increasing apoptosis [37]. Cannabinoid receptors are also found in macrophages and monocytes; activation of CB2 receptors causes monocytes migration inhibition while inducing phagocytosis with chemokine release [6,12].

Immunomodulation is primarily regulated by the inhibition of immune cell mobilization. The endocannabinoids decrease neutrophils and macrophages' migration to the inflammation site. Mast cells activation is downregulated by CB1 receptors agonists. Also, CB1 decreases the inflammatory symptoms mediated by a hypersensitivity reaction. CBD causes a decrease in neutrophil number [12,38].

The induction of regulatory immune cells is another mechanism by which CB can control immune function. For example, CBD, THC, and CB2- selective CB induce regulatory phenotype by changing the balance from inflammatory TH_{17} to regulatory T-cells; this can be seen by anti-inflammatory induction and reducing pro-inflammatory cytokines [38,39].

Suppression of transcription factors in immune cells by CBD causes a reduction in IL-2 in T-cells; IL-2 is an essential cytokine for T-cells activity and differentiation; it is synthesized by T-cells, Natural killers (NK) cells, and by dendritic cells (DC). The involvement of both CB1 and CB2 leads to a reduction in IL-2 production [6]. Maresz K et al. have shown through an in-vivo model of experimental autoimmune encephalomyelitis that T-cells in the CNS that lack CB2 had low levels of apoptosis with a high rate of T-cells proliferation and production of inflammatory cytokines; the result was severe clinical disease [40].

It seems that the endocannabinoid system significantly influences immune system activity and function. All of the above information must be considered when considering cannabis as an immunomodulator in autoimmune diseases [6,12].

4. Use of cannabinoids in medicine

As mentioned before, CBD is one of the more abundant CB, second only to Δ^9- THC. CBD lacks the psychoactivity that Δ^9THC causes. The term CB includes both groups' phytocannabinoids, endocannabinoids, and their synthetic analogs. It is well known that ECS involves in physiological processes such as appetite stimulation, energy balance, blood pressure, pain relief, nausea and vomiting control, immune response, etc. It is known that in pathological conditions, ECS has a protective role in developing some disorders. It seems that changes in endocannabinoid levels can be related to some neurological diseases, such as MS, Parkinson's disease, and Huntington's disease. It also seems that changes in ECS are associated with cancer by affecting the growth, migration, and invasion of some tumors [41].

Today there are ongoing clinical studies on cannabinoids base therapy and drugs for some medical conditions [6,41].

4.1 Medical cannabis formulations that are in use today in medicine

The first group of MC formulations that will be mentioned is the single-molecule synthetic pharmaceutical. This group includes Dronabinol, which is FDA-approved; it has synthetic THC suspended in sesame oil. This drug is distributed in the form of a capsule. The indications

for the usage are chemotherapy-induced vomiting, nausea, and appetite stimulants for AIDS patients. The second drug in this group is Nabilone. It is also approved by the FDA. It is a synthetic compound that mimics THC. Its current indications are treatment chemotherapy-induced nausea and vomiting therapy [19].

The second group of MC formulations is oral cannabis. Nabiximols (known as Sativex) is a natural cannabis extract with a ratio of 1:1 of THC:CBD. This drug activates both CB1 and CB2 receptors. This drug is given in the form of a spray, and its indication is MS-related spasticity. This group's second drug is Cannador, a natural cannabis extract containing a 2:1 ratio of THC and CBD. It is being used in clinical research in Europe. Epidiolex is an oral solution formulation that is being used in treatment-resistance epilepsy syndrome [19].

4.2 Medical cannabis use in autoimmune diseases

CB has immunomodulating characteristics on cells of the immune system, and these immune cells play a part in the pathogenesis of several autoimmune diseases such as Crohn's disease, ulcerative colitis, immune thrombocytopenia, rheumatoid arthritis (RA), and MS. Cannabis therapy needs to be tailored for each of those autoimmune diseases. The endocannabinoid system, especially CB2 receptors activation, is a target for the therapy of diseases that occur due to the involvement of immune cells in their pathogenesis [6,42].

The expression of CB receptors can be found in synovia of RA patients with high levels of endocannabinoids. Those facts are the indications of using MC as a therapeutic agent in RA disease [43]. CBD causes an increase in the intracellular calcium level and activity and production reduction of IL-6, IL-8, and matrix metallopeptidase 3 (MMP3) [44].

Preclinical studies show that the ECS has a role in regulating intestinal inflammation. This finding supports the use of MC in treating inflammatory bowel diseases (IBD) [45]. Immunohistochemical studies have shown that during the inflammatory flares in IBD, there is an increase in CB2 receptors; this amply that ECS has potential for therapeutic targets [12].

4.3 Medical cannabis use in pain

CBD analgesic potential was investigated in preclinical and clinical studies. Those studies examined the anti-nociceptive effect of both CBD and CBD combined with other compounds in some pain-related diseases. Clinical trials confirmed the positive effects of CBD confirmation. In those clinical trials, it was proven that CBD is safe in humans. Transdermal CBD-containing gel used in patients with peripheral neuropathy showed diminished pain [46].

Some preclinical studies have shown that the systemic application of cannabinoids receptors ligand causes an analgesic effect in the case of acute and chronic pain models [47].

4.4 Medical cannabis use in neurologic disorders

The most supportive evidence for the use of MC in neurological disorders is the use of CBD for epilepsy therapy. A randomized study showed that CBD helps in the reduction of seizure episodes on a monthly seizure scale of 0-3 in patients with secondary generalized epilepsy. [48]. Later, another open-labeled study examined the CBD effect in patients with childhood-onset seizures and febrile infection-related epilepsy. This study showed a clinically significant reduction in seizures in most of the patients who participated in the study [49]. Recently it was proven that CBD is effective in treating Dravet and Lennox-Gastaut syndromes [48].

Investigation of CBD effects on Parkinson's and Huntington's diseases showed that CBD had no effect on the improvement of Huntington's disease-related symptoms [48]. In Parkinson's disease, the clinical trials using CBD for treating Parkinson's symptoms look promising [50].

4.5 Medical cannabis use in oncology patients

Cannabinoid-based therapies are given to palliative oncology patients as part of analgesic and antiemetic effects [51]. Few new in vitro studies found that some cannabinoid-based treatments potentially have antitumor effects [51,52].

