Cannabis for Multiple Sclerosis Symptoms

Cole Crowson MD, Jessica Rice MD, and Michelle Cameron MD, PT, MCR
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Key Points

- People with multiple sclerosis (MS) experience symptoms that may not be adequately controlled with FDA-approved medications. Some people with MS use cannabis products to manage these symptoms.
- There are no cannabis-based FDA-approved medications indicated to treat MS or MS symptoms.
- Based on high quality randomized clinical trials, cannabinoids modestly improve patient-reported spasticity and pain in people with MS.
- Based on existing evidence, cannabis may be effective for bladder dysfunction, however, is probably not effective for MS-related tremor, ataxia or sleep dysfunction.
- Cannabis has a range of potential short and long-term adverse effects including cognitive impairment, psychosis, cannabis use disorder, and various drug-drug interactions.

Introduction

Over 20 disease-modifying therapies (DMT) are FDA-approved to reduce the frequency of MS relapses and slow progression of MS disability, however, symptoms persist despite treatment with a DMT. Not all symptoms can be effectively managed with medications and patients are seeking new approaches to manage symptoms. A 2021 survey of over 3,000 people with MS in North America found that 31% reported having used cannabis to treat their MS symptoms and that 20% were currently using cannabis for this purpose, mostly for spasticity (80%) and pain (69%) (Salter, 2021). It is worth noting that these percentages may be affected by variables such as access and legal regulations. This review provides an overview of cannabis and cannabinoids as well as evidence related to benefits and risks of cannabis use for treating MS symptoms.

Legal Considerations

Currently, cannabis is federally prohibited under the Controlled Substances Act of 1970. Under this Act, drugs are placed into one of five categories, Schedules I – V, based on their medical usefulness and potential for abuse. The Drug Enforcement Administration (DEA) is responsible for enforcing the Controlled Substances Act and can initiate proceedings to change a drug's schedule, along with the ability to add or remove any drug from a specific schedule.

Current legal status of cannabis

Within the United States, Cannabis is a Schedule I Controlled Substance, meaning it is deemed to have a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision. Learn more about the Controlled Substance Schedules and definitions here.

In recent years, legal regulations on cannabis have evolved. At the federal level, Congress amended the CSA in 2018 to remove cannabis products containing no more than 0.3 percent delta-9 tetrahydrocannabinol (THC) from the controlled substance classification. Clinical research on cannabis and its derivatives has been historically very limited due to federal restrictions, leading to the current

lack of high-quality evidence of cannabis and MS. In 2022, regulations on scientific research involving cannabis have been eased after the enactment of the Medical Marijuana and Cannabidiol Research Expansion Act (H.R. 8454), expediting approval processes for cannabis research and manufacturing cannabis products for research use.

In addition, states have diverged from federal government on decriminalization and legalization of cannabis use. As of March 2023, 37 states and the District of Columbia (D.C.) have legalized the use of cannabis for medical purposes. In addition, 21 states and the District of Columbia have also passed legislation allowing the sale of cannabis for recreational use (Hansen, et. al, 2023). Numerous proposals on the legal status of cannabis continues to be introduced at both the state and federal levels, suggesting possible changes in regulation in coming years.

Cannabis and Cannabinoids

Cannabis sativa, colloquially known as marijuana, is a plant native to central Asia that contains cannabinoids. Cannabinoids interact with endocannabinoid receptors in both the central and peripheral nervous system, altering signaling pathways throughout the body and are mostly known for their neurological impact (Andre, 2016). While first discovered in cannabis, cannabinoids are also present endogenously and can be synthetically manufactured. Over 100 cannabinoids have been identified in the cannabis plant, with the two major ones being Δ^9-tetrahdrocannabinol (THC) and cannabidiol (CBD).

- **THC** is the main psychostimulant cannabinoid.[2] The concentration of THC in cannabis flowers varies and can be from < 1% to > 20% by dry weight but can be > 60% in extracts (Smart, 2017).
- **CBD** is the main non-psychotropic cannabinoid in cannabis and is one of at least 85 active cannabinoids identified within the cannabis plant. CBD is a major phytocannabinoid accounting for up to 40-50% of the cannabis plant's extract (Andre, 2016).
- **Other Cannabinoids** such as cannabivarin and cannabigerol, are present in cannabis in lesser amounts but still hold potential for impacting the cannabinoid system independently as well as interacting with CBD and THC to modify their pharmacological effects.

