

Cannabis for Multiple Sclerosis Symptoms

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Key Points:

- People with MS experience symptoms that may not be adequately controlled with FDA-approved medications. Some people with MS have tried cannabis products to relieve these symptoms.
- Although cannabis has been legalized for recreational and/or medical use in a growing number of states, its use remains prohibited by federal laws. The legal status of cannabis is in flux.
- Despite its use by humans for thousands of years, the scientific study of cannabis and its components is still in its infancy. High-quality research in the United States remains limited.
- Based on existing evidence, cannabis products are probably effective for treating patient-reported symptoms of spasticity and pain.
- Based on existing evidence, cannabis is probably not effective for MS-related tremor or urinary incontinence.
- People with MS should be aware of potential adverse effects of cannabis products, including new or worsening cognitive symptoms, psychosis, tolerance and dependence, as well as drug-drug interactions.
- The use of cannabis to treat MS symptoms remains controversial. Patients are encouraged to discuss these issues with their health care providers.

Introduction

Multiple sclerosis (MS) is a disease that affects the central nervous system (CNS), which includes the brain, spinal cord and optic nerves. MS involves an abnormal response of the body's immune system, which is directed against the person's own CNS. The immune system targets myelin, a substance that surrounds and insulates nerves. Damaged myelin then forms scars (sclerosis), giving the disease its name, and these scars are thought to be responsible for most of the wide ranging symptoms that people with MS experience.

Various FDA-approved medications can help reduce the frequency of MS relapses, slow progression of disability from MS, and relieve symptoms of MS, but none of these medications are completely effective. Many people continue to experience relapses, progression, and symptoms from their MS. It is now becoming more common for some people to use cannabis (marijuana) to try to alleviate their MS symptoms. A survey of people with MS published in 2017 found that 47% of respondents have considered using cannabis to treat their MS symptoms, 26% have used cannabis for their MS symptoms, 20% have spoken with their physician about using cannabis, and 16% are currently using cannabis. [1] Although people have used cannabis for thousands of years, systematic study of the compounds in cannabis as therapeutic treatment has only occurred in about the last 20 years. **This paper provides an overview of the use of cannabis for treating symptoms caused by multiple sclerosis.** Although some very preliminary research suggests that cannabis may also affect the immune system and thus impact the immune attacks of MS, this research is not discussed in this paper.

LEGAL ISSUES

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 perceived medical usefulness and potential for abuse and cannabis is in Schedule I. The Drug Enforcement Administration (DEA) is responsible for enforcing the Controlled Substances Act and can initiate proceeding to change a drug’s schedule or add or remove any drug from a specific schedule.

CALL-OUT BOX

CONTROLLED SUBSTANCE SCHEDULES

Schedule I Controlled Substances are defined as those with “no currently accepted medical use and a high potential for abuse”. Some examples of Schedule I drugs are heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, and 3,4-methylenedioxymethamphetamine (“Ecstasy”).

Schedule II/IIN Controlled Substances: a high potential for abuse which may lead to severe psychological or physical dependence (e.g., hydromorphone (Dilaudid®), methadone (Dolophine®), meperidine (Demerol®), oxycodone (OxyContin®, Percocet®), fentanyl (Sublimaze®, Duragesic®), morphine, opium, codeine, hydrocodone, amphetamine (Dexedrine®, Adderall®), methamphetamine (Desoxyn®), and methylphenidate (Ritalin®))

Schedule III/IIN Controlled Substances: a potential for abuse that is less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence (e.g., products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with Codeine®), and buprenorphine (Suboxone®), benzphetamine (Didrex®), phendimetrazine, ketamine, and anabolic steroids such as Depo®-Testosterone)

Schedule IV Controlled Substances: low potential for abuse relative to substances in Schedule III (e.g., alprazolam (Xanax®), carisoprodol (Soma®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), lorazepam (Ativan®), midazolam (Versed®), temazepam (Restoril®), and triazolam (Halcion®))

Schedule V controlled Substances: low potential for abuse relative to Schedule IV substances (e.g., cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams (Robitussin AC®, Phenergan with Codeine®), and ezogabine)

Cannabis is a Schedule I category drug, which is considered to be the most dangerous category. This means that, along with heroin, LSD and other psychoactive drugs, in the United States cannabis is deemed to have a high potential for abuse, no currently accepted medical use in treatment, and a lack of accepted safety for use under medical supervision.