4.5.1 The use of cannabis in treating chemotherapy-induced nausea and vomiting

In 1975 Sallan et al. examined the clinical efficacy of cannabis in treating chemotherapy-induced nausea and vomiting (CINV). They observed that administration of oral Δ^9-THC had antiemetic properties in chemotherapy patients [41]. A preclinical study by Daramni showed that the inhibition of CB1 receptors and not CB2 receptors, with specific antagonists, causes emesis. In contrast, selective agonists to BC1 receptors intraperitoneally administered reversed it [53]. Regarding CBD, another preclinical study showed that only at low doses in a CB1 independent manner CBD could reduce emesis induced by lithium chloride or cisplatin in shrews [41].

A randomized, double-blinded study showed that Nabilone in a 1 mg dose helped control CINV more efficiently than prochlorperazine or domperidone when given orally, the night before, and 8 hours after the chemotherapy [54].

A clinical study performed by Abrahamove et al. showed that Δ^8-THC, a cannabis plant with low psychoactive activity, was given orally 2 hours before chemotherapy and then every 6 hours for 24 hours after chemotherapy, which prevented vomiting in these children with Hodgkin's lymphoma, Burkitt lymphoma, and acute lymphoblastic leukemia [55].

4.5.2 Use of cannabis in treating cancer pain

The pain in cancer patients can occur through different mechanisms such as chemotherapy, a side effect of medication, the tumor itself, or postoperative pain [9]. Pain in oncology patients is usually treated with the three-step analgesic ladder, in which non-steroidal anti-inflammatory drugs (NSAID) and opioids are the most commonly used [56]. Pain is associated with a decrease in quality of life, sleep disruption, and an increase in anxiety and depression. The treatment of pain in oncology patients is a challenge that leads to trying and finding new treatment options for pain, and one of those options is cannabis-based medication [9].

A clinical study performed on oncology patients suffering from cancer-related pain compared the efficacy of THC:CBD extract, THC by itself, and a placebo group. The study result showed a significant change in the numerical rating scale (NRS) in favor of THC: CBD compared to the placebo group. There was no change in NRS of the group who got THC alone [57].

Even with all the results from clinical studies, the use of cannabis as a single therapy for pain in oncology patients is still not recommended [9].

4.5.3 Use of cannabis in treating cachexia due to cancer

Cachexia is a multifactorial syndrome characterized by the loss of skeletal muscle mass, which cannot be fully reversed by conventional nutritional support. A critical aspect of cachexia is an absence of appetite [58]. Concerning cachexia, two studies showed no difference between appetite and nausea between the cannabis and placebo groups. A third study showed that THC is superior to the placebo by increasing the patients' appetite [9].

Table 1. Current clinical trials of synthetic and botanical CB - based therapies in immune-related diseases modified according to Almogi-Hazan et al. [6]

Indication	Treatment	BOT/SYN	phase	status
Inflammation - an observational study	Cannabis	BOT	NA	Recruiting (August 2018)
Cachexia in advanced cancer	THC/CBD	SYN	Phase 3	No recruiting yet (May 2020)
Glioblastoma	THC/CBD	NA	Phase 1-2	Not recruiting yet (April 2020
Nausea and vomiting induced by chemotherapy in pancreatic cancer	Dronabinol	SYN	Phase 3	Recruiting (April 2020)
Peripheral neuropathy induce by chemotherapy	Cannabinoids	SYN	Phase 2	Recruiting (September 2019)
Solid cancer tumor	Cannabis	BOT	NA	Recruiting (March 2020)
RA	THC/CBD	BOT	NA	Temporarily halted (October 2018)
IBD	Nabilone	SYN	NA	Not recruiting yet (March 2019)
SLE	JBT-101	SYN	Phase 2	Recruiting (March 2020)
DM type 2	Cannabis	BOT	NA	Recruiting (March 2020)
Spasticity in MS	BX-1	BOT	Phase 3	Recruiting (January (2020)

Abbreviation: BOT-botanical, DM-diabetic Mellitus, IBD- inflammatory bowel diseases, MS-multiple sclerosis, NA-not available, RA-rheumatoid arthritis, SLE- systemic lupus erythematosus, SYN-synthetic

5. Multiple sclerosis

5.1 Definition of multiple sclerosis

The most common chronic demyelinating autoimmune disease of the CNS is MS, affecting more than two million people worldwide. MS is part of a group of demyelinating diseases and is categorized as a primary inflammatory demyelinating disease of the CNS [13]. In the early stage of MS, the neurological deficits are primarily reversible, but there is progressive neurological deterioration with the advance of the disease [21].

The characteristic of MS is inflammation-related injury, mainly to the brain's and spinal cord myelin structures and nerve composition, which causes axonal damage and neurodegeneration [13].

5.2 Epidemiology and prevalence of multiple sclerosis

MS is a disease that is more common in women than in men and most commonly diagnosed in adults between 20 and 45 years of age. MS etiology is unknown and has a heterogeneous and unpredictable course of development [21]. MS is also the leading cause of non-traumatic neurologic disability in young adults [13].

5.3 The classification of clinical phenotypes of MS

MS is traditionally divided into three clinical phenotypes based on the clinical course of the disease [8,13,21].

In actual clinical practice, this division can adequately present the complexity of the disease phenotypes due to the overlapping between the clinical features of the phenotypes [59].