Current Cannabinoid Formulations

Prescription pharmaceutical cannabis preparations

Plant Derived

- Nabiximols (Sativex®) – a natural cannabis extract in an oromucosal spray with a 1:1 ratio of THC and CBD. Nabiximols is approved in Canada, New Zealand and several European countries for treatment of moderate to severe spasticity due to MS who have not responded adequately to other anti-spasticity medications and who demonstrate meaningful improvement during an initial trial of therapy. In the United States, Nabiximols is not FDA-approved for any indication, is not available and the manufacturer announced in November 2022 that it is discontinuing its program to seek U.S. approval of Nabiximols.

- Cannabidiol (Epidiolex®/Epidyolex®) – a natural cannabis extract available as a solution containing 99% CBD and 1% THC. This product is FDA-approved for seizures associated with Lennox-Gastaut Syndrome, Dravet Syndrome, or tuberous sclerosis complex in patients 1 year of age or older.

Synthetic

- Dronabinol (Marinol®, Syndros ®) – synthetic THC suspended in sesame oil, available as a capsule. Dronabinol is FDA-approved for the treatment of chemotherapy-induced nausea and vomiting and as an appetite stimulant in patients with HIV or cancer.

- Nabilone (Cesamet®) – a synthetic compound that mimics THC, available as a capsule. Nabilone is FDA-approved for the treatment of chemotherapy-induced nausea and vomiting and as an appetite stimulant in patients with HIV or cancer.

Medical Marijuana Formulations

While cannabis refers to the plant *Cannabis sativa,* medical marijuana is any cannabis-derived product used for medical purposes. There are multiple medical marijuana products and routes of administration. These include:

- inhaled products (smoked flower or vaporized extracts)
- oral formulations (liquid oils, tinctures, sprays and extracts; foods such as gummies, cookies, or brownies, with cannabinoids in them, also known as “edibles”)
- formulations for topical application (lotions, gels, creams, etc.)

These products vary in their concentration and proportions of cannabinoids and may be labeled with this information. It should be noted that while inhaled cannabis products has shown reduced pain scores per patient report, cognitive function has been shown to be compromised (Corey-Bloom, 2012). Evidence suggests that risks outweigh benefits when considering use of inhaled products.

Illicit Synthetic Cannabinoids

Illicit synthetic cannabinoids (e.g., “K2” and “spice”) may be added to plant components for smoking, to oils for e-cigarettes and vape pens, and to counterfeit prescriptions. These are illegally produced THC analogs that bind to the cannabinoid receptors with higher potency than THC. Severe neuropsychiatric and cardiovascular adverse effects are associated with use of these substances (Tamama, 2021).

Evidence Supporting the Use of Cannabis or Cannabinoids to Treat MS Symptoms

Clinical trials have evaluated the impact of cannabinoids on a variety of MS symptoms. These trials have used various cannabinoid preparations but, as of 2020, of the cannabinoid products, nabiximols (1:1 THC:CBD oromucosal spray) had the largest dataset from randomized clinical trials targeting MS symptoms, with over 7,500 patients included (Fragoso, 2020). Most of the high-quality trial data relate to the MS symptoms of spasticity and pain.

Spasticity

Overview: Over 85% of people with MS experience spasticity, with 50% having at least mild spasticity, and up to 17% having severe spasticity (Rizzo, 2004). Medications such as baclofen, tizanidine, and botulinum toxin are commonly used to treat spasticity in people with MS; however, barriers associated with these medications include lack of efficacy, side effects, and cost.

Study Data: Randomized controlled trials comparing the effect of cannabinoids with placebo on MS-related spasticity have included over 2,000 patients. Most of these studies have used mixed THC/CBD products and support that cannabinoids are associated with improvements in self-reported spasticity. However, the effects are modest, and improvements in objective measures of spasticity do not reach statistical significance (Whiting, 2015, Nielsen, 2018). This is congruent with the American Academy of Neurology (AAN) published guideline on cannabis use for patients with MS, stating that Nabiximols, oral cannabis extract, and synthetic THC are probably effective at reducing patient-reported symptoms of spasticity (Yadav, 2014).