However, as of September 2017, 29 states and the District of Columbia (DC) have legalized the use of cannabis for medical purposes. In addition, eight states and DC have also passed legislation allowing the sale of cannabis for recreational use. [2] The legal status of cannabis is subject to change.

The National MS Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes when this may be beneficial and is in accordance with legal regulations. In addition, the Society supports advancing research to better understand the potential benefits and risks of marijuana and its derivatives for people with MS.

Cannabis and Cannabinoids

Cannabis sativa is a plant native to central Asia. [3] There are many types of chemical compounds in cannabis. The best understood of these are:

1. Terpenoids – Aromatic chemicals found in many plants, which are responsible for the unique smell of cannabis. [3]
2. Flavonoids – A large family of compounds found as part of pigments in most plants. Flavonoids may impact cell-signaling cascades and thus immune responses. [3]
3. Cannabinoids – Chemicals that bind to cannabinoid receptors in the body and alter the release of neurotransmitter in the brain. Phytocannabinoids are cannabinoids found in plants. Endocannabinoids are cannabinoids produced naturally by the body. Synthetic cannabinoids are manufactured artificially. The two major cannabinoids in cannabis that have been studied are:
 - **THC** (tetrahydrocannabinol), also known as delta-9-tetrahydrocannabinol, is thought to be the most psychoactive substance in cannabis. [3] The concentration of THC in cannabis varies and can be anywhere from 1% to 24%. [4] However, higher potency cannabis exists.
 - **CBD** (cannabidiol), is the major non-psychoactive cannabinoid found in cannabis. [3] The concentration of CBD in cannabis is typically less than 1%, but many strains have higher CBD concentrations.

There are many different strains of cannabis that have different concentrations and proportions of THC and CBD. Typical products in dispensaries have high THC to CBD ratios, up to 20:1, but with the growing interest in CBD products, cannabis products with high CBD to THC ratios are now available.

The endocannabinoid system

The human body produces its own cannabinoids called endocannabinoids and has receptors for these chemicals. The exact function of endocannabinoids is still being studied, but they appear to have endorphin-like effects lasting minutes, and may play a role in the “runner’s high” experienced after exercise. [5]

The cannabinoid receptors in the body fit like a lock and key with the endocannabinoids produced naturally in the body and also with the THC, CBD, and other cannabinoids in cannabis and in synthetic cannabinoid products. [6] Two of the cannabinoid receptors identified, CB1 and CB2, are the subject of ongoing research:

- CB1 are cannabinoid receptors located primarily in the central nervous system, especially the cerebellum, basal ganglia, hippocampus, cerebral cortex, and spinal cord, as well as on peripheral nerves. [6,7] Activation of CB1 receptors is thought to be responsible for the symptomatic effects of cannabis use.
- CB2 are cannabinoid receptors located primarily on cells of the immune system. [6,7]

Current cannabinoid formulations

Single molecule synthetic pharmaceuticals (available by prescription in the US for specific conditions):

- Dronabinol (Marinol®) – an FDA-approved, schedule III, medication consisting of synthetic THC suspended in sesame oil and sold in capsules. Currently, dronabinol is FDA-approved for the treatment of chemotherapy-induced nausea and vomiting and as an appetite stimulant in patients with AIDS. [8]
- Nabilone (Cesamet®) – an FDA-approved, schedule II, synthetic compound that mimics THC and comes in capsules. Nabilone is currently FDA approved for the treatment of chemotherapy-induced nausea and vomiting. [9]

Oral cannabis extracts (not currently available in the U.S.):