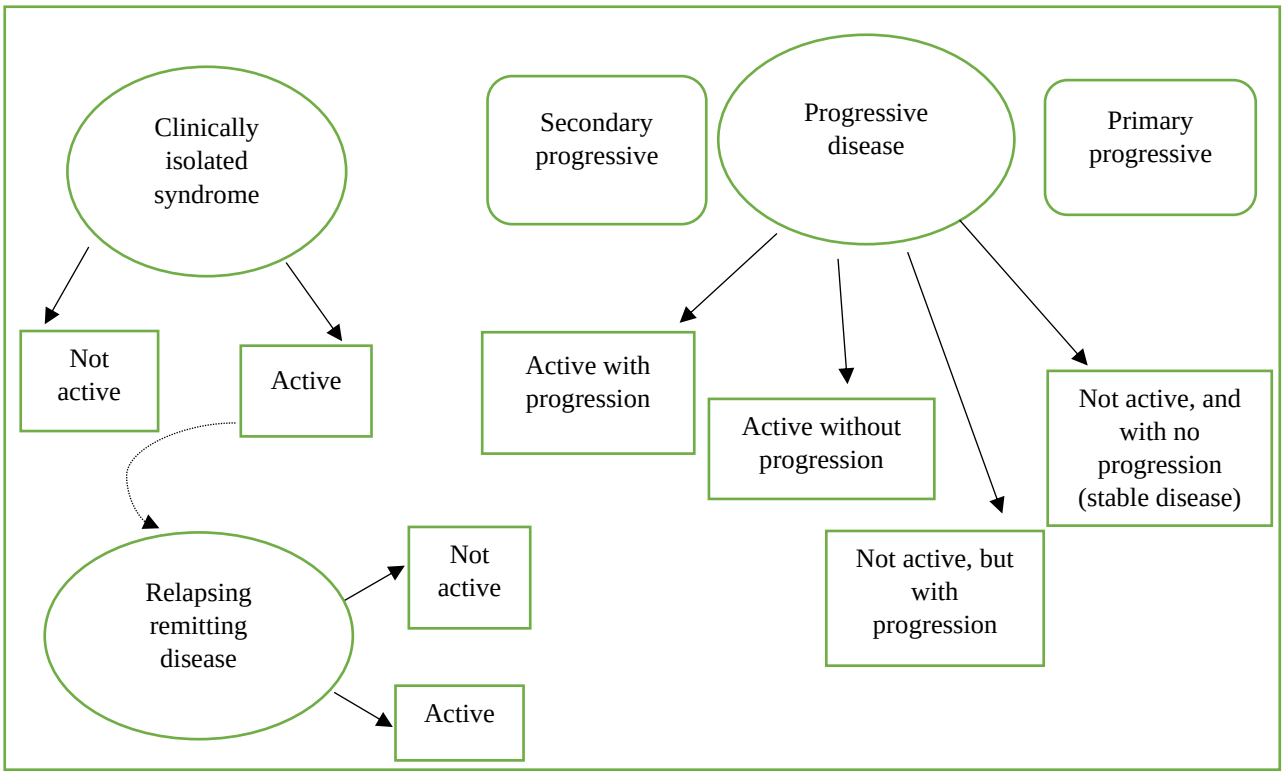

Figure 1. MS phenotype description modified accordining to [60]

5.3.1 Clinically isolated syndrome

Clinically isolated syndrome (CIS) is the initial clinical presentation of MS disease. Characteristics of inflammatory demyelination that can fit MS, but at that time of presentation, they do not fulfill the dissemination criteria, can be seen in CIS [60]. CIS is defined as a solitary episode of neurological disturbance due to the demyelination process in the absence of fever, infection, or encephalopathy. The neurology disturbance is monophasic, peaked within days to weeks, lasting at least 24 hours. The most common presentation of CIS includes monocular optic neuritis, focal supratentorial syndrome, brainstem or cerebellar syndrome, or partial myelitis [61]. See table 2 for more details about the signs and symptoms.

Radiologically isolated syndrome (RIS) applies when performing magnetic resonance imaging (MRI) for the brain or spine in other indications and discovering incidentally finding of demyelinating lesions in typical distribution for MS with no history of CIS [62].

Table 2. The common sites, signs, and symptoms of the clinically isolated syndrome are modified according to Travers et al. and Bennett et al. [61,63]

Site of lesion	Condition	Symptoms	Signs
Optic nerve	Optic neuritis- inflammation of an optic nerve	Pain with eye movement and blurred vision	Decrease monocular visual acuity and color desaturation. A fundoscopy exam can be normal, or swollen optic disc may be shown
Cerebrum	Focal supratentorial syndrome	It depends on the cerebral location	
Cerebellum	Cerebellar disease	unsteadiness	Ataxia; horizontal or torsional gaze-evoked nystagmus
Spinal cord	Partial myelitis affecting pyramidal tracts	Upper and lower limb weakness	Pyramidal distribution weakness
	Partial myelitis affecting spinothalamic, posterior columns	Uni/bilateral limb numbness or paraesthesias; Lhermitte's phenomenon	Sensory level
	Any spinal cord lesion	Urinary frequency, incontinence, constipation, and erectile dysfunction	
Brainstem - medial longitudinal fasciculus	Internuclear ophthalmoplegia	Blurred vision or double vision	Internuclear ophthalmoplegia
Brainstem- pyramidal tracts, spinothalamic and posterior columns	Similar to spinal cord lesions		

5.3.2 Relapsing-remitting multiple sclerosis

The second phenotype of MS is relapsing-remitting multiple sclerosis (RRMS), the most common form of MS, and it affects 85% of patients with MS (21). This phenotype is defined by an acute exacerbation, from which the patients usually completely or incompletely recover, with relative clinical stability between exacerbations. The exacerbation is also known as relapse. The international panel diagnosis of MS defines relapse as "patient-reported symptoms" or objectively observed signs typical for an acute inflammatory demyelinating event in CNS with a duration of at least 24 hours [(8)].

The diagnostic criteria of RRMS have been based on the patient clinical features of typical symptoms and signs related to demyelinating lesions and MRI that is consistent with MS [(8)].

5.3.3 Progressive multiple sclerosis

Progressive MS is defined as the deterioration of neurological function that is associated with new symptoms and signs that progress for at least one year. Disease progression occurs primarily due to neurodegeneration, with widespread neuroaxonal loss in the white and grey matter.

5.3.3a Secondary progressive multiple sclerosis

Secondary progressive multiple sclerosis (SPMS) is the second stage of MS. It is defined as the gradual progression of the RRMS form of the disease that occurs after the signs of remission of symptoms no longer occur. SPMS occurs in 40% of RRMS patients, usually 20 years from the MS onset [(8,21)].

Gradual neurologic function decline that most commonly occurs predominantly in the CNS areas involved during the disease's relapse course is one of the characteristics of SPMS. It is hard to define when the point of transition to SPMS occurs, and this transition will often be recognized in retrospective history taking, usually, years after the progression occurs [(8)].

5.3.3b Primary progressive multiple sclerosis

Primary progressive multiple sclerosis (PPMS) affects 10% of patients with MS. PPMS is characterized by progressive neurological function decline from disease onset. The most common clinical presentation of PPMS is progressive myelopathy [(8,21)].

In order to determine that a person has PPMS, according to 2017 McDonald's criteria, at least one year of progression of clinical disease and at least two of the following condition are needed: lesion dissemination in space (DIS) in the brain, DIS in the spinal cord, or positive cerebral spinal fluid (CSF) [(8)].

