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Multiple Sclerosis: III. Treatment and Prognosis

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Abstract

In this article, I present the many symptomatic treatments available for multiple sclerosis (MS). Disease-modifying drugs are not curative but can slow down or reduce the number and severity of relapses or inflammation seen on MRI scans. They work the better the sooner they are started, but taking them later can still have benefits. These drugs/therapies can have side effects, some serious, but not being treated entails the risk of more relapses and more long-term disability. There are 34 available such drugs, all reviewed here, which are taken either as a pill, an injection, or an infusion. Recent developments and emerging pharmacotherapies are also discussed as well as non-pharmacological therapies whose interventions for chronic pain is insufficient to recommend them alone including rehabilitation in its various forms (physical, cognitive, occupational, speech language, vocational, and palliative). Research on the immunobiology of MS has resulted in a variety of potent anti-inflammatory therapies but they are of extremely limited efficacy in the more important and disabling progressive phase, which has emerged as the greatest clinical and research challenge. The application of autologous human stem cell therapy is also abundantly discussed in terms of its benefits and effectiveness in the relapsing form of the disease. The prognosis of MS depends on the subtype and progression of the disease. The guidelines usually followed to infer prognosis are lastly summarized.

Abbreviations

ACTH: Adrenocorticotropic hormone; AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; AML: Acute myeloid leukemia; aSCT: autologous stem cell therapy; BTKI: Bruton's tyrosine kinase inhibitor; CAMT: Complementary and alternative medicine therapies; CIS: Clinically-isolated syndrome; CNS: Central nervous system; