Last Section Update: 05/2025

Contributor(s): **Stephen Tapanes**, PhD

Table of Contents

Start

1 Overview

Summary and Quick Facts for Multiple Sclerosis (MS)

- Multiple sclerosis (MS) is a disease in which the immune system damages nerve cells and impairs their ability to communicate. It can cause symptoms that come and go, including numbness or tingling, muscle weakness, vision problems, trouble walking or talking, and cognitive difficulties.
- Doctors can diagnose MS by using tools such as magnetic resonance imaging (MRI) and monitoring symptoms over time. In some cases, a lumbar puncture or “spinal tap” may be needed and other tests such as electrical nerve conduction tests are helpful.
- Medical treatment of MS focuses on preventing relapses and treating relapses when they occur.
- Taking a vitamin D supplement has been shown to modulate the immune response in MS and help improve symptoms in some clinical trials. Other nutrients, such as coenzyme Q10 (CoQ10), lipoic acid, and high doses of omega-3 fatty acids may be beneficial as well.
- Eating a healthy diet, such as the Mediterranean diet, which is rich in plant-based foods, and getting regular physical activity, as one is able, is important as well.

What is Multiple Sclerosis?

Multiple sclerosis (MS) is a neurodegenerative disease characterized by autoimmune destruction of the myelin sheath within the central nervous system (CNS). The myelin sheath acts as an insulator and helps facilitate conduction of electrical signals in neurons. Myelin loss prevents effective signaling within the brain and spinal cord resulting in impaired motor and cognitive function. Although the exact cause of MS is still unknown, genetic and environmental factors that cause inflammation and oxidative stress within the CNS are thought to contribute.

What are the Signs and Symptoms of Multiple Sclerosis?

Symptoms associated with MS vary considerably depending on the parts of the CNS affected and severity of myelin destruction. Common symptoms include:

- Fatigue
- Ocular and visual problems
- Muscle weakness, tremors, or spasms
- Bladder and bowel dysfunction
- Depression, anxiety, and mood alterations
- Pain, numbness, and tingling
- Difficulty walking, balancing, or breathing
- Loss of taste or hearing
- Cognitive impairment
- Sexual dysfunction

Most people with MS experience a relapsing-remitting form of the disease, in which symptoms come and go. However, there is also a more progressive form of MS, which also has aspects of relapse and remission, that progressively worsens over time.

Nutrients

- **Vitamin D:** Epidemiological studies suggest that the prevalence and severity of MS increases in areas with lower levels of sunlight, which promotes the production of vitamin D. Vitamin D is involved in multiple aspects of immune health, and a vitamin D supplement is generally recommended for individuals with MS.
- **Coenzyme Q10 (CoQ10):** CoQ10 is an antioxidant involved in mitochondrial energy production. Clinical trials suggest CoQ10 supplements help reduce oxidative stress and inflammation in people with MS. CoQ10 may also improve symptoms of the disease, including fatigue, depression, and pain.
- **Lipoic acid:** Lipoic acid, which is another critical component in mitochondrial metabolism, possesses a variety of antioxidant and anti-inflammatory properties. Studies in people with MS suggest lipoic acid can help reduce inflammation and may improve functionality in some patients with progressive disease.
- **Omega-3 fatty acids:** Omega-3 fatty acids modulate immune cell activity and possess anti-inflammatory properties. Supplementation with omega-3 fatty acids may reduce inflammation in people with MS and has been linked to lower relapse rates and improved quality of life.
- **L-carnosine:** Carnosine helps promote mitochondrial activity in skeletal muscle and prevents exercise-induced oxidative stress. Carnosine levels are decreased in the muscles of MS patients, and supplementation with L-carnosine has been linked to improvements in disease symptoms.

Dietary and Lifestyle Considerations for Multiple Sclerosis

In a pilot clinical trial of the effects of the Mediterranean diet on MS symptoms in 128 participants, people who adhered to a Mediterranean diet had significant reductions in disability and MS risk factors compared with those who did not, with a significant decline in trajectory of neurological fatigue.

Exercise can help improve functionality in MS. According to a thorough scholarly review, physical activity had the greatest effects on fatigue, day-to-day function, and balance in MS.

Stress reduction is important as well. Mindfulness and emotional wellness programs can help reduce stress and improve mood in people with MS.

How is Multiple Sclerosis Diagnosed?

People with MS typically present to their doctor with symptoms suggestive of demyelination in the CNS. Ocular and visual problems are common presenting features, as are sensory problems in the limbs and motor difficulties. If your doctor suspects you might have MS, they will do a physical exam and take a full clinical history. They will order imaging of the brain and spinal cord as well. If initial tests are inconclusive, cerebrospinal fluid tests may be ordered as well. The National Multiple Sclerosis Society states that the diagnosis of MS requires evidence of at least two areas of damage in the CNS, which have occurred at different times.

How is Multiple Sclerosis Treated?

Almost two dozen disease-modifying therapies are available to treat MS, including:

- Interferons
- Glatiramer acetate (helps mitigate myelin destruction by T cells)
- Fumarates (dimethyl fumarate, diroximel fumarate, monomethyl fumarate)
- Cladribine (purine analog)
- Teriflunomide (pyrimidine synthesis inhibitor)
- S1P receptor modulators (siponimod, fingolimod, ponesimod, ozanimod)
- Monoclonal antibodies (ocrelizumab, natalizumab, alemtuzumab, ofatumumab)

The efficacy of these drugs, in terms of reduction of annualized relapse rates, ranges from about 29% to 68%.

Treatment may also involve cognitive rehabilitation, physical and/or occupational therapy, and symptomatic therapy geared toward generally improving quality of life. Patients may also receive medication to combat specific symptoms of MS as needed.

2 Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS). Over 900,000 adults in the United States are estimated to have MS, with the highest prevalence observed at more northern latitudes. The incidence of MS has increased steadily over the past several decades.[1] MS typically presents in early adulthood, between age 20 and 30 years, and risk of MS is nearly three times more common in women than men.[2]

Although the exact cause of MS is unknown, a combination of genetic and environmental factors are thought to contribute to the destruction of the *myelin sheath*, the fatty tissue that insulates and protects nerve cells. This progressive demyelination causes neurodegeneration, which leads to physical disability and cognitive impairment.[2] The symptoms of MS vary considerably based on the parts of the CNS affected. Symptoms can include sensory or motor dysfunction, nerve or muscle pain, fatigue and sleep disturbances, cognitive changes, bladder or bowel problems, mood disorders, and sexual dysfunction.[2,3] MS progression and degree of disability experienced by those affected by the disease are commonly measured using the expanded disability status scale (EDSS), a method of quantifying disability in people with MS and monitoring changes in level of disability over time. The EDSS, which is widely used in clinical trials and in the assessment of people with MS, is based on measures of impairment in eight functional systems and ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. EDSS scores of 1.0–4.5 refer to people with MS who are able to walk without any aid; 5.0–9.5 are defined by impairment to walking; and 10 is defined as death due to MS.

The most common type of MS is *relapsing-remitting MS (RRMS)*, which accounts for about 85% of cases. This

type of MS is characterized by spontaneous relapses or episodes of worsening symptoms separated by prolonged periods of remission in which symptoms resolve or improve.[4] Quality of life can be generally good for people living with MS, particularly for individuals with healthy coping strategies.[5] In about 10–15% of cases, known as *primary progressive MS (PPMS)*, the disease progresses steadily, without intermittent periods of remission. Compared with RRMS, which is associated with a more gradual progression of disability, PPMS is associated with a more rapid deterioration of function.[2] There also is a secondary progressive form, in which progressive disease develops in someone initially having RRMS.

Several modifiable risk factors, including smoking and a low vitamin D level, are associated with an increased risk of MS. Consequently, preventive strategies include smoking cessation and maintenance of an adequate vitamin D level.[6] About two dozen disease-modifying therapies are available for the treatment of MS; these drugs can reduce disease progression and associated disability, as well as the risk for relapse.[7] Medication, cognitive rehabilitation, and physical and occupational therapy may improve symptoms associated with MS. Lifestyle interventions, including low-fat diets, exercise, and stress reduction techniques may help improve symptoms and quality of life as well.

In this protocol the different types of MS will be discussed, as will MS risk factors and potential causes of the disease. Conventional treatments will be reviewed, as well as integrative strategies to help manage the physical, cognitive, and emotional symptoms associated with disease, including lifestyle interventions and nutritional support.

3 Background

MS is a chronic, demyelinating, neurodegenerative disease that affects the CNS, which consists of the brain and spinal cord.[4] It is most often diagnosed in early adulthood but can occur at any age, including childhood or old age.[2,4] Although MS is often described as an autoimmune disorder, disease-specific autoantibodies differ between patients and can target different components of myelin.[8] The exact cause of MS is still unknown, but the destruction of the myelin sheath is thought to be engendered by several factors, including autoimmune activation of the complement system,[9] activation of pro-inflammatory complexes known as inflammasomes,[10] non-protein-coding RNA molecules,[11] the gut microbiome,[12] and metabolic changes that lead to oxidative stress.[13] There is also thought to be an environmental component to the development of MS, as epidemiological studies repeatedly demonstrate an increasing prevalence of MS at higher latitudes away from the equator, where the population's vitamin D level tends to be lower.[1,2,14]

Inflammation and demyelination are hallmark features of MS. The myelin sheath is a fatty protective layer that surrounds the axons of nerve cells and promotes the conduction of electrical signals, called impulses, in the CNS.[15] In MS, immune cells, including both T and B cells, accumulate within the CNS and promote pro-inflammatory processes that cause damage to brain cells and promote demyelination.[14] When demyelination occurs, impulse conduction is reduced, and signaling in the brain is disrupted, which leads to the cognitive, motor, and sensory dysfunction characteristic of the disease.[14,16] As MS progresses, axons themselves become irreversibly damaged, leading to the chronic and progressive nature of the disease.[14] Other cells in the brain are damaged by chronic inflammation as well, including oligodendrocytes, which are the myelinating cells in the CNS; astrocytes, which provide metabolic support; and microglial cells, which remove myelin debris and damaged nerve cells to promote remyelination.[17]

Types of Multiple Sclerosis

There are three main types of MS that are characterized by the course of disease:

- **Relapsing-remitting MS (RRMS)** is the most common form of MS, accounting for about 85% of diagnoses. RRMS is characterized by intermittent exacerbation of symptoms, known as relapses, separated by prolonged periods with resolved or improved symptoms. During these periods of relapse, new symptoms may occur due to expansion of existing lesions or development of new ones within the CNS. In order to be considered RRMS, relapsing symptoms must last at least 24 hours and be separated from the previous relapse by at least 30 days.[4] Relapsing symptoms typically last about 24 to 48 hours in RRMS, but may gradually develop over days or weeks.[18] Research suggests the annualized relapse rate for people with MS is

about 0.30 to 0.38, corresponding to about 1 relapse every 3 years.[19]

- **Primary progressive MS (PPMS)** is less common, accounting for about 10–15% of initial MS diagnoses.[20] In PPMS, deterioration of function progresses gradually from onset, without the sporadic relapses observed in RRMS.[18,20]
- **Secondary progressive MS (SPMS)** occurs when RRMS becomes progressive later in the course of disease. Estimates have shown that if left untreated about 50% of people with RRMS will develop SPMS within 10 years of diagnosis and up to 90% will develop SPMS within 20 to 25 years.[21] However, with treatment advances these numbers have been reduced—just 20% of people with RRMS will progress to SPMS within 15 years of diagnosis if they receive treatment.[2] Although it remains unclear which individuals will progress to SPMS, research suggests individuals with SPMS are more likely to be older and male than people with RRMS.[21]

While MS itself is generally not fatal, complications of advanced disease can be. Loss of brainstem function can lead to respiratory failure and disability can significantly reduce activity levels, increasing the risk for cardiovascular disease, pneumonia, sepsis, and uremia.[22] As a result, the life expectancy for people with MS (about 76 years) is about 7 years less than people without MS (about 83 years for the general population).[2,23]

4 Signs and Symptoms

Signs and symptoms of MS can vary considerably from patient to patient based on the parts of the CNS affected.[2,3] Symptom severity is also dependent on the number of lesions and degree of tissue injury. Depending on the type of MS, symptoms may come and go, or improve for prolonged periods, or may progressively worsen over time without periods of remittance.[18] Managing symptoms of MS is key to maintaining quality of life over the course of disease.

Vision changes are the first symptoms reported by many people with MS.[24] Optic neuritis, a condition in which demyelination occurs within the optic nerve, is the first symptom for up to one in five people with MS, and occurs in about half of MS patients over the course of the disease.[25] Although vision loss can occur with relapse, it commonly returns during remission, such that most people with MS report only mild-to-moderate vision problems over the course of the disease.[26]

Other common symptoms of MS include fatigue, reduced or loss of mobility, cognitive impairment, mood changes, bowel or bladder problems, sensory disturbances, pain, sexual dysfunction, and muscle tremors or spasticity.[3,26] A 2013 review of the North American Research Committee on Multiple Sclerosis Registry found that for many of these symptoms the prevalence and severity remains relatively stable over the course of disease, even up to 30 years after diagnosis.[26] This is consistent with approximately 85% of patients exhibiting a relapsing-remitting disease course, in which progression is slow and gradual.[4] Some symptoms, however, worsen markedly over time, including impaired mobility, fatigue, bladder and bowel dysfunction, and spasticity.[26]

Fatigue in Multiple Sclerosis: A Physical, Mental, and Emotional Burden

Fatigue is thought to be the most common symptom experienced by individuals living with MS, affecting an estimated 80% of MS patients. Fatigue in MS can take on many forms.[3]

Physical fatigue and lack of energy is most often reported by MS patients, which can further limit mobility, functionality, and socialization beyond the disabling effects of the disease.[3] Physical fatigue may be exacerbated by a high burden of sleep disorders in MS patients, which affect an estimated 70% of people with MS.[27]

People with MS often experience mental exhaustion after completing complex tasks, more so than their healthy counterparts. This MS symptom is referred to as *cognitive fatigue*. Cognitive fatigue may be caused by disruption of monoamine signaling and loss of connectivity in the frontal and prefrontal cortices of the brain, which are responsible for higher cognitive function such as processing of memories and emotions, critical thinking, and problem solving.[28]

MS can also lead to *emotional fatigue*, in which patients generally feel overwhelmed or exhausted by their

diagnosis.[3]

A number of medications, including amantadine, modafinil (Provigil), and methylphenidate (Ritalin), are commonly used to treat fatigue in MS. These drugs modulate neurotransmitter signaling in the brain, such as that of dopamine, norepinephrine, glutamate, and gamma-aminobutyric acid (GABA).[28,29] However, a recent randomized clinical trial found that these medications are no more effective than placebo for reducing MS-associated fatigue.[29] In contrast, research suggests cognitive behavioral therapy can help support people with MS who experience fatigue.[30] Fatigue in MS has been linked to poor coping strategies, and cognitive behavioral therapy can help individuals with MS learn strategies to reframe the way they think about their disease and situation.[31] Exercise can also help reduce the burden of fatigue.[30,32]

For a comprehensive overview of integrative strategies to manage fatigue in general, please see the **Chronic Fatigue Syndrome** protocol.

Table 1: Common Symptoms in Multiple Sclerosis[3,18,24,26,33]

Types of Symptoms	Examples	Prevalence in MS
Vision changes	Vision loss (in one or both eyes), double vision, reduced color or contrast sensitivity, blurred vision, eye pain, optic neuritis, nystagmus	~80%
Motor dysfunction	Muscle weakness, tremors, spasticity, physical fatigue, stiffness	80–90%
Digestive symptoms	Constipation, diarrhea, reflux	80–90%
Bladder/Urinary	Increased frequency, urgency, incontinence, increased nighttime urination, recurrent urinary tract infections (UTIs)	≥80%
Psychiatric symptoms	Depression, anxiety, mental and emotional fatigue	50-85%
Sensory problems	Loss of sensation, numbness or tingling, pain, itching	55–95%
Vestibular symptoms	Vertigo, gait impairment, trouble balancing	50–90%
Cognitive symptoms	Memory impairment or loss, trouble concentrating, difficulty processing information, reduced problem-solving and organizational skills	34–65%[34]
Sexual dysfunction	Erectile dysfunction, difficulty ejaculating, vaginal dryness, decreased sensitivity, lower libido	31–92%[35]

Table 1 shows some of the most common symptoms observed in individuals with MS, but symptoms can vary considerably between individuals as well as over the course of the disease based on the parts of the brain and spinal cord affected. Other symptoms can also occur that can have profound effects on quality of life:

- **Dysphagia**, or difficulty swallowing, has been estimated to occur in about 43% of people with MS.[36] Dysphagia occurs when demyelination occurs within the cranial nerves, which control the muscles within the neck and throat.[24]
- **Speech difficulties**, such as slurred speech, can also occur with damage to the cranial nerves.[18] Speech difficulties can occur in about one-third to one-half of people with MS.[37]
- **Heat intolerance** or sensitivity to heat has been estimated to occur in about 60–80% of patients with MS. Heat intolerance may be correlated with other symptoms of MS, including pain, difficulty concentrating, fatigue, and urinary urgency.[38]

- **Seizures** are relatively uncommon in MS but have been estimated to occur in about 2–4% of patients, a prevalence roughly 3-fold higher than observed in the general population.[39,40]

Depression, Anxiety, and Quality of Life in Multiple Sclerosis

Depression and anxiety are common among people living with MS. An estimated 50–85% of patients have at least some form of depressive symptoms over the course of their disease, and approximately 35% of people with MS will experience clinically significant anxiety or depressive symptoms.[26,41] Depression is an important predictor of quality of life in MS, second only to disability status.[42,43] According to the results of a study involving nearly 500 individuals with RRMS, women are significantly more likely to experience depression than men, particularly with regard to the physical manifestations of their disease.[44]

Research suggests that effective coping strategies and acceptance of illness can significantly improve quality of life in people with MS.[5] In a 2020 clinical trial involving 80 patients with MS, participation in a group psychoeducation program focused on educating patients about their disease, symptom management, and effective coping strategies significantly reduced symptoms of anxiety and depression and improved quality of life.[45] A treatment approach combining behavioral and pharmaceutical management of depression may help as well, but the research on these strategies in people with MS is limited.[46] The **National Multiple Sclerosis Society** also provides various resources and support to help individuals cope with their diagnosis.