5.3.4 Progression and activity assessment of multiple sclerosis

MS phenotypes can generally be described as relapsing or progressive following the clinical features and history. This division does not provide information on the ongoing disease, and disease activity detected by imaging or clinical relapses and a disability progression are the essential tools [(59,60)]. Proof of disease activity and clinical progression reflects ongoing inflammatory or neurodegenerative processes and can impact the prognosis, therapy, clinical trial designs, and outcomes [(60)].

Relapsing MS disease activity is assessed by annual clinical evaluation and brain imaging criteria, while the progression of MS disease activity is examined by annual clinical evaluation [(60)].

For example, PPMS patients with acute attacks are considered to have PP active MS. In contrast, patients who do not have an acute attack and have no MRI activity are considered to be PP, not active MS [60].

Progression assessment is another critical aspect of the disease course. It assesses the presence or absence of the progression, independently of relapses in patients with progressive disease course, either PPMS or SPMS. It is important to note that progressive disease does not progress uniformly and that the disease can stay stable over time [60,64].

Progression of MS is determined annually by the history of the disease and objective measures of change. Patients with PPMS who did not progress over a year are classified as having no progressive PPMS. Patients with SPMS who gradually worsened and have gadolinium-enhancing lesions in MRI are classified as active and progressing SPMS [60,64].

5.4 Multiple sclerosis pathology

MS is characterized by disseminated plaque-like sclerosis. The lesion in MS can appear all over the CNS, and they are most recognized in the white matter, where they look as focal areas of demyelination, inflammation, and glial reaction [65].

According to MRI and pathological assessment, the earliest stages of white-matter demyelination are heterogeneous, and those lesions grow over months. The analysis of the active lesions over time and space implies that a single immune-effector mechanism is dominant in each patient [65,66].

Demyelination in MS occurs not only in the white matter but also in the gray matter. More than half of the cortical lesions occur in the perivascular area. In some of those cortical lesions, the inflamed vessel can be found close to the leukocortical junction, where the demyelination affects the juxtacortical white matter. The rest of the cortical lesions appear to arise inward from the pial surface of the brain [65,67].

The leading causes of clinical disability are spinal cord lesions. Atrophy of the spinal cord atrophy occurs due to focal inflammatory demyelination and neuroaxonal degeneration. MRI imaging can demonstrate these lesions [21,65].

The optic nerve is another primary target in MS that is affected as a part of the CNS lesions. Assessment of retinal damage is done by optical coherence tomography. This test shows substantial thinning of the retina nerve fibers and ganglion-cell layers. Injury to axons in the optic nerve is the reason for the thinning [65,68].

5.5 Pathogenesis of multiple sclerosis

The main characteristics of MS, as mentioned before, are inflammation, demyelination, and neurodegeneration. All of the tissue damage occurs due to autoreactivity of myelin-specific T lymphocytes entering the CNS, which leads to a dynamic interplay between the immune system, glia, and neurons [21,65].

A big part of our understanding of the immunopathogenesis of MS is due to studies of experimental autoimmune encephalomyelitis (EAE). EAE is an animal model of CNS inflammatory demyelination that can be induced by peripheral immunization with myelin protein components. EAE shares similar histologic features to MS, such as active demyelination, oligodendrocytes loss, and axonal loss, which are all believed to be mediated by myelin-specific T-cells [7].

The pathogenesis of MS is thought to involve a breach of self-tolerance toward myelin and other CNS antigens, which ultimately leads to persistent peripheral activation of autoreactive T-cells. With their activation, the T-cells migrate across the blood-brain barrier [7].

In the CNS, the T cells undergo reactivation by local antigen-presenting cells. This reactivation leads to the activation of the inflammatory cascade and releases of pro-inflammatory cytokines such as interferon-gamma (INF-γ) and tumor necrosis factor-alfa (TNF-α) that activate more immune T cells and B cells. Constant activation of macrophages leads to oligodendrocytes death, which causes more demyelination and tissue damage [10,69]. The "epitope spreading" phenomenon occurs due to additional targets for self-reactivity T-cells, which occurs due to exposure of sequestrated myelin autoantigens from the local inflammation and demyelination [7].

In the early stage of MS, axons are mostly preserved, but irreversible damage to axons occurs with the progression of the disease, which may cause disability progression [7,70].

5.6 The clinical features of multiple sclerosis

Usually, MS is suspected when a patient presents with CIS. This presentation can either be mono- or poly-symptomatic, depending on the location of the lesion in the CNS [70]. The sign and symptoms of MS can be due to the involvement of sensory, motor, visual, and brainstem pathways. MS symptoms and signs include fatigue, spasticity, gait instability, Lhermitte's sign, Uhthoff's phenomenon, urinary retention or urinary incontinence, or cognitive decline [10].

In most cases, the patients initially present with a remitting progressive episode; the first clinical event is CIS, which typically presents as optic neuritis, incomplete myelitis, or brainstem syndrome [71]. Focal weakness, numbness, tingling, or unsteadiness in the limb are the typical initial complaints of MS patients [72].

Optic nerve neuritis, brainstem, and spinal cord syndrome are the most common clinical presentation of MS; other less common presentations, for example, dominant parietal lobe syndrome, which is a part of cortical presentions, also exist. Cognitive impairment is seen in all MS phenotypes and usually can be seen early in the disease. Relapses in MS occur subacutely over hours to days, and then reaching a plateau continues for weeks and slowly recovers [8,70]. MS patients can have pain, muscle spasms, headaches, fatigue, and depression. Those symptoms' appearance depends on the lesion's location [73,74].

5.6.1 Neurological findings on examination of multiple sclerosis patients

On the neurological examination, cerebellar signs will be present in one-third of cases. Nystagmus, dysarthria, and limb ataxia are common findings. In 10 to15% of MS cases, gait ataxia is the presenting complaint; this usually occurs because of cerebellar involvement [72].

5.6.2 Features of optic neuritis features

Optic neuritis is the inflammation of the optic nerve and is a common cause of acute optic nerve injury. There are many causes of optic neuritis, and MS is one of them [63]. The typical presentation of optic neuritis due to MS is an acute unilateral, painful reduction in the visual acuity that peaks within a few days and starts to recover within a few weeks. Bilateral presentation can also occur. MS-related optic neuritis is characterized by the presence of pain with eye movements, and the pain is usually mild to moderate in its nature [8]. On physical examination, impairments in acuity, low contrast vision, and color discrimination are common

findings. Also, it is common to find central scotoma. Funduscopy examination can be normal or show optic disc swelling [8,61].