- Nabiximols (Sativex®) – a natural cannabis extract with a 1:1 ratio of THC and CBD that activates both CB1 and CB2 receptors. Nabiximols is administered as a mouth spray. Nabiximols is not currently FDA-approved for any application and is therefore not available in the U.S. In Canada, New Zealand, and several European countries, nabiximols is approved for treatment of MS-related spasticity. [10]
- Cannador© – a natural cannabis extract with a 2:1 ratio of THC and CBD that comes as a capsule. It has been used in research studies in Europe and is produced by the Institute for Clinical Research in Berlin, Germany. [11]

Botanicals (smoked, inhaled, edible, and topical cannabis sativa products):

- Cannabis sativa is the natural plant cannabis, which is federally prohibited and designated as a Schedule I substance. There are multiple cannabis products and ways to take cannabis including via inhalation (smoked plant or vaporized extracts), orally (oils, tinctures, extracts, baked products also known as “edibles”), or as a topical application (lotions and salves). These products vary in their concentration and proportions of cannabinoids and may be labeled with this information.
- Botanical cannabis preparations have been legalized in many states for medical use and for recreational use in a smaller number of states. The laws governing the growers, dispensaries and prescribing of botanical products vary across these states. Information on state laws can be found on the Americans for Safe Access website.
- There are concerns about inconsistencies between cannabis products sold at dispensaries. Rules and regulations vary between states that have legalized the medical and/or recreational use of cannabis. Production is not standardized, and it can be unclear exactly how herbicides, pesticides or other potential contaminants are used or removed from the final product. The cannabis products people receive can also vary in potency. One survey published in 2015 in the Journal of the American Medical Association (JAMA) found that of 75 edible cannabis products tested, only 17% contained the claimed amount of CBD/THC (within 10% accuracy). Meanwhile, 23% were under-labeled, containing more THC and/or CBD than claimed, and 60% were over-labeled, containing less THC and/or CBD than claimed. [12] Additionally, the appropriate dose of cannabinoids for different medical conditions is not known.

Guideline from the American Academy of Neurology

The American Academy of Neurology (AAN) is a professional association representing over 32,000 neurologists and neuroscientists dedicated to promoting high-quality care for people with neurological disorders. In 2014, they published a systematic review of the available high-quality evidence published

in peer-reviewed journals concerning the “efficacy and safety of medical marijuana in selected neurologic disorders” [7]. Based on this review, they created an evidence-based guideline that includes the following conclusions on the evidence for cannabinoids for the treatment of MS-related symptoms [13]:

- **Spasticity:** Nabiximols (Sativex oral spray), oral cannabis extract (OCE) and synthetic THC are probably effective at reducing patient-reported symptoms of spasticity.
 - However, OCE and synthetic THC were not found to be effective for spasticity when it was measured on tests administered by a physician
- **Pain:** Nabiximols (Sativex oral spray), OCE and synthetic THC are probably effective at reducing MS-related pain.
- **MS-related tremor:** Nabiximols (Sativex oral spray), OCE and synthetic THC were not found to be effective for MS-related tremor.
- **Urinary symptoms:** Nabiximols was found to be probably effective for urinary frequency, but not effective for bladder incontinence.
- **Smoked cannabis:** research studies have not produced enough evidence to assess the safety or effectiveness of smoked cannabis for treating MS symptoms, including spasticity, pain, balance, posture, and cognition changes.
- The long-term safety of marijuana use for MS symptom management is not yet known.

Evidence supporting the use of cannabis to treat symptoms of MS

Cannabis has been studied for many uses in many different conditions. This section focuses on the evidence about cannabis to treat symptoms commonly experienced by people with MS. This is not a comprehensive review of all studies that have been conducted, but highlights the largest and highest quality studies.

Spasticity

Spasticity that causes muscle spasms and stiffness is common in people with MS – over 85% of people with MS have some spasticity, 50% have at least mild spasticity, and up to 17% have severe spasticity. [14] Although several medications can be used to treat spasticity, they may not be completely effective and their use or dose may be limited by side effects.