A thorough review of strategies to manage psychological comorbidities associated with MS can be found in the **Anxiety** and **Depression** protocols.

5 Diet and Lifestyle Considerations for Multiple Sclerosis

Cardiovascular and metabolic diseases, such as obesity and diabetes, are MS risk factors associated with worsened disability and quality of life in MS. Therefore, a lifestyle that promotes good cardiometabolic health is important for individuals with MS.[47] Maintaining cardiometabolic health involves a number of lifestyle factors, including diet, exercise, sleep, and stress reduction.

Diet

A variety of diets, including the Mediterranean diet, have been investigated for their effects on disease progression and cardiometabolic health in MS. The Mediterranean diet emphasizes fats from olive oil, fruits and vegetables, whole grains, legumes, nuts, fish, and fermented dairy products, and limits intake of red meat, refined grains, highly processed foods, and sweets. It is associated with a number of cardiovascular and metabolic benefits, and it has anti-inflammatory properties.[48] In a study of 435 people with MS, higher rates of adherence to the Mediterranean diet were associated with less MS severity and disability.[49] In a pilot clinical trial of the effects of the Mediterranean diet on MS symptoms in 128 participants, people who adhered to a Mediterranean diet had significant reductions in disability compared with those who did not, with a significant decline in trajectory of neurological fatigue.[50]

In addition to its benefits on cardiometabolic health, the Mediterranean diet is high in polyphenols, retinoids, omega-3 fatty acids, fiber, vitamins, and minerals that are thought to reduce neuroinflammation based on animal models and preclinical research.[47,51,52] Similar diets, including the Swank, Wahls, and McDougall diets, which emphasize fruits, vegetables, and foods low in unsaturated fats (but do allow some meat) have also been investigated for their potential benefits in MS.[52,53] Although evidence to support their use for disease management in people with MS has been limited, a preliminary clinical trial involving 61 participants with MS found that those who participated in a very-low-fat, plant-based diet for 1 year reported lower levels of fatigue as well as reductions in body mass index (BMI), LDL-cholesterol, and total cholesterol. The study was too small to detect meaningful changes in severity of disease, disability, or relapse rate, but provided support for larger clinical trials examining the benefits of these diets on MS.[54]

Calorie restriction and fasting have also gained interest as a way to support healthy immune system function, metabolism, and gut microbiome health.[55] Preliminary studies have thus far been limited, but some evidence suggests they may provide a neurologic benefit. In a mouse model of demyelination, a 33% calorie restriction was

associated with improved remyelination rates, reduced cell death, and increased expression of oligodendrocyte-associated genes.[56] In human studies of fasting diets and calorie restriction in patients with MS, adherence to these dietary interventions has been found to be associated with improved mood and weight loss, but overall rates of adherence have been low.[57,58] More research is needed to understand the effects of these dietary patterns on severity and progression of MS, as well as on quality of life for patients with MS.[59]

For more information on calorie restriction, please refer to the **Caloric Restriction** protocol.

Exercise

Exercise therapy can be used to support improved functionality in MS. According to a review of nonpharmaceutical treatment options for symptom management in MS, physical activity had the greatest effects on fatigue, day-to-day function, and balance.[60] A variety of exercise plans have been shown to provide benefit to individuals with MS, including aerobic training, strength training, Pilates, and yoga.[61-64] In a clinical trial involving 38 patients with MS, participating in mat or reformer Pilates (a form of Pilates using a bed-like apparatus to facilitate strengthening) two days per week for eight weeks was associated with significant improvements in balance, functional mobility, core stability, fatigue, and quality of life. These same benefits were not observed in control participants who received breathing and relaxation exercises only.[62] In a review of 10 clinical trials that included 693 participants with MS, yoga and exercise were associated with significant reductions in fatigue compared with control interventions.[63] As functionality and energy levels may be comprised, particularly with advanced disease, exercise guidelines should be tailored to the individual and a trained assistant may be needed.[65] Pelvic floor exercise, with or without electrostimulation, can provide additional benefits to people with MS, with studies suggesting that pelvic floor training can reduce symptoms of urinary incontinence (for both males and females), female sexual health, overactive bladder, and quality of life.[66-68]

It has also been proposed that exercise may act as disease-modifying therapy, playing a protective role in the prevention of MS and providing protection against disease progression and relapse.[69] Studies in animal models of demyelination have found that exercise is associated with anti-inflammatory effects, decreasing proliferation of pro-inflammatory cells and stimulating anti-inflammatory activity in the CNS.[70] Resistance training may also support neuroplasticity in spinal motor neurons in the context of some neurological diseases.[71]

Stress Reduction

Mindfulness and emotional wellness programs can help reduce stress and improve mood in people with MS.[72,73] A review of 21 studies involving over 2,300 participants with MS found that emotional wellness programs are associated with significant improvements in stress, depression, anxiety, and quality of life.[72] An analysis of clinical trials examining the effects of mindfulness- and acceptance-based interventions among people with MS found that these programs resulted in significant improvements in stress, depression, anxiety, pain, fatigue, coping, attention, and quality of life in the immediate period following their implementation, as well as sustained benefits for stress, depression, anxiety, fatigue, and quality of life.[74,75]

6 Nutrients

Vitamin D

Beyond its role in skeletal health, vitamin D plays a crucial role in immune function. Vitamin D deficiency has been linked to several autoimmune disorders, including MS.[78,288] Preclinical research has shown that vitamin D contributes to the induction of immunological tolerance and reduces inflammatory reactions in immune cells such as macrophages, dendritic cells, and B and T cells.[289] Geographic locations that have low exposure to ultraviolet B (UVB) radiation from sunlight, and by extension greater prevalence of low vitamin D levels, also tend to have higher prevalence of MS than regions with more UVB exposure.[290]

Despite some findings that vitamin D supplementation may reduce evidence of lesions in the brain on MRI scanning in MS patients,[291,292] clinical research has not shown that vitamin D supplementation improves the overall disability status of people with MS.[80,168] Nevertheless, some studies have shown that vitamin D supplementation may result in a minor relief of certain symptoms. In a meta-analysis of 13 prospective cohort studies totaling about 3,500 people with MS, each 10 ng/mL increase in vitamin D serum levels was associated with a 10% reduction in clinical relapse rate and a 19% reduction in new active lesions (as measured by MRI). However, no

clear effect on disability progression was observed.[81]

Some evidence suggests that correcting vitamin D deficiency early on may help prevent the development of MS. A 2025 randomized controlled trial studied 303 people with **clinically isolated syndrome** with a duration of less than 90 days. Participants were supplemented with 100,000 IU (2,500 mcg) vitamin D every two weeks. During the 24-month follow up the results showed:

- **lower disease activity**: Disease activity was observed in 94 people in the vitamin D group and 109 people in the placebo group.
- **delayed progression:** The median time for second occurrence of CIS was 432 days in the vitamin D group and 224 in the placebo group.
- **improved MRI outcomes**: All three secondary MRI outcomes (activity, new lesions, and contrast enhancing lesions) were significantly improved in the vitamin D group compared with the placebo group.[293]

Coenzyme Q10

Coenzyme Q10 (CoQ10) helps regulate energy metabolism in the mitochondria and is one of many antioxidant supplements that help reduce oxidative stress. A clinical study of 45 people with RRMS found that 12 weeks of CoQ10 supplementation (500 mg/day) was associated with increased antioxidant activity and decreased markers of oxidative stress in the blood.[82] These changes were also associated with significant decreases in levels of inflammatory markers among CoQ10-treated individuals compared with placebo.[83]