5.6.3 Features of brainstem or cerebellar syndrome

Diplopia is the most common brainstem presentation of MS. Diplopia occurs most commonly due to internuclear ophthalmoplegia or due to sixth nerve palsy. The diplopia can be bilateral [8]. Other typical brainstem or cerebellum features are ataxia and gaze-evoked nystagmus, sixth nerve palsy, paroxysmal phenomena, and multifocal signs [61,71]. In relapsing MS, the onset of brainstem or cerebellar symptoms is over hours to days. Around 15% of patients with PPMS present with progressive cerebellar or brainstem syndrome, characterized by gradually worsening ataxia [8].

5.6.4 Features of spinal cord syndrome

The typical features of spinal cord syndrome are partial transverse myelitis, Lhermitte's syndrome, sphincter symptoms, asymmetric limb weakness or paraesthesias, constipation, and erectile dysfunction [61,71]. Acute onset of partial transverse myelitis is one of the common presentations of MS. Typically the sensory symptoms are consistent with the involvement of the dorsolateral cord. Symptoms of transverse myelitis can be uni or bilateral at or below the lesion level, depending on the extent of the lesion. In MS, the lesions occur most commonly in the cervical cord. MS-related myelitis occurs in the course of days and spontaneously begins to recover over a few weeks. Brain MRI is helpful for diagnosis. For more details, see the chapter on diagnosis [8].

5.6.5 Features of cognitive impairment

Cognitive impairment is a typical feature of MS phenotypes; it is more common in progressive diseases. Cognitive problems usually present with other MS symptoms. PPMS can present with cognitive dysfunction with no apparent simultaneous focal neurological symptoms [8].

5.6.6 Other symptoms of multiple sclerosis

MS patients can suffer from fatigue, depression, muscle spasms, spasticity, headaches, pain, and depression. Those symptoms depend on the lesion location in the CNS [9].

In this section, other common symptoms of MS will be mentioned.

5.6.6a Spasticity

The defenition of Spasticity is as an abnormal increase in muscle tone secondary to lesions affecting the descending corticospinal and para-pyramidal tracts. Spasticity has two components: a constant tonic component and an episodic phase component. Limb stiffness and hypokinesia occur as a consequence of the tonic component. The tonic spasm and hyperkinetic movements are the consequence of the phasic component. Spasticity can cause impairment of residual function and pain and limit the range of motion [75].

5.6.6b Pain

MS-related pain affects two-thirds of MS patients. In 43% of cases, the pain will be present as a headache, in 26% of cases as neuropathic pain, 20% as back pain, 15% as painful spasm, and 4% as trigeminal neuralgia [9].

5.6.6c Tonic spasm

Spinal cord syndrome in MS can cause tonic spasms. Tonic spasms, also called paroxysmal dystonia, are the second most common movement disorder in MS after tremors. Tonic spasms episodes can happen up to 100 times a day for a period of several weeks, and those episodes last from 30 seconds to 5 minutes. The tonic spasms consist of asymmetric extension posturing of the legs and arms with opisthotonus and facial contractions. Those tonic spasms can be painful [75,76].

5.6.6d Fatigue

MS-related fatigue is prevalent and affects approximately 80% of MS patients. In up to 65% to 70% of cases, fatigue is severe and tends to persist over time. MS-related fatigue can be divided into primary and secondary. The term primary fatigue is applied when fatigue appears without a known cause and is specific to MS. While the term secondary fatigue is applied when fatigue appears due to other conditions [75,77].

The cause of MS-related fatigue can be depression, sleep disorders, pain, muscular spasms, bladder dysfunction that cause nocturia, and medication-related fatigue [77].

5.6.6e Multiple sclerosis-related depression

Depression is defined as a syndrome that occurs across a dimension of symptom severity. Clinical significant depressive symptoms occur in approximately 20% to 40% of MS patients [78]. Depressive disorders influence MS patients' quality of life; the depressive disorder frequency also increases with disease progression [79].

5.7 Comorbiditys of multiple sclerosis

Any other disease that coexists in an individual with a given index disease that is not a complication of the primary disease is the definition of comorbidity. Some comorbidities are more common in MS patients, such as depression and anxiety, hypercholesterolemia, chronic lung diseases, hypertension, and ischemic heart disease. Autoimmune comorbidities diseases such as Diabetes Mellitus type 1, psoriasis, and IBD [80].

5.8 Diagnosis of multiple sclerosis

Diagnosis of MS cannot be made by single diagnostic tests and relies upon clinical presentation, neuroimaging, and in some cases, CSF analysis and evoked potential studies [7].

In order to make an MS diagnosis, there must be clinically and radiological presentation of dissemination in space (DIS) and dissemination in time (DIT). MRI can detect the presence of brain and spinal cord lesions in MS [59,70]. An MRI of the brain in MS patients shows an ovoid, well-circumscribed, perpendicular to the ventricles lesions in characteristic locations such as periventricular, juxtacortical, and infratentorial. Spinal cord lesions in MRI are also well-circumscribed and relatively small, often with spinal cord involvement [8].

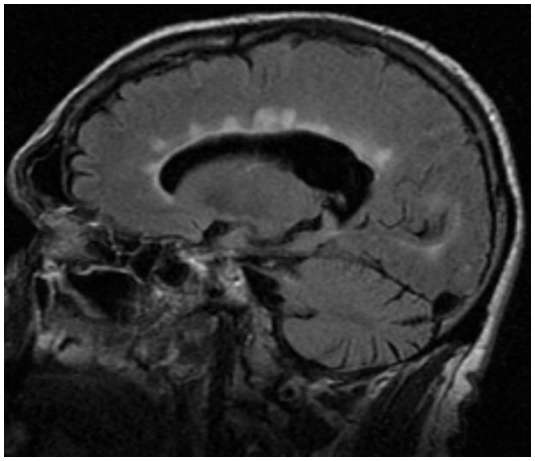

Figure 2. Single parasagittal FLAIR image demonstrating multiple periventricular demyelinating plaques extending radially away from the body of the lateral ventricle. These are characteristic of Dawson's fingers in a patient with known multiple sclerosis [81]

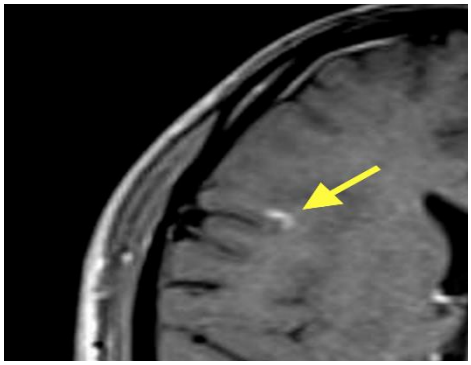

Figure 3. In the lateral aspect of the right frontal lobe, a juxtacortical lesion demonstrates contrast enhancement [82].