The CAMS (Cannabinoids in MS) study is the largest randomized control trial to date to examine the effectiveness of cannabis on MS symptoms. [15] In this study, 630 people with MS from 33 centers in the United Kingdom were assigned to receive dronabinol, cannador or placebo twice daily for 15 weeks. Although there was no significant difference between groups in changes in the physician-administered test of spasticity, those taking either of the cannabis products (dronabinol or cannador) reported significantly greater improvements in spasticity, spasms, and sleep compared to those taking placebo. There were no significant changes in tremor or bladder symptoms in any of the groups. At the end of the study, participants could elect to continue taking their assigned study medication and were followed for another 12 months. [16] At that time, they found that those taking dronabinol had a small improvement on the physician-administered test of spasticity, the Ashworth scale, but this was not seen in the Cannador or placebo group, and no other measures were administered. The explanation for these findings is unclear.

The MUSEC trial (MS and Extract of Cannabis) in 2012 also examined patients' perceptions of changes in muscle stiffness. [17] In this study, 279 people with MS took either Cannador or placebo for 12 weeks. People taking cannabis extract had almost twice as much relief from muscle stiffness as those taking placebo at both 4 and 8 weeks, and they also had improvements in spasms and sleep.

Studies have also looked at the effect of nabiximols on spasticity. In two similar studies, one study with 160 people and another with 189 people, the groups using nabiximols had statistically significantly greater improvement in self-reported spasticity compared to those using placebo [18,19], but there were no significant improvements in other symptoms, including pain or urinary symptoms. [18] Next, a study with 337 patients found that nabiximols improved self-reported spasticity more than placebo, and that the response in the first four weeks tended to predict the ongoing response for the entire 15-week study. [20] Finally, a two-part study in 2011 looked at the effects of nabiximols on patient-rated spasticity. [21] First, 572 people with MS-related spasticity that was not relieved by medications were treated with either nabiximols or placebo for 4 weeks. Those in the nabiximols group who had at least a 20% reduction in spasticity went on to the second part of the study. This group of 241 individuals was assigned to use either nabiximols or placebo for 12 weeks. The group taking nabiximols had significantly improved self-reported spasticity.

Overall, as of a 2015 systematic review, there have been 11 randomized studies with a total of 2138 patients comparing the effect cannabinoids of any type with placebo on spasticity related to MS. Although the specific details of the studies vary, most studies suggest that cannabinoids are associated with improvements in self-reported spasticity, but the improvements in objectively measured spasticity generally do not reach statistical significance [22].

MS-related pain

Pain is a complex phenomenon involving many different chemicals, neurotransmitters, and receptors. Pain is a common symptom of MS, affecting around two-thirds of people with MS. People with MS can experience many different types of pain, including headache (43%), nerve pain in their arms or legs (26%), back pain (20%), painful spasms (15%) and trigeminal neuralgia (3.8%). [23] Most pain experienced by people with MS is central neuropathic pain (pain caused from damage to the central nervous system) or pain from spasms. The role of cannabis in pain relief is complex and not well-understood. Some evidence suggests that the CB1 receptors in the brain and peripheral nerves play a role in modulating and processing pain. [24] Cannabis may also decrease pain by decreasing inflammation. [25]

Several studies have looked at the effect of cannabis on neuropathic pain in people with MS. One study lasting four weeks in 64 people with MS found a 41% decrease in mean pain intensity in the group taking nabiximols compared to a 22% decrease in pain in the group taking the placebo. [26] Similar effects on pain were found in two additional studies, one with 630 people and the other with 279 people, comparing the effects of oral cannabinoids (cannador or dronabinol), with placebo. [15,17] In addition, a recent small study with 15 people with MS with neuropathic pain found that adding nabilone to gabapentin was effective and well-tolerated for MS-related neuropathic pain. [27]

Fewer studies have examined the effectiveness of inhaled cannabis on pain and none of these have been carried out in people with MS. Two studies comparing the effectiveness of inhaled cannabis with placebo for neuropathic pain due to peripheral neuropathy or other neurologic conditions found that

neuropathic pain was reduced more in the group using inhaled cannabis when compared to the placebo group. [28,29]