Clinical trials in a variety of disease states, including MS, have found that CoQ10 supplementation (in doses ranging from 100 to 500 mg/day) is associated with significant improvements in levels of fatigue and depression.[84,85] A 2019 clinical study involving 60 people with RRMS treated with interferon beta-1a also found that three months of CoQ10 supplementation (200 mg/day) reduced markers of oxidative stress, increased levels of anti-inflammatory factors, and lowered levels of pro-inflammatory factors. Furthermore, those who received CoQ10 had lower levels of disability, fatigue severity, depression, and pain compared with those who received interferon treatment alone.[86] Additionally, in a mouse model of demyelination, CoQ10 supplementation was associated with enhanced evidence of remyelination within the brain.[87]

Lipoic Acid

Lipoic acid serves as a cofactor in mitochondrial metabolism and has a number of antioxidant and anti-inflammatory properties.[88] In a small pilot clinical study of 37 patients with MS who received oral lipoic acid supplementation (1,200–2,400 mg/day), a dose-dependent relationship between serum levels of lipoic acid and reductions in inflammatory markers was observed.[89] A subsequent clinical study comprising 52 patients with RRMS found that 12 weeks of lipoic acid supplementation (1,200 mg/day) improved serum total antioxidant capacity and was associated with significant reductions in several pro-inflammatory factors.[90,91] Following these results, a 2-year clinical study was conducted that examined the long-term effects of lipoic acid supplementation (1,200 mg/day) on symptoms and disability in 21 patients with SPMS. The results of this clinical study suggest lipoic acid can help improve walking performance in people with SPMS, particularly among those with lower levels of disability.[92]

Omega-3 Fatty Acids

Polyunsaturated omega-3 fatty acids have a variety of anti-inflammatory properties due to their ability to modulate macrophage and T-cell activity.[93] In a rat model of demyelinating disease, omega-3 fatty acids were found to inhibit several pro-inflammatory signaling cascades that promote activation of T cells.[93] In patients with MS, omega-3 fatty acids and fish oil supplementation (in doses ranging from 1 to 10 grams/day) significantly reduced inflammatory markers and were associated with reductions in relapse rate and improvements in quality of life.[94] The authors note in their conclusions from the studies reviewed that a dose of 4 grams/day of omega-3s or fish oil is recommended. However, in another review of four clinical trials, of which only one utilized a 4 gram/day dose of fish oil, omega-3 supplementation did not appear to have a significant effect on disability in MS but did reduce levels of the inflammatory mediator tumor necrosis factor-alpha (TNF-α).[95] Further research considering the impact of dose on MS symptoms and disease progression is needed.

Docosahexaenoic acid (DHA), a fatty acid found in seafood and algae, possesses a number of neuroprotective properties.[96] Preclinical studies done in animal models of MS suggest DHA may play an anti-inflammatory role in MS as well. One study found that DHA treatment was associated with improved regulation of dendritic cell activity, which resulted in reduced production of pro-inflammatory signals.[97] In another study, a DHA-rice diet delayed the onset and reduced the severity of demyelinating disease in a mouse model of MS.[98]

Vitamin A

Vitamin A is one of the antioxidant vitamins that is thought to provide dual protective activity in MS by simultaneously reducing inflammation and protecting the brain from degeneration.[99] In a clinical study of 36 patients with RRMS, vitamin A supplementation was associated with significant upregulation of genes involved in regulating T-cell activity.[100] In a concurrent trial involving 101 patients with RRMS, 12 months of vitamin A supplementation as retinyl palmitate (7,500 mcg RAE [25,000 IU]/day for six months followed by 3,000 mcg RAE [10,000 IU]/d for six months) was associated with significant improvements in functionality compared with patients who received placebo, but no effect was observed on disability, relapse rate, or active brain lesions.[101]

L-carnosine

Found at high concentrations in skeletal muscles, carnosine is thought to play a protective role against exercise-induced oxidative stress by promoting mitochondrial respiration and buffering acid levels in the muscles.[102] One study found that, in a rat model of demyelination, muscle carnosine levels were decreased by up to 64% at 17 days after disease induction. Similarly, in MS patient muscle cells, carnosine levels were decreased by 25% compared with healthy controls.[102] A pilot trial involving three people with MS found L-carnosine supplementation (2 g/day for eight weeks) was associated with improvements in severity of symptoms associated with MS, including numbness, pain, weakness, depression, and fatigue.[103]

Melatonin

Melatonin not only promotes sleep health but is involved in regulation of the immune system and is produced by a variety of cells including astrocytes, macrophages, and T cells.[77] Clinical trials involving patients with MS found that six months of melatonin supplementation (3 or 25 mg per day) on top of regular care was associated with significant reductions in serum levels of pro-inflammatory factors compared with standard treatment alone.[104,105] Additionally, markers of oxidative stress have been found to be significantly reduced in the blood of patients with both RRMS and SPMS who received melatonin supplementation (5 or 10 mg per day).[105-107]

Probiotics

Probiotics are thought to have a therapeutic benefit in a variety of conditions by promoting optimal gut microbiome health, which can modulate inflammation within the gut and throughout the body.[108] Given the inflammatory nature of MS, there has been increasing interest in the use of probiotics in these patients. A 2021 review of three clinical trials comprised of 173 people with MS found that use of probiotics was associated with significant improvements in mental health, including depression and anxiety. The study authors also described two previous reports of probiotics' ability to positively affect immune and inflammatory markers in MS patients. These reports indicated that probiotic supplementation promoted abundance of *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* species in MS patients' gut microbiomes and suggested these microbiome modulations could mediate the beneficial effects of probiotics in this context. Preclinical studies have also found that the use of probiotics may reduce the severity of MS, delay disease progression, and improve motor function, but larger clinical trials are needed to confirm these results.[109]

The Gut-Brain Connection: Role of the Microbiome in Multiple Sclerosis

The bacteria and microbes that live within the gut are collectively referred to as the gut microbiota. Although this relationship is largely symbiotic, the gut microbiome can have profound effects on human health when disturbed, including an MS risk in susceptible individuals.[110] Disturbances in the balance of microbes within the gut can lead to activation of immune cells within the intestines, resulting in pro-inflammatory signaling cascades that promote the proliferation of immune cells, including T cells and B cells.[110,111] The resulting systemic inflammation is thought to contribute to the potential development of autoimmune disorders, including MS.[110]

One of the earliest studies demonstrating the role of the gut microbiome in the development of MS was a study done in a mouse-model of demyelination. In this study, oral treatment with a broad-spectrum antibiotic, which reduced the bacterial load within the gut, was associated with a significant reduction in the production of pro-inflammatory cytokines and prevented the development of demyelination disease.[112] A more recent clinical study involving 20 Japanese patients with RRMS and 40 healthy controls found that there were significant differences in the balance of bacterial species within the gut of MS patients, particularly with regard to *Clostridia* species.[113]

For a complete discussion on factors leading to gut dysbiosis and how to maintain a healthy microbiome, please refer to the **Maintaining a Healthy Microbiome** protocol.

N-acetylcysteine

N-acetylcysteine (NAC) has been found to exert cell-survival effects within the brain and may help facilitate recovery after CNS injury.[114] In a pilot study involving 24 participants with MS who received either NAC supplementation (1,000 mg/day orally or 50 mg/kg via infusion) plus standard care or standard care alone, NAC use was associated with significant improvement in glucose metabolism within the brain as well as self-reported improvements in cognition and attention compared with standard care alone.[115] A small pilot study found that, among 15 individuals with progressive MS, NAC supplementation (1,250 mg three times daily) exhibited a positive effect on levels of antioxidants within the blood and was possibly associated with sustained improvements in fatigue.[116]

Flavonoids

Flavonoids are molecules found in fruits, vegetables, grains, teas, and wine that possess antioxidant and anti-inflammatory properties.[117] In both human and animal studies of demyelinating disease, flavonoid supplementation, including with the green tea catechin epigallocatechin gallate (EGCG), has been associated with significant improvements in disease outcomes, including functional capacity and anxiety, which are thought to be primarily driven by antioxidant activity.[118,119] Clinical trials have also examined the effects of cocoa, which has a naturally high flavonoid content, on symptoms in MS. In these studies, consumption of flavonoid-rich cocoa improved symptoms of fatigue over the course of a day.[120,121]

B Vitamins

B vitamins play a number of important roles in the body and especially the brain. These include supporting energy metabolism, myelin formation, and exhibiting antioxidative and other neuroprotective effects.[122] Results from animal models of B vitamin deficiency have found some evidence of mild neurodegeneration, including myelin degeneration, which has led to increasing interest in the role of B vitamin deficiency and supplementation for people with MS.[123,124] Studies of vitamin B status in individuals with MS have been inconclusive, with some finding vitamin B deficiency among MS patients and others reporting no difference compared with healthy controls.[125] However, in a clinical study of 16 patients with RRMS and persistent visual loss after optic neuritis, supplementation with B vitamins, including vitamins B1 (300 mg/day), B6 (450 mg/day), and B12 (1,500 mcg/day), on top of conventional treatment was associated with significant improvements in visual acuity after 90 days.[126] In animal models, pantetheine, an analog of vitamin B5, has been found to provide neuroprotective activities in other neurodegenerative diseases, but research in MS is lacking.[127-129]