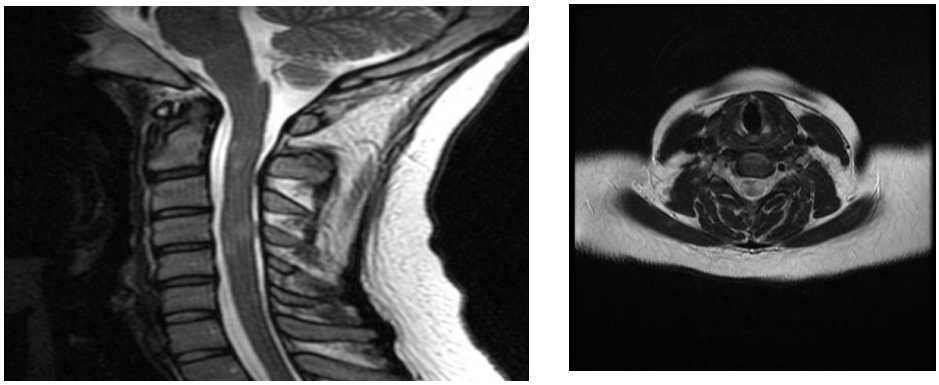

Figure 4. MRI shows multiple hyperintense cord lesions, some of which enhance peripherally following gadolinium administration. The cord is mildly expanded, secondarily to the lesions and cord edema [83].

McDonald's criteria classify MS phenotypes diagnosis according to the clinical presentation of the disease [8]. See table 3 below. McDonald's criteria are a great tool in helping diagnose MS. It is essential to mention that they can be accounted for when used in the appropriate clinical context; they must be applied to patients with CIS [59].

Table 4. revision of 2017 McDonald criteria for diagnosis of MS in patients with an attack at onset modified according to Thompson et al. [84]

Clinical presentation		Additional information that is necessary for MS diagnosis
Number of clinical attacks	**Number of lesions with objective clinical evidence**	
≥ 2	≥ 2	None*
≥ 2	1 as well as clear-cut historical evidence of a previous attack that involves a lesion in a distinct anatomical location ◘	None*
≥ 2	1	DIS showed by additional clinical, suggesting a different CNS site or by MRI▪
1	≥ 2	DIT is shown by an additional clinical attack or show of CSF-specific oligoclonal bands●
1	1	DIS is shown by the additional clinical attack suggesting a different CNS site or by MRI▪ ALSO DIT showed by additional clinical attack or by MRI⁜ or shows of CSF-specific oligoclonal bands●

Abbreviation: CNS- central nervous system, CSF- cerebrospinal fluid, DIS- dissemination in space, DIT- dissemination in time, MRI- magnetic resonance imaging, MS- multiple sclerosis
* -None- no additional tests are needed to show DIS and DIT.
◘- clinical diagnosis based on the objective clinical finding for two attacks is the most secure.
▪- MRI criteria for DIS are found in table 4.
⁜- MRI criteria for DIT are found in table 4
●- the presence of CSF-specific oligoclonal bands does not show DIT per se, but it may substitute for the need to show DIT.
An explanation for diagnosis: if the 2017 McDonald criteria are satisfied, and there is no other explanation for the clinical presentation, then the diagnosis is MS. If McDonald's criteria are not fully met, but the suspicion to MS is based on CIS, then MS is a possible diagnosis.

Table 4. revision of McDonald's diagnostic criteria 2017 for MS modified according to Oh et al. [59]

DIS	The presence of at least one lesion in at least two out of four CNS areas: periventricular, cortical or juxtacortical, infratemporal[a], and spinal cord[a]
DIT	A new T2 and or Gd- enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of baseline MRI
	The simultaneous presence of asymptomatic Gd- enhancing and non-enhancing lesions at any time
	In patients fulfilling DIS, the presence of OB in CSF could demonstrate DIT allowing MS diagnosis

Abbreviation: CNS- central nervous system, CSF- cerebrospinal fluid, DIS- dissemination in space, DIT- dissemination in time, Gd- gadolinium, MS- multiple sclerosis, OB- oligoclonal band.
[a] if an individual has a brainstem or spinal cord syndrome, the symptomatic lesions are NOT excluded from the criteria and Can contribute to lesion count (differ from the 2010 criteria)

As part of the routine, blood tests as part of routine diagnostic workup are made. Autoantibodies must be checked only when the presenting symptoms imply the presence of other autoimmune diseases [59].

In patients suspected of having MS, lumbar punction needs to be done to support the diagnosis and provide a prognostic profile baseline. Also, standard laboratory tests are needed to exclude other diseases [8,59]. The basis of performing CSF analysis in the diagnostic procedure is searching for inflammatory markers, IgG oligoclonal bands, and or an elevated IgG index. In approximately 85% of MS patients, there is evidence of inflammatory markers in CSF analysis [7].

Evoked potential studies are done to look for clinically silent lesions in the visual, brainstem, or spinal cord pathways [7].

5.9 Multiple sclerosis treatment

Today strategies for treating MS can be divided into treating an acute attack, eliminating or reducing disease symptoms, and reducing the biological activity of the disease that is done through disease-modifying therapies (DMTs). Modulation or suppression of immune function is how disease-modifying therapies act and change MS course. These DMTs have anti-inflammatory activity mainly in MS relapsing stage. DMTs also decrease relapses, reduce the accumulation of lesions seen in MRI, and delay the appearance of disability [85].

In general, the treatment for MS is divided into three categories. These categories are acute relapse attacks, disease-modifying treatment (DMT), and symptomatic treatment [86].

5.9.1 Management of acute relapse in multiple sclerosis

One of the difficulties in managing MS relapse attacks is distinguishing whether the attack is a true relapse or an exacerbation or fluctuation of the disease due to the already existing demyelinating lesions [87]. Gadolinium-enhancing MRI can show new lesions up to 6 weeks after relapse onset. In case of moderate or severe functional severity, a high dose of methylprednisone needs to be considered. Even though corticosteroids are not disease-specific DMT, they shorten the relapse duration [86].