Conclusions: Given the supportive evidence from randomized controlled trials, authors generally conclude that treating MS-related spasticity with cannabinoids is a reasonable option for people with MS spasticity, however only a modest benefit should be expected.

MS-Related Pain

Overview: About 2 out of 3 people with MS experience MS-related pain. Pain in people with MS includes headache (43%), nerve pain in the extremities (26%), back pain (20%), painful spasms (15%) and trigeminal neuralgia (3.8%) (Foley, 2013). Establishment of the endocannabinoid system's involvement in pain modulation led to the initial investigations for applications of cannabis for pain management (Fragoso, 2020).

Study Data: Data on the efficacy of cannabinoids for the treatment of pain in people with MS are mixed. Some systematic reviews conclude that THC and THC with CBD are effective, or probably effective, for reducing pain in patients with MS, while others conclude that the evidence is inconclusive (Nielsen, 2018). A common critique of studies of cannabis and cannabinoids for treatment of pain is that the supporting RCTs tend to be of low to medium quality (Hauser, 2018).

Conclusions: Similar to the observation for cannabinoid use for MS spasticity, recent reviews conclude that the benefit of cannabinoids for MS-related pain is likely only modest but that the evidence is sufficient to consider clinical use of cannabinoids to treat MS-related pain (Fragoso, 2020, Nielsen, 2018).

Other MS-Related Symptoms

Some studies have evaluated the impact of cannabinoids for MS-related symptoms other than spasticity and pain, including bladder dysfunction, ataxia, tremor, and sleep disturbances. In most studies, these symptoms were secondary rather than primary outcomes. THC and THC with CBD have shown benefits for bladder dysfunction in some studies in people with MS resulting in fewer voids, reduced nocturia, and improved incontinence quality of life; however, these findings were not found consistently in all studies. Data do not support the use of cannabinoids for use in MS-related ataxia, tremor, or sleep dysfunction (Nielsen, 2018).

Adverse Events and Safety of Cannabis

Cannabis can have a range of adverse events that can vary depending on the cannabinoid content and dose, route of administration, the individual's sensitivity and tolerance, and concurrent medications. The following is a discussion of the common adverse events of cannabis in the general population and specifically in people with MS. This discussion is not comprehensive and does not include the less common adverse events of cannabis or those less clearly associated with cannabis itself.

Concerns about the safety of cannabis are mostly related to the psychotropic effects of THC, drug-drug interactions with other medications, and impacts on pre-natal and pediatric brain development. There is no known risk of cannabis overdose, since a lethal dose is thought to be 1500 pounds smoked in 15 minutes – an essentially impossible feat (WHO, 2018, Adams, 1996). However, there may be other acute indirect lethal events. For example, cannabis is associated with impaired driving skills and has increased the risk of motor vehicle crashes by about 30% (Simmons, 2022, Rogeberg, 2016). Heavy use of cannabis products has also been associated with altered axonal connectivity, yielding concern that cannabis may impair prenatal and pediatric neurodevelopment (Zalesky, 2012) The surgeon general recommends avoidance of prenatal cannabis exposure due to childhood psychopathology. Cannabinoids also interact with several hepatic enzymes in the CYP enzyme system causing drug-drug interactions (Lindsey, 2012). Synthetic cannabinoids ("K2" and "spice") have significant health risks due to their high potency, with adverse events including seizures, psychosis, and death (Tamama, 2021).

THC

Most of the adverse events associated with cannabis are thought to be due to the psychotropic intoxicating effects of THC.

- Short-term Use
    - Euphoria, impaired attention, impaired judgement, acute hypotension and tachycardia (WHO, 2018).
- Chronic Use
    - Hyperemesis syndrome (a cyclic vomiting syndrome), myocardial infarction, chronic bronchitis, and testicular cancer; depression, anxiety, psychosis, and schizophrenia can occur in at-risk individuals (WHO, 2018, Patton, 2002, Levinsohn, 2020).
    - Chronic cannabis use can also result in physiologic tolerance, dependence and withdrawal symptoms, leading to the inclusion of cannabis use disorder (CUD) in the 5th Edition of the Diagnostic and Statistical Manual (DSM-5).
        - About 10% of cannabis users meet criteria for CUD (WHO, 2018).