The Rise and Fall of Biotin Supplementation in Progressive Multiple Sclerosis

Biotin, another of the B vitamins known as B7, is involved with energy metabolism and fatty acid synthesis and may play a role in the formation of myelin. A 2015 pilot study examined the use of high-dose biotin supplementation (100–300 mg/day) for 2 to 36 months on disease symptoms in patients with progressive MS. The study found that all four patients with visual impairment experienced improvements in visual acuity and 89% of patients with spinal cord involvement experienced improvement in symptoms.[130]

Results from this study created significant excitement about the potential use of biotin in MS treatment. A 2016 clinical trial exploring the use of MD1003 (300 mg/day), a highly concentrated, pharmaceutical-grade form of biotin, found that among 154 people with progressive MS, 12.6% of patients had disability reversal after nine

months of MD1003 supplementation compared with none of the placebo-treated patients. Additionally, MD1003 supplementation significantly reduced the progression of disability and improved participants' clinical status.[131] However, in a 2018 study involving 93 MS patients with chronic vision loss, six months of MD1003 supplementation (300 mg/day) did not improve visual acuity in people with MS and chronic visual loss.[132] Additionally, another study involving 43 patients with progressive MS found that while biotin supplementation (300 mg/day) was safe and well-tolerated, none of the patients experienced any improvement in disability status after one year of supplementation. Moreover, over one-third of patients experienced worsening symptoms while on biotin, many of which improved after biotin discontinuation.[133]

The final nail in the coffin for biotin supplementation in MS was delivered in December 2020 with the results of the SP12 trial, which included 642 participants with progressive MS from 13 countries.[134,135] In this trial, no improvement in disability or walking speed was observed after one year of MD1003 supplementation (300 mg/day), and the presence of adverse side effects, including severe ones, was high.[135] Following the results of this trial, experts agreed biotin and MD1003 cannot currently be recommended for the treatment of progressive MS.[134,135]

Vitamin E

Vitamin E, one of the antioxidant vitamins found in a variety of heart-healthy foods, has immune-modulating properties. In a study involving 88 patients with RRMS, for every 4.3 mg/L increase in serum concentration of alpha-tocopherol, a common form of vitamin E, there was a 36.8% lower likelihood of developing new brain lesions.[136] Another clinical study found that among 34 patients with MS, vitamin E supplementation (alpha-tocopherol, 400 mg/day) for three months was associated with significant reductions in serum markers of oxidative stress.[137]

Curcumin

Curcumin, which is found in turmeric, has antioxidant and anti-inflammatory properties and is thought to provide potential therapeutic benefit to individuals with MS by providing protection against oxidative stress and regulating pro-inflammatory signaling in the CNS.[138,139] In some preclinical and preliminary clinical research, nano formulations of curcumin were beneficial. Nanoparticles such as this may enhance curcumin bioavailability as well as delivery to the CNS and cells. However, more research is needed on nano-curcumin preparations.[140-142]

7 Causes and Risk Factors

While the precise cause of MS is unknown, it is thought to be driven by a complex interplay of genetic and environmental factors. Several risk factors for MS have been identified.

Genetics

Public health data suggest that MS tends to run in families.[18] An epidemiological study of over 2.5 million twins, half-siblings, and siblings in Sweden revealed a positive correlation between MS incidence and genetic inheritance.[143] The evidence for a genetic component to MS is most strongly supported by studies in twins, which demonstrate that the co-occurrence of MS is more common in monozygotic (identical) twins than in dizygotic (fraternal) twins or non-twin siblings.[143,144] Compared with the general population, people with an affected sibling are 10 to 20 times more likely to develop MS; people with an affected twin are over 100 times more likely to have MS.[145]

Evidence suggests MS is a polygenic disease caused by mutations in several genes.[145] A series of studies since the early 2000s have identified approximately 80 different genetic variants that are associated with the development of MS in various populations, and more recent genomic studies have revealed that non-mutation genetic factors (epigenetics), such as DNA methylation, are associated with susceptibility to MS as well.[145,146] Although the effects of some of these genetic alterations are still unknown, many disrupt the activity of genes encoding proteins involved in the immune response associated with MS.[145]

Female Gender

Worldwide, the prevalence of MS is two times higher in females than in males.[147] This trend is more pronounced in

the United States where females are nearly three times more likely than males to have MS.[1] Data from the United States reflect a trend observed around the world in recent decades, in which the prevalence of MS has increased over time in women more so than in men.[148] Both cisgender and transgender women are more likely to experience MS than men, with one study finding that male-to-female transgender individuals are over 6.6 times more likely to develop MS than cisgender men.[149]

Differences in MS prevalence are thought to be due to a combination of behavioral and environmental factors, as well as immune effects of sex hormones. Gender differences do not appear until after puberty, and MS relapse rates significantly fluctuate during pregnancy and peripartum.[150] Sex hormone effects are thought to be regulated by estrogen, which acts as a signaling molecule in a wide variety of immune processes, including T-cell activity.[151,152] Estriol, a form of estrogen that is higher in pregnancy, has been shown in clinical trials to improve cognitive symptoms, immune markers, and brain changes in women with RRMS.[153-155]

The effect of gender on disease progression remains unclear. Early studies of MS have identified male gender as a risk factor for faster disease progression and greater disability, with one study finding that MS progresses about 38% faster in males than in females.[148,156,157] However, this association has not been demonstrated in more recent studies.[158,159] A relationship between male infertility and MS has been shown with infertile males having a 61% greater risk of developing MS. Hormones, genetics, or environmental influences may be factors connecting these conditions.[160]

Geographic Location

International and national epidemiological studies demonstrate an association between geographic location and risk for MS, with the prevalence of MS increasing at greater distances from the equator, particularly in the northern hemisphere.[1,147,148] Globally, the prevalence of MS is highest in North America and western Europe and is lowest in sub-Saharan Africa and Oceania.[147] In the United States, a north-south gradient exists, with the highest rates of MS observed in the Northeast and Midwest, and the lowest rates observed in the South.[1]

Studies of migrants suggest this geographic distribution of MS is directly related to environmental exposures, such as amount of sunshine, which may affect vitamin D synthesis and lead to a low vitamin D level. While the risk of developing MS remains low in adults who migrate from low- to high-risk locations, children born to immigrants in high-risk locations are at increased risk for MS.[14]

Sunlight, Vitamin D, and Multiple Sclerosis Risk

The latitudinal gradient of MS prevalence suggests the development and progression of MS may be correlated with sunlight and ultraviolet B (UVB) exposure, which stimulates production of vitamin D.[14] Vitamin D plays a variety of critical roles in the immune response, including modulation of the activity of immune cells involved in the development of MS.[76]

Studies looking at the association between sunlight, vitamin D level, and MS risk have been contradictory.[76] For example, an Australian study involving over 600 people found individuals with increased sun exposure over their lifetime had a lower risk of MS, and that for every 4 ng/mL increase in serum 25-hydroxyvitamin D levels there was a 7% lower risk for CNS demyelination.[161] In a 2020 clinical study involving 36 patients with MS, vitamin D deficiency was associated with reduced activity levels and increased disability in individuals with RRMS, but not SPMS, suggesting the effects of vitamin D may vary based on the disease state.[162] Furthermore, an analysis of two population-based case-control studies (7,069 cases, 6,632 matched controls) found that low sun exposure correlated with a 26% increased risk of MS.[163]

In an analysis of data from a 2020 randomized controlled trial of patients with RRMS, those with a vitamin D level of at least 30 ng/mL had fewer CNS lesions compared to those with a vitamin D level below 30 ng/mL, and vitamin D levels were found to negatively correlate with disability.[164] The study did not have enough participants to determine if a vitamin D supplement attenuated the course of disease, however, highlighting the need for more research on the relationship between vitamin D status and the risk for and progression of MS.[165]

In contrast, in a clinical study of over 1,000 patients with MS or optic neuritis, a common first symptom of MS that also can have other etiologies, people with MS had a significantly higher vitamin D level than people with optic neuritis, and there was no association between vitamin D levels and risk of progression from optic

neuritis to MS.[166] Similarly, no association between vitamin D levels and severity of visual symptoms was found in people with PPMS or SPMS.[167]

In 2018, the Cochrane Collaboration undertook a comprehensive review of published reports of randomized controlled trials of vitamin D in MS. The conclusion of this review was that evidence was generally low quality and not suggestive of benefit on outcomes important to patients such as relapse recurrence or worsening disability.[168]