5.9.2 Multiple sclerosis disease-modifying treatments

The aim of DMT is no evidence of disease activity, which is demonstrated by the combination of the absence of clinical disease activity, including no relapses or progression of disability, and absence of MRI activity with no new T2 or Gadolinium enhancing lesions [86]. Also, the goal of DMT is to decrease the number, severity, and duration of relapses, maintain remission, and slow the progression [88].

Due to the lack of proof for combination therapy, DMT is used one at a time [61]. DMT for RRMS are medium efficacy therapies: β-interferons, glatiramer acetate, teriflunomide, and dimethyl fumarate, while fingolimod, cladribine, natalizumab, ocrelizumab, ofatumumab, and alemtuzumab are considered to be high efficacy treatment. [86]. DMT for PPMS is ocrelizumab which reduces the annualized relapse rate (ARR) when given every six months. DMT for SPMS is siponimod which modestly slowed disability accumulation in those patients. For more information, see table 5 below.

Table 5. DMT, which are licensed for MS modified according to Travers et al. [61]

Name of the drug	mode of action	Route of administrating the drug	Side effects
INF-β1a	immunoregulatory actions, including antagonism of INF-γ, reduction of cytokine release, and augmentation of suppressor T-cell function	IM	Injection site reaction, headache, Flu-like symptoms
peginterferon β1a		SC	
INF-β1b		SC	
Glatiramer acetate	synthetic polypeptide, a possible mechanism of action is blocking the presentation of myelin antigens to T leucocytes	SC	Injection site reaction, post-injection systemic reactions
Dimethyl fumarate	antioxidative, immunomodulatory effects via activation of nuclear factor	Oral	Flushing, GI upset, nausea and vomiting, diarrhea, and abdominal pain.
Teriflunomide	prodrug of leflunomide, it inhibits pyrimidine synthesis in leucocytes.	Oral	nausea and diarrhea.
Fingolimod	sphingosine-1-phosphate receptor modulators. It prevents lymphocyte trafficking through the lymph node and causes reversible lymphopenia.	oral	first dose bradycardia, macular edema
Spionimod			
Ozanimod			
Cladribine	Synthetic adenosine analog interferes with DNA synthesis and reduces circulating lymphocytes	oral	Lymphopenia, leukopenia, neutropenia, infection, hypersensitivity, headache, rash, and alopecia

Natalizumab	recombinant humanized monoclonal antibody to α4-integrins. It inhibits leucocyte migration from blood to CNS.	IV infusion	PML
ocrelizumab	Humanized monoclonal antibody to CD20. Cause depletion of B lymphocytes	IV infusion	Hypersensitivity and infusion reactions, infection, and neutropenia. In rare cases PML
ofatumumab	Fully human monoclonal antibody to CD20	SC	Hypersensitivity and infusion reactions, infection, and neutropenia
alemtuzumab	humanized monoclonal antibody to CD52	IV infusion	Infusion-related reactions, autoimmune disorders
Abbreviations: CNS- central nervous system, IM- intramuscular injection, IV- intravenous, PML- progressive multifocal leukoencephalopathy, SC- subcutaneously			

5.9.3 Multiple sclerosis symptomatic treatments

MS patients have a large display of disabling symptoms, such as fatigue, cognitive impairment, bladder dysfunction, pain, and spasticity. Nowadays, available therapy is pharmaceutical and non-pharmaceutical [86]. The pharmaceutical therapy includes anticholinergics medication for bladder dysfunction, typical tricyclic antidepressants, or gabapentin drugs for neuropathic pain. Baclofen, gabapentin, tizanidine, and clonazepam can be given to treat spasticity. For focal spasticity, tonic spasms, neuropathy pain, and overactive bladder, botulinum toxin can be used, or injections of amantadine to treat fatigue [75,86]. Particular drugs that have a specific license for MS are Sativex, licensed for MS spasticity, and fampridine, licensed for walking difficulty [70]. The primary key in treating MS symptoms is the removal of co-existent underlying causes [86].

6. Multiple sclerosis and cannabis as an immunomodulator

In a survey that was performed in the UK, among MS patients, it was found that of the patients with MS who responded to the survey, 47% of responders thought about using cannabis to relieve their symptoms, 26% used cannabis, and 20% spoke with their doctor about cannabis use. The group who admitted intake of cannabis, used it for several indications, such as spasticity, pain, sleep and relaxation, anxiety, and tremor [3].

6.1 Animal models of cannabis usage as a therapy in multiple sclerosis patients

Model of MS mice that were made using EAE shows the importance of the ECS in constricting the disease activity. Clinical remission of MS was shown in mice with low fatty acid amide hydrolase (FAAH). Downstream targets mediate the FAAH effect; one of those targets is the cannabinoid receptors [89].

Also, CB2 receptor knock-out mice had worse clinical EAE scores. Reduced levels of apoptosis, higher proliferation rates, and an increase in inflammatory cytokines are characteristics of CB2-negative T-cells [12].

Animal models implied that activation of the CB1 receptor might reduce neuropathic, visceral, and inflammatory pain [90].

6.2 Human models of the cannabis usage as a therapy for multiple sclerosis patients

It is known that velocity-depending tonic stretch reflexes with severe tendon jerks are known as spasticity. This spasticity occurs due to hyperactive spinal reflexes, which cause disability in patients with MS [(91)]. According to the literature, it seems that CB reduces spasticity in EAE models of MS in mice. However, it only partly supports that CB decreases the symptoms of spasticity of MS in human models [(16)].

Sexton et al. have found a significant increase in endocannabinoids in the serum of individuals with MS compared to the control group. They tested the effect of cannabis on immunological properties, and they got a similar result in both the control and patient groups. One example is that IL-17 was significantly reduced in both groups [(92)].

6.2.1 Studies that support cannabis use for spasticity in multiple sclerosis patients

Marinelli, Mori, Canneva, et al. conducted research that supported the claim that CB decreases spasticity in MS patients. They investigate the effects of Δ^9- THC: CBD sprays in MS patients at baseline and after four weeks of the treatment phase. They showed that after four-week treatment, there was a reduction in electromyography data in 20 out of 36 patients. They noted a significant reduction in muscle stretch reflex and the modified Ashworth scale (MAS) during the therapy in their study [(16)]. MAS is a universally accepted tool to measure the increase of muscle tone. The MAS was published in 1964 by Bryan Ashworth as a scale to grade spasticity. Bohannon and Smith modified MAS. MAS grade spasticity from 0-4 (see table 6) [(93)]. It is essential to mention that during this study, the patients were still taking their treatment with first-line spasticity medication, which could have influenced the results [(16)].