A 2011 systematic review of randomized controlled trials performed before 2010 examined the effects of cannabinoids of any type (smoked cannabis, oral extracts, nabilone, synthetic THC, nabiximols) on chronic non-cancer pain (including but not limited to pain from MS). In 15 of the 18 studies, the cannabinoids provided at least modest pain relief. [30] A 2015 update by the same authors that evaluated 11 additional studies performed between 2010 and 2014 found that 7 of these 11 studies also showed that cannabinoids were more effective than placebo. [31]

Adverse effects and safety of cannabis

Cannabis can have a range of adverse effects. These may vary depending on the product and the individual. How much cannabis the person uses, what type and proportions of cannabinoids the product contains, how it is taken (smoked, eaten, etc.), as well as the person's sensitivity and tolerance, other medications that are taken, and other factors can all impact the adverse effects a person may experience. The following is a discussion of some of the better understood and more common adverse effects of cannabis. This is not a comprehensive list and does not include the less common adverse effects of cannabis or those less clearly associated with cannabis itself. There is ongoing research to better understand the short and long term effects and safety of cannabis use.

The COMPASS trial (Cannabis for the Management of Pain: Assessment of Safety Study) is the only study focused on examining the safety of cannabis. [32] In this study, 215 Canadian patients with chronic pain were given a standardized herbal cannabis product (12.5% THC) and 216 patients with chronic pain who were not cannabis users served as controls. A variety of serious and non-serious adverse events occurred in both groups. But, none of the serious adverse events were considered to be probably or likely related to cannabis and there were not significantly more serious adverse events in one group than in the other. However, there were significantly more non-serious adverse events in the cannabis group than in the non-user group, particularly events causing neurologic, psychiatric, or respiratory symptoms. The most common non-serious adverse events in the cannabis group were:

- Headache (5%)
- Nasopharyngitis (4.5%)
- Nausea (4.4%)
- Somnolence (3.6%)
- Dizziness (3.3%)
- Upper respiratory tract infection (2.6%)
- Vomiting (2.1%)
- Cough (2%)

Some other adverse events were less common but were felt to be "certainly/very likely" related to cannabis, including:

- Amnesia (0.5%)
- Euphoric mood (0.4%)
- Sweating (0.2%)
- Paranoia (0.2%)

Psychiatric symptoms

Cannabis use is specifically thought to increase the risk of developing psychosis in at-risk individuals. [33] These include adolescents, those who have previously experienced psychotic symptoms, and those with a family history of schizophrenia. The risk is higher with more cannabis use. Cannabis use has also been associated with an increased risk of developing schizophrenia. [34] Although there are case reports of suicide associated with use of cannabis products, a 2016 systematic review and meta-analysis of the available data found insufficient evidence that acute cannabis use increases imminent risk for suicide. Although some data suggested there may be an association between chronic cannabis use and suicide, it is not clear from the studies that cannabis use really increases the risk for suicide because different studies measured cannabis exposure differently, and factors other than cannabis that could influence risk of suicide were not adequately accounted for. [35]

Cognitive effects

Cannabis can worsen cognitive problems in people with MS. One study compared cognitive performance in 25 people with MS who regularly smoked or ingested cannabis and 25 people with MS who did not use cannabis. The cannabis users performed significantly less well on information processing speed, working memory, executive function, and other cognitive function tests, and the cannabis users were twice as likely as the nonusers to be considered cognitively impaired. [36] Another study found that people with MS who smoked cannabis regularly had worse working memory than those who did not smoke cannabis. [37]

Cardiovascular effects

There is growing evidence that cannabis can increase the risk for cardiovascular diseases, including heart attacks, high blood pressure, heart failure, and stroke. [38,39] One study also found that the risk of heart attack was increased 4.8 times in the hour after smoking cannabis. [40]

Cancer

There is conflicting evidence regarding the effects of cannabis use on different types of cancers. To read more about this, please visit the National Cancer Institute's [website](#) on cannabis and cancer.