Race or Ethnicity

The incidence of MS is higher among Black Americans than White Americans. Compared with White Americans, Black Americans are also more likely to develop MS at an earlier age, experience greater disability and poorer recovery, and have shorter periods between first and second MS attacks. Similar trends are observed for Asian and Hispanic Americans with MS.[169] Imaging studies suggest nerve atrophy progresses faster in Black Americans than White Americans, which may explain why Black patients with MS are more likely to experience vision loss from optic neuritis than White patients.[169,170] Differences in prevalence of severity of MS may be driven in part by genetic differences, but socioeconomic factors such as access to healthcare likely contribute as well.[169,171]

Smoking Status

Compared with people who never smoked, the relative risk for MS is 50% higher for people who smoke or have a history of smoking.[172,173] Cigarette smoke causes irritation in the lungs, increases oxidative stress, and may promote the pro-inflammatory cascades seen in MS. Chemicals in cigarette smoke are also neurotoxic and can increase the disease activity, brain atrophy, and resulting disease burden in people with MS.[174] Cigarette smoke has also been shown to influence disease progression and accelerate the conversion from RRMS to SPMS.[175] Smoking cessation is recommended for individuals with MS.[18]

Viral Infection

Viral infection, particularly with **Epstein-Barr virus (EBV)**, may increase the risk of MS. EBV is a nearly ubiquitous viral infection, affecting over 90% of people worldwide, and is the causative agent of infectious mononucleosis.[176] In a 2010 meta-analysis of 18 studies involving over 35,000 people, previous history of infectious mononucleosis was associated with more than double the risk of MS compared with no history of infectious mononucleosis.[177] A 2017 analysis showed that 96% of studies assessed found a significant association between previous infectious mononucleosis and risk for MS.[178]

In 2022, a cohort study examined the link between EBV infection and MS development in active-duty U.S. military personnel. This cohort included 801 MS cases and 1,566 controls monitored over 20 years. Participants previously infected with EBV were approximately 32 times more likely to develop MS after generation of EBV antibodies (seroconversion). The median time to onset was 7.5 years (range 2–15 years).[179,180] Serum levels of neurofilament light chain, a biomarker for axonal degeneration suggestive of MS disease activity, were also increased in individuals after EBV infection.[179] These findings could not be explained by any known MS risk factors, suggesting EBV infection may trigger MS development.

It is unclear exactly how EBV potentially increases MS risk—some have suggested it may be because EBV triggers a “two-hit mechanism,” in which EBV first increases the permeability of the blood-brain barrier, then allowing infiltration of lymphocytes which promote subsequent inflammation.[181]

Intrathecal levels of antibodies against measles, rubella, and varicella zoster viruses have also been found to be elevated in people with MS and are sometimes used as laboratory markers to aid in diagnosing MS.[182]

8 Diagnosis

A comprehensive clinical history and physical exam are important aspects of the MS diagnostic process. If MS is suspected, imaging techniques, such as magnetic resonance imaging (MRI) or optical coherence tomography; neurophysiological testing; evoked potentials (which measure brain electrical activity in response to audible or visual stimuli and can aid in detecting subclinical CNS dysfunction); and examination of the cerebrospinal fluid (CSF) may be required.[183]

Diagnosis of MS is based on the revised McDonald criteria, which require the demonstration that demyelinating lesions are spreading to multiple locations within the brain (dissemination in space) and are worsening over time (dissemination in time). Dissemination in space can be demonstrated by multiple types of clinical attacks that are characteristic of different affected portions of the CNS, or can be observed using brain and spinal cord imaging. Progression of disease, or dissemination in time, may mean two or more distinct clinical attacks occur, separated by at least 30 days. Alternatively, a *lumbar puncture*, or spinal tap, can be used to demonstrate the presence of proteins in the CSF that are indicative of inflammation in the CNS, which correlates with disease progression and fulfills the dissemination in time criterion.[183] The expanded disability status scale (EDSS) is method of quantifying disability in MS and monitoring changes in level of disability over time.

A single, clinically isolated event that causes neurologic symptoms for at least 24 hours, such as an attack of optic neuritis, is known as **clinically isolated syndrome (CIS)**. A single isolated episode does not meet the diagnostic criteria for MS, but research suggests approximately 85% of people diagnosed with a CIS will experience a second clinical demyelinating event and progress to RRMS within 20 years.[184]

Because MS is a complicated disorder characterized by a wide variety of presentations, it can be difficult to diagnose. One study involving 431 people initially diagnosed with MS found that 30% were misdiagnosed and had a different condition.[185] The differential diagnoses of MS are broad and can include[18,186]:

- **CNS inflammatory disorders and demyelinating diseases**, such as neuromyelitis optica spectrum disorder (NMOSD), partial transverse myelitis, or Marburg virus disease
- **Other inflammatory or autoimmune disorders**, including systemic lupus erythematosus, sarcoidosis, or Sjögren syndrome
- **Infectious diseases** such as human immunodeficiency virus (HIV), Lyme disease, syphilis, and herpes virus infections
- **Vascular conditions** such as migraine or stroke
- **Metabolic disorders**, including vitamin deficiencies and thyroid disease
- **Brain tumors** or **metastases**

9 Treatment

Although a cure for MS is yet to be discovered, there are currently close to two dozen disease-modifying therapies approved for the treatment of MS that function to reduce inflammation within the CNS. Treatment with these agents focuses on preventing relapse, slowing disease progression, and preventing disability.

Interferon-based therapies and glatiramer acetate (Copaxone) were the first treatment options available for MS.[7] In phase 3 clinical trials, these agents reduced the frequency of relapse by 29–34% and slowed disease progression by 12–37%.[187] Although not as potent as newer therapies, these injectable agents tend to have fewer side effects and still have a place in the treatment landscape of MS, particularly for people who cannot tolerate higher-efficacy medications or women who are pregnant or may become pregnant.[188-192] For most people, however, starting with a higher-efficacy therapy is warranted since research suggests earlier treatment with high-efficacy therapies is associated with less disability and lower rates of relapse within the first decade of disease.[193,194]

Oral Multiple Sclerosis Disease-modifying Therapies

A variety of oral agents are available for the treatment of MS that represent a step up in efficacy compared with interferons and glatiramer acetate, including teriflunomide (Aubagio), cladribine (Mavenclad), fumarates, and sphingosine-1-phosphate (S1P) receptor modulators. Compared with placebo, these agents reduce the annual relapse rate by about 48% to 69%, although some S1P receptor modulators (siponimod [Mayzent]) exhibit lower efficacy.[7] This represents a growing class of drug options for the treatment of MS, with some of the most recently approved agents including fumarates (diroximel fumarate [Vumerity] and monomethyl fumarate [Bafiertam]) and S1P receptor modulators (ozanimod [Zeposia] and ponesimod [Ponvory]).

Fumarates. The therapeutic effects of dimethyl fumarate in MS are somewhat unclear, but it is thought to act in

part by activating nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is a transcription factor responsible for regulating the expression of genes related to inflammation and oxidative stress.[195,196] In a mouse model, dimethyl fumarate was found to prevent demyelination and loss of axons by decreasing pro-inflammatory cytokine production and the proliferation of T cells in addition to blocking the infiltration of pro-inflammatory macrophages into the CNS.[197] A modified form of dimethyl fumarate, known as diroximel fumarate, was recently developed and causes less reactivity with cells in the gastrointestinal tract.[198] Gastrointestinal upset, including nausea, vomiting, and diarrhea, are common with dimethyl fumarate use, but were observed less frequently with diroximel fumarate use in the EVOLVE-MS-2 phase 3 clinical trial (49.0% vs. 34.8%, respectively).[199] These reductions in gastrointestinal symptoms are associated with improved quality of life compared with dimethyl fumarate, including improved productivity and fewer interruptions to daily activities.[200] In the phase 3 EVOLVE-MS-1 trial, use of diroximel fumarate reduced the number of active, inflammatory lesions in the brain by 77% and was associated with a low annualized relapse rate of 0.16.[198]

Both dimethyl and diroximel fumarate are prodrugs and are quickly metabolized to monomethyl fumarate in the body. These prodrug forms are more easily absorbed by the body than monomethyl fumarate, but monomethyl fumarate can also be taken directly as a monotherapy for MS.[201]

S1P receptor modulators. S1P receptors are expressed on the surfaces of a variety of immune cell types, including B cells, T cells, and oligodendrocytes, and are responsible for regulating movement of these cells throughout the body. One of the functions of S1P receptor modulators is to promote the internalization of the S1P receptor within immune cells, which results in their sequestration within the lymph nodes and prevents their trafficking to the CNS.[202]

Fingolimod (Gilenya), isolated from the *Isaria sinclairii* fungus, was the first S1P receptor modulator approved for use in MS.[202] In a phase 3 clinical trial, fingolimod reduced the risk of progression of disability by about 30% over two years compared with placebo and was associated with significant reductions in relapse rates.[203] Use of fingolimod was found to be associated with reductions in disability progression similar to those observed with interferon beta-1a, but resulted in significantly lower relapse rates.[204]