Table 6. MAS score modified according to Harb et al. (93)

0	**no increase in muscle tone**
1	**slight increase in muscle tone with minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension**
+1	**A slight increase in muscle tone manifested as a catch, followed by minimal resistance through the remainder of the range of motion.**
2	**A marked increase in muscle tone throughout most of the range of motion, but the affected part are still moving**
3	**Considerable increase in muscle tone, with difficulty in passive movement**
4	**The affected part is rigid in flexion or extension**

Markova et al. conducted a study on the effect of Sativex as an add-on therapy in MS patients [(94)]. Sativex is a drug that contains Δ^9THC+CBD, used as an oromucosal spray to reduce spasticity symptoms in MS patients [(95)]. This study further supports the results of the animal studies. This study is a randomized, parallel-group, 2-phased, and double-blinded study. Phase one was a single-blind, four weeks trial in which the patients got THC:CBD spray as an add-on therapy. The study participants were allowed to titrate their dose up to 12 sprays a day until they achieved maximum symptoms relief. Patients who had ≥20% improvement in spasticity on their NRS were classified as responders for phase one of the studies. They were 70.5% of the sample. In the study's second phase, the responder's patients from phase one were randomized into a placebo group and a treatment group. The patient's results were compared to baseline measures. The patients who responded had improved mean spasticity NRS, mean pain NRS, and MAS scores compared to the placebo group. This study concluded that adding

Δ^9THC:CBD spray to optimize antispasticity treatment will be beneficial for patients with moderate to severe MS spasticity [94].

Akgün et al. systematically reviewed publications on THC:CBD spray treatment for refractory spasticity-related MS. They discover that about 41.9% to 82.9 of cases reach the threshold of minimal clinically significant difference with spasticity NRS reduction of at least 20% in the four weeks of the clinical trials [96].

6.2.2 Studies that do not support the use of cannabis treatment for spasticity in multiple sclerosis patients

Leocarni et al. studied Sativex (Δ^9THC:CBD) therapy-induced changes in the neurophysiological aspects of spasticity in progressive MS patients. This study was a randomized, double-blinded, placebo-controlled, crossover study and could not show the changes that Sativex induced on neurophysiological measures of spasticity between the placebo group and the Sativex group. They noted a significant improvement in the MAS scale with Sativex therapy in comparison to the placebo group. In general MAS scale is considered less sensitive to changes in spasticity in MS. The results showed that Sativex was only partially proven effective for treating MS spasticity [95].

Van Amerongen et al. studied the effects of CB on spasticity related to MS. They checked the efficacy of the oral formulation of Δ^9- tetrahydrocannabinol (ECP002A) in progressive MS patients. A significant decrease in pain only when measuring it immediately after taking ECP002A but not in daily diaries measurements was shown in the study. The same was shown when measuring muscle spasticity. The conclusions from this study are that, in contrast to the results in animal studies, in this human study, there is no significant difference in spasticity NRS and stretch reflex MAS scores between the placebo group and the group who received the ECP002A. However, it is essential to note that this study found 200 adverse events classified as mild, which consisted primarily of dizziness, euphoric mood, headache, somnolence, and fatigue, moderate, and severe, which was a euphoric mood that disrupted patient life [97].

Da Rovare et al. did not find a significant difference concerning spasticity between CB and placebo [98].

MC and cannabinoid-based medicine are under investigation for MS-associated spasticity [12].

6.3 Cannabis use in patients with multiple sclerosis-related pain

MS-related pain affects two-thirds of MS patients [9]. The pain can manifest itself most commonly as a headache which accounts for 43% of cases, neuropathic pain in either upper or lower limbs, which accounts for 26% of cases; back pain, which accounts for 20% of all cases; painful spasms 15% of cases, and trigeminal neuralgia which account for 4% of all cases [99]. One trial checked the role of THC: CBD spray for treating central pain in MS patients. In this randomized study, there were two groups, the placebo, and the treatment group. The result of the study showed that THC: CBD spray significantly reduced the pain and improved the sleep quality in MS patients [100].

The CAMS study had 630 patients with muscle spasticity. In this study, the patients got THC cannabis extract [9], but the results provide limited evidence for a longer-term treatment effect of cannabinoids. Another study, the MUSEC study, included MS patients from 22 different centers in the UK. The leading focus of this study was stiffness in MS patients, and they examined the effectiveness of CB on pain as a secondary outcome. The results showed a reduction in pain in comparison to the placebo group [101].

Conclusions

Cannabis is a plant; the two main components of cannabis plants are THC and CBD. CB1 and CB2 are 2 of the cannabinoid receptors in the body. CB1 receptors are mainly found in CNS and some peripheral organs, while CB2 receptors are mainly in the immune system.

CBD and CBN act as immunomodulating substances, which can change the function of the immune cells. They are doing it by decreasing pro-inflammatory cytokine production and increasing the anti-inflammatory cytokines' production. Those characteristics of cannabis brought cannabis to new light in the modern medicine world.

The interest in the use of cannabis in medicine raised during the last 20 years of the last century, and it continues nowadays. Some preclinical and clinical trials were performed, which examined the effects of cannabinoids as an immunomodulator for symptom relief for diseases such as neurological diseases such as seizures, cancer-related pain, and CINV autoimmune diseases such as RA and MS.

MS is an inflammatory autoimmune demyelinating disease. Some of the symptoms of MS are spasticity, spasm, pain, cognitive impairment, and fatigue. During the years, there have been improvements in the therapy for MS, especially for the relapsing-remitting multiple sclerosis; still, there is a need for new therapies to improve symptoms and stop the progression of the disease.

Some clinical trials were performed on patients with MS to examine the effects of Cannabis on MS-related pain and MS-related spasticity. The results of those studies were inconclusive, with some studies showing a significant improvement in spasticity and pain and some showing no significant improvement.

The main problem is that there are not enough human studies of the effect of cannabinoids on MS patients and other diseases. There is a great need for a more and larger-scale clinical trial for the use of Cannabis in MS and other diseases.

CBD generally has significant medical potential, but to this day, it is understudied [102].

In conclusion, medical cannabis has the potential to be used as an immunomodulator in inflammatory and autoimmune diseases like MS, but its potential is yet to be understood. It can be used with great caution and only in several specific indications.

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Bibliography

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