Tolerance and Dependence

Over time, people who use cannabis more often tend to develop tolerance to it. This means they need to use more cannabis to get the same effect. Also, some people who use cannabis very frequently develop physical dependence on it. Physical dependence means that a person who stops using cannabis has withdrawal symptoms. These symptoms can include irritability, insomnia, hot flashes, restlessness, nausea, and cramping. Cannabis withdrawal symptoms are usually mild and resolve after a few days but, in chronic, heavy users, withdrawal symptoms can be more intense. [41] Cannabinoids are stored in a person's fat and leave the body slowly. Therefore, a person who suddenly stops using cannabis generally does not have sudden severe withdrawal because the level of cannabinoids in the blood decreases gradually as the fat stores get used up. [42] Cannabis withdrawal syndrome was added to the DSM-V (a comprehensive list of psychiatric diagnoses and their diagnostic criteria) for the first time in 2013. [41] About 9% of people who use cannabis develop physical dependence. This rate of physical dependence is lower than with tobacco (67.5%), alcohol (22.7%), or cocaine (20.9%). [42]

Overdose

A lethal dose of marijuana is thought to be 1500 pounds smoked in 15 minutes – an essentially impossible feat. [43] So, in effect, there is no risk of death directly related to smoking cannabis plant. Opioids can cause death because there are opioid receptors in the brainstem, an area that controls breathing, and an excessive opioid dose can cause respiratory depression. There are no cannabinoid receptors in the brainstem so this does not happen with cannabinoids. [43] However, there are now highly concentrated cannabis products (for example, hash oil or wax containing up to 80% THC) that have been associated with deaths, generally from injuries sustained while intoxicated.

Drug-drug interactions

Cannabis may interact with a person's prescription and non-prescription medications. Specific enzymes in the liver help break down THC and CBD. THC and CBD can also affect how quickly or effectively liver enzymes process medications. For example, tricyclic anti-depressants (TCAs), such as amitriptyline (Elavil) and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac), are metabolized by a liver enzyme that also metabolizes THC, called CYP2C9. Smoking cannabis can also reduce the metabolism of warfarin (Coumadin, a blood thinner), causing an increase in blood levels of the drug, increasing the risk for bleeding. [44]

Conclusions

The medical use of cannabis remains controversial. In addition to the legal status of the drug, the limited research evidence remains a major barrier to our understanding of the potential benefits and risks of cannabis use in people with MS. The last two decades have seen an increase in the amount of scientific research in this area. However, case report, and anecdotes still greatly outnumber high-quality studies. High quality scientific methods and standards like those used to study conventional medications need to be applied to the study of cannabis to fully understand its potential for medical use.

Clinical trials researching cannabis are limited in part because cannabis research is difficult. In the USA, researchers must file an Investigational New Drug (IND) application with the FDA, obtain a Schedule I license from the US Drug Enforcement Administration (DEA), and obtain cannabis for the study. When botanical or smoked cannabis is investigated, it must come from the same plot grown by the FDA, leaving unexplored other strains and hybrids that patients may encounter. These obstacles can make conducting these studies more time-consuming and challenging than other investigations. There is also the question of how widely the results of these studies can be applied since some studies examine liquid extracts, others use the single molecule preparations, others use smoked cannabis.

Despite the restrictions and limitations, scientific research on cannabis and cannabinoids continues to grow. Also, more and more people are showing interest in using cannabis to treat their MS symptoms. It is therefore important for people with MS and their providers to understand the available evidence and to work together to make the choices that are right for them. For specific questions about cannabis and your health, do not hesitate to contact your physician.

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Additional Resources

[Cannabis in Canada](#) – Cannabis was recently legalized for recreational use in Canada. This website briefly outlines what the process entailed.

[National Cancer Institute](#) – Patient information on cannabis and its use in cancer

[Americans for Safe Access](#) - This is a non-profit organization that aims to “ensure safe and legal access to cannabis (marijuana) for therapeutic use and research.” Up to date information regarding the legal status of cannabis can be found on their website.