Fingolimod's success led to the development of three new S1P receptor modulators for the treatment of MS: siponimod, ozanimod, and ponesimod. Results from the phase 2 BOLD study demonstrated that use of siponimod over a range of doses reduced the number of new active lesions as early as three months after starting treatment and was associated with low annualized relapse rates (0.14–0.33) in individuals with RRMS.[205,206] Subsequent studies in patients with SPMS, which remains notoriously difficult to manage,[207] found siponimod use (2 mg daily) was associated with a 21% reduction in risk of progression of disability after three months of treatment compared with placebo, and provided significant cognitive benefits over 24 months.[208,209]

Ozanimod and ponesimod represent the most recently approved S1P receptor modulators for individuals with MS. In phase 3 clinical trials, ozanimod use reduced the annual relapse rate by 52% over the course of 12 months and 62% over 24 months compared with interferon treatment.[210,211] Compared with other S1P receptor modulators, ozanimod targets the S1P receptor more selectively and has reduced risk of off-target effects, which is associated with an improved cardiac safety profile.[212] Ponesimod, another highly selective S1P receptor modulator, was approved for use in relapsing MS in March 2021 based on the results of the phase 3 OPTIMUM trial, which found ponesimod reduced the annual relapse rate by 30.5% and presence of new, active lesions by 59% compared with teriflunomide.[213]

Monoclonal Antibody Therapies

Monoclonal antibodies are a class of drugs that specifically target proteins involved in the development of disease. The specificity of these agents has led to an explosion in their development for a variety of diseases, including MS. There are currently four monoclonal antibody therapies approved for use in individuals with MS (ocrelizumab [Ocrevus], natalizumab [Tysabri], alemtuzumab [Campath, Lemtrada], and ofatumumab [Kesimpta, Arzerra]) and a fifth that is often used off-label to treat patients with MS (rituximab [Rituxan]).[214] Monoclonal antibody therapies are among the most effective options for the treatment of MS and are generally recommended as a first-line treatment option.[7,188,214] Because these antibodies target components of the immune system, they can cause immunosuppression, which can increase the risk for infection or illness.[214] Monoclonal antibody

therapies are administered intravenously or via subcutaneous injection.[7]

For people with PPMS, there are not many treatment options and ocrelizumab is the only disease-modifying therapy approved for use in these patients.[188] In a phase 3 clinical trial in patients with PPMS, ocrelizumab reduced the risk of disability progression by 25% over 24 weeks compared with placebo and reduced the total volume of brain lesions by 3.4% compared with a 7.4% increase during the same time period with placebo.[215]

Symptom-specific Therapies

Although MS disease-modifying therapies prevent relapse and disability progression, most of the symptoms of MS are not effectively managed with these therapies, and many people will also require symptomatic treatment.

Pharmacotherapies. A wide variety of medications can be used to manage the symptoms of MS. However, these medications do not reverse or prevent the progression of disease.

- **Muscle relaxants** can be used to treat muscle spasms, which affect up to 90% people with MS.[7] In a 2013 clinical trial involving 52 MS patients experiencing leg muscle spasms, use of the muscle relaxant baclofen (Lioresal, Gablofen) (10 mg twice daily, increasing over three weeks to 25 mg) significantly reduced the frequency of muscle spasms after four weeks of treatment.[216]
- **Anticonvulsants** can also be used to help control muscle spasms, as well as ataxia and tremors.[7]
- **Botulinum toxin** is used to reduce local signaling between muscles, which can help manage muscle spasms and tremors in MS.[7] A meta-analysis of six studies involving 245 participants found that while botulinum toxin A injections are unlikely to benefit individuals with hand tremors in general, they may provide specific benefit to people with MS.[217]
- **Pain medication** is commonly used as over 80% of people with MS experience some amount of pain over the course of their disease.[7,26] Some pain medications can help resolve other symptoms of MS, such as gabapentin (Neurontin), which helps with muscle tremors, and duloxetine (Cymbalta), which is an antidepressant.[218]
- **Glucocorticoids** may be used to treat acute exacerbations of MS. While not indicated for long-term treatment of MS, glucocorticoids may resolve MS relapse symptoms more rapidly. Typically, this either includes a short course of intravenous or oral methylprednisolone or oral prednisone, possibly followed by a prednisone taper.[219,220] Alternately, an injection of corticotropin (adrenocorticotropic hormone [ACTH]) gel may be used and has similar efficacy to IV methylprednisolone.[221]

Other symptoms, such as **depression**, **bladder dysfunction**, **secondary infections**, cognitive impairment, and **sleep disorders**, may require specialized treatment.

Cognitive Training and Rehabilitation

Cognitive training and rehabilitation involve the use of strategies intended to improve cognitive function, including the ability to process and interpret information and utilize that information in daily life. Several studies have examined the use of cognitive rehabilitation in people with MS and have observed benefits related to attention, communication, memory, and psychological symptoms.[222] Computer-based cognitive training programs have also been developed to help support cognitive rehabilitation. In a study involving 62 people with stable MS with mild-to-moderate cognitive impairment, participation in a 12-week computer-assisted cognitive training program was associated with significant improvements in verbal memory, working memory, and phonetic fluency, as well as reduced levels of anxiety and improved quality of life.[223] A review of 20 clinical trials involving 982 participants found participation in computerized cognitive training programs was associated with small-to-moderate improvements in attention, processing speed, executive function, and verbal and visuospatial memory.[224]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive treatment option that may be helpful for some types of pain. TENS involves stimulation of peripheral nerves by low-level (non-painful) electrical signals. Researchers are not entirely sure how TENS works, but it is thought that electrical stimulation of peripheral nerves modulates central pain processing.[225,226] Overall, evidence supporting the effectiveness of TENS in general is not very robust.[227]

Several small studies have evaluated the effect of TENS on a variety of MS-related symptoms, including pain, motor function, and spasticity.[228-233] These trials have generally been suggestive of some potential benefit but have not been methodologically sound enough to provide convincing evidence. Nevertheless, since TENS is generally well-tolerated, it may be worth trying if other options prove insufficient.

Physical and Occupational Therapy

Physical and occupational therapy can help people with MS manage the severity and effects of the physical symptoms of their disease, both during relapses and periods of remission.[234,235] A review of 32 studies involving patients with MS or **amyotrophic lateral sclerosis (ALS)**, a neurodegenerative disease with some similarities, found participation in occupational therapy was associated with significant improvements in levels of fatigue, manual dexterity, and cognitive function, including memory and communication; reduced the risk for falls and depression; and was associated with improved quality of life.[236] Research also suggests physical therapy can help reduce muscle spasticity and improve muscle tone in people with MS.[237]

Neuromuscular electrical stimulation, also known as functional electric stimulation (FES), may support or augment the benefits of physical and occupational therapy. FES differs from TENS in that TENS targets the sensory nerves while FES involves the delivery of mild electrical stimulus to affected muscles which lost their signaling capabilities due to the demyelinating activity of MS.[238,294] Clinical trials of FES have primarily focused on its use in patients with impaired leg mobility and have found that FES is associated with significant improvements in balance, walking performance (including speed and endurance), and overall self-esteem.[239-241] Neuromuscular electrical stimulation has been found to improve other symptoms of MS caused by poor muscle activity as well, including dysphagia[242] and overactive bladder.[243,244]

Virtual Reality in Multiple Sclerosis Therapy

The use of virtual reality (VR) has emerged as a complement to traditional cognitive, physical, and occupational rehabilitation in MS.[245,246] VR allows therapists to place MS patients into immersive scenarios that allow them to practice physical functions in a safe, controlled manner. In this way, VR can help physical and occupational therapists quickly and safely evaluate functionality, such as through simulation of driving a car, crossing a street, and other tasks that require complex integration of sensory inputs.[247-249]

In a 2019 clinical trial involving 26 people with MS, addition of VR-based training to traditional occupational therapy was compared with occupational therapy alone. VR-based training was associated with significant improvements in the precision of movements, as well as speed and execution of various functional tasks, such as picking up small objects or writing with the non-dominant hand.[250] A 2020 clinical trial involving 30 patients with RRMS, SPMS, or PPMS found participation in a specially designed VR-based game in addition to conventional physical therapy was associated with significant improvements in coordination, movement speed, and fine and gross upper limb motor dexterity compared with physical therapy alone.[251] Another clinical trial involving 39 people with MS found VR-based therapy may support aspects of balance and mobility training by improving cognitive-motor function and helping reduce the risk of falls.[252]