CBD

CBD is not intoxicating and has minimal psychotropic effects and thus a more favorable side-effect profile. Short-term dose-dependent side effects of CBD include somnolence, diarrhea, and anorexia (WHO, 2018). Long-term side effects of CBD are not well studied.

Special Considerations for Adverse Events in People with MS

In addition to adverse events described in the general population, several studies have evaluated cannabis adverse events specifically in people with MS. A 2018 meta-analysis of 17 randomized, placebo-controlled trials, which included 3161 participants, analyzed the effect of medicinal cannabinoids by oral or oromucosal route in people with MS. Patients in the cannabinoid arms had a higher risk of vertigo, dry mouth, fatigue, imbalance, memory impairment, and somnolence when compared to placebo. There was no significant difference in risk of serious adverse events (death or threat to a patient's life or functioning) (Torres-Moreno, 2018).

Cognitive Effects

Overview: Cognitive impairment is reported in 40-80% of people with MS (Kobelt, 2017). Therefore, investigations have attempted to examine the effect of cannabis on cognition in people with MS. To date, there are no large scale randomized, placebo-controlled intervention trials specifically examining the cognitive effects of cannabis or cannabinoids in people with MS.

Study Data: A small cross-sectional study compared cognitive performance in 25 people with MS who regularly smoked or ingested cannabis to 25 people with MS who did not use cannabis. The cannabis users performed significantly less well on tests of information processing speed, working memory, executive function, and other cognitive function tests. The cannabis users were also twice as likely as the non-users to be considered cognitively impaired (Honarmand, 2011). Another small cross-sectional study in 20 people who smoked cannabis regularly had worse working memory than a group

of 19 non-cannabis users (Pavisian, 2014). Neither study was a randomized controlled trial, and both were limited by self-reporting of cannabis use.

A 2019 randomized controlled trial attempted to examine whether the cognitive effects of chronic cannabis use in people with MS are reversible. Forty people with MS who regularly used cannabis were randomized to a control condition of cannabis continuation or an active condition of cannabis abstinence for 28 days. The cannabis abstinence group had significant improvements on repeat cognitive testing at 28 days compared to the cannabis continuation group, with no significant MRI changes in either arm (Feinstein, 2019).

Conclusions: Although most reports associate cannabis use with worsening of cognitive function in people with MS, the authors of a qualitative systematic review published in 2022 evaluating 18 studies of various design had more nuanced conclusions. This review suggests that effects of cannabis on cognition may be dependent on the type of product, the duration of use, and the indication. When used chronically, whole-plant cannabis adversely impacts cognitive performance in people living with MS. However, in the short-term, medicinal cannabis does not adversely affect cognition and may even improve cognition when being utilized to manage MS symptoms such as spasticity and/or pain (Landrigan, 2022).

Drug-Drug Interactions

Cannabinoids, including THC and CBD, are metabolized and interfere with metabolism by several hepatic enzymes in the CYP system (Lindsey, 2012). Common medications used for symptomatic management of multiple sclerosis, such as selective serotonin reuptake inhibitors and tricyclic anti-depressants are also metabolized by the CYP system. However, no high-quality human trials have evaluated the effects of cannabinoids on these classes of medications (Petersen, 2021). Animal data has implicated higher effective levels of gabapentin when combined with THC and has implicated that cannabis may decrease effects of NSAIDS (Atwal, 2019, Anikwue, 2002). A randomized placebo controlled cross over trial in 12 patients concluded that it was safe to combine 400mg of modafinil with 15mg of oral THC daily (Sugarman, 2011).

Note: Studies have not evaluated interactions between cannabis and MS disease modifying therapies.

Conclusions

People with MS experience symptoms that may not be adequately controlled with off-label use of FDA-approved medications and some people with MS use cannabis products to manage these symptoms. Although there are no cannabis-based FDA-approved medications to treat MS or its symptoms, high quality randomized clinical trials support that cannabinoids modestly improve patient-reported spasticity and pain in people with MS and may reduce bladder dysfunction. There is not enough clinical research to support the finding that cannabis is effective for MS-related tremor, ataxia or sleep

dysfunction and has potential short and long-term adverse effects including cognitive impairment, psychosis, cannabis use disorder, and drug-drug interactions.

Additional Resources:

Congressional Research Service: Developments in Marijuana Law

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