10 Novel and Emerging Strategies

Cell-based Therapies

Stem-cell therapies have emerged as a potential option to help reduce autoimmune activity in MS. Stem cells give rise to other cells within the body. Hematopoietic stem cells (HSCs) are responsible for repopulating the blood and immune cells that are regularly recycled to make way for new, healthy cells. In an autologous HSC transplantation, the patient is first given medications such as cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) to stimulate the production of HSCs, which are collected from the bone marrow. Chemotherapeutics are then used to deplete the existing immune cells circulating within the blood before the patient is infused with their own HSCs. In this process, the immune system is effectively “reset” and the body can begin making new immune cells with the hope of reduced autoimmune activity within the CNS.[253]

In an analysis of 210 patients with MS who received autologous HSC transplantation, 85.5% of people with RRMS

and 71% of people with progressive MS experienced no worsening of their disability within five years post-transplant. At 10 years, 71.3% with RRMS and 57.2% with progressive MS still had no progression of disability. On average, disability status improved after transplantation in individuals with RRMS.[254] Similarly, another analysis of 259 people with RRMS, 228 with SPMS, and 130 with PPMS found that 86%, 78.5%, and 78% of patients, respectively, self-reported no progression in their disability a median of 12 months post-treatment.[255] In a smaller study involving 10 people with RRMS, half of patients had sustained, complete remission of their disease symptoms for up to five years post-transplant, including three patients whose MS was considered resolved.[256] In the absence of control groups, these results cannot be compared with other common treatments for MS. While past clinical trials of immunomodulatory drugs have shown that about 56–75% of patients with RRMS are free of disability worsening at five years,[257,258] the trials differed in study design and patient populations.

Autologous HSC transplantation has also been studied as a first-line treatment option for people with more aggressive forms of MS. A retrospective analysis of 20 patients found autologous HSC to be associated with significant improvement in disability status, with no evidence of relapse or disease activity as measured on MRI.[259]

Autologous mesenchymal stem cell (MSC) transplantation has also been investigated as a potential treatment option for MS. MSCs give rise to a variety of cell types including adipocytes (fat cells) and the cells involved in bone and cartilage remodeling. MSCs also produce compounds that help regulate immune processes and can prevent the proliferation of immune cells involved in MS, such as T cells and macrophages.[260] Research in animal models of demyelination have found that MSC transplantation is associated with remyelination, reduced inflammation, and regeneration of oligodendrocyte precursor cells.[261] In a study involving 48 people with progressive MS, 40.6% and 58.6% of patients who received autologous MSC transplantation intravenously or intrathecally, respectively, had no evidence of disease activity during one year of follow-up compared with 9.7% who received sham treatment.[262] Clinical trials have thus far been small but suggest about 70% of MS patients experience disease stabilization after MSC transplantation.[261]

Cannabis

Cannabinoids are compounds found in cannabis that can be used to manage a variety of MS symptoms, including muscle cramps or spasms, ataxia, tremors, pain, mood disorders, and insomnia.[7,263] A 2020 trial involving 15 patients with SPMS found that use of a cannabis-based oral spray was associated with significant improvements in spasticity, as well as pain.[264] According to the results of a survey on cannabis use in MS, 86% of patients reported that they had stopped or reduced other medications used to treat the symptoms of their disease because they found cannabis to be more effective.[263] Concerns have been raised, though, about the effects of cannabinoids on cognitive function.[265]

In addition to the use of cannabinoids for symptom management in MS, there has been increasing interest in its role as a disease-modifying therapy. Cannabinoid receptors are found in a variety of cell types involved in MS, including several types of immune cells; nerve cells in the brain, spinal cord, and peripheral nervous system; and astrocytes, oligodendrocytes, and microglia.[266] Induction of these receptors is associated with a variety of anti-inflammatory effects, and experimental evidence from animal models suggests that the use of cannabis-based therapies is associated with reductions in pro-inflammatory cytokines and increases in anti-inflammatory factors.[266,267]

The effects of cannabis use on inflammation in MS were explored in a 2021 study involving 150 people with MS (including 28 cannabis users) and 150 healthy controls. Compared with healthy controls, people with MS had higher levels of almost all examined pro-inflammatory factors and lower levels of anti-inflammatory factors. Among MS patients, these trends were more pronounced for individuals who did not use cannabis, such that cannabis use was associated with significantly lower levels of pro-inflammatory and higher levels of anti-inflammatory factors compared with non-use. Additionally, cannabis users reported significantly higher rates of improvement in symptoms, including pain, muscle spasms, fatigue, walking difficulties, anxiety, and mood disorders.[268] These results are preliminary, and large-scale clinical trials examining the effects of cannabis use on disease progression and relapse are still needed to fully understand its potential as a disease-modifying therapy in MS.[266]

Importantly, biases likely influence preliminary cannabis research. Some authors have suggested that MS patients' perception of benefits attributable to cannabis use differs substantially from that of their clinicians in many cases.[269]

Remyelination Therapies

Evidence from animal and human studies have found that oligodendrocytes may help promote remyelination in MS.[270] To this end, various therapeutic strategies to promote oligodendrocyte survival and activity have been investigated in the hope that they can facilitate remyelination in MS.[271-274] The effects on remyelination and disease activity in preclinical and preliminary clinical studies have been highly variable, and several agents that appeared promising in early research have thus far failed to reach clinical trials in humans.[271,275]

Nonetheless, remyelination-enhancing therapies represent emerging treatment options with great potential to not only prevent but reverse progression of MS.[271,275] Ongoing clinical trials aim to determine whether existing medications can be repurposed to promote remyelination. Clemastine, an antihistamine medication, was recently investigated in a small interventional case series that included 25 patients with acute optic neuritis. Compared with those who received clemastine (1 mg twice daily), placebo patients had greater reductions in nerve thickness over 90 days and clemastine-treated patients had greater improvements in visual signaling following treatment.[276] In addition to clemastine, ongoing clinical trials seek to evaluate the potential for the diabetes drug metformin to promote remyelination in MS when used in combination with clemastine.[277]

Emerging Biomarkers

There has been significant interest in identifying biomarkers that can help diagnose MS as well as predict disease progression and treatment response. Some biomarkers, such as CSF oligoclonal bands and seropositivity for certain viruses, have been validated in MS patients, but many remain investigational and require additional validation.[278]

Investigational biomarkers include several molecular- and imaging-based approaches:

- **MicroRNAs (miRNAs)** are short, non-coding RNA molecules that help regulate gene expression in cells. A variety of miRNAs have been found to be associated with MS, including miR-155, miR-145, and miR-128-3p.[279-281] According to a review of nine studies, a panel of four miRNA biomarkers can distinguish MS patients from non-MS controls with 73% sensitivity and 68% specificity, whereas the sensitivity increased to 79% and specificity to 87% when using a single miRNA (miR-145).[279] More research is needed to validate the use of miRNA biomarkers to independently diagnose MS, but the current research suggests they may be a valuable tool alongside existing diagnostic techniques for early identification of MS.[282]
- **Neurofilament light chains** are polypeptides that help make up neurofilaments, which help provide structural support to neurons. Elevated levels of neurofilament light chains in the CSF of MS patients have been linked to increased risk of progression to SPMS and brain atrophy.[283,284] Recently, the utility of plasma and serum levels of neurofilament light chain as a biomarker has been of interest given the less invasive nature of their measurement compared with CSF testing. In a study involving 4,385 people with MS and 1,026 matched controls, higher levels of plasma neurofilament light chains were associated with increased risk for disability.[285] Additionally, in a study of 80 patients with RRMS, low levels of serum neurofilament light chains were found to be predictive of optimal response to treatment with dimethyl fumarate.[286]
- **Imaging** using MRI is a well-established step in diagnosing MS, but new research suggests it may be able to help predict the progression of disease. Using MRI data from over 6,000 patients with MS, machine learning identified three subsets of patients based on presentation, location, and severity of brain lesions. One of these subsets, characterized by the early and rapid accrual of lesions and severe brain atrophy, was found to be associated with the highest rates of disability progression and highest relapse rates.[287]

Update History

consult with and seek clearance from a physician or other qualified health care professional. Pregnant women in particular should seek the advice of a physician before using any protocol listed on this website. The protocols described on this website are for adults only, unless otherwise specified. Product labels may contain important safety information and the most recent product information provided by the product manufacturers should be carefully reviewed prior to use to verify the dose, administration, and contraindications. National, state, and local laws may vary regarding the use and application of many of the therapies discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.

The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. Life Extension has not performed independent verification of the data contained in the referenced materials, and expressly disclaims responsibility for any error in the literature.

References

†Ratings based on results of the 2025 ConsumerLab.com Survey of Supplement Users. Multivitamin rating based on results of the 2024 ConsumerLab.com Survey of Supplement Users. For more information, visit **www.consumerlab.com/survey**.

These statements have not been evaluated by the Food and Drug Administration.
These products are not intended to diagnose, treat, cure, or prevent any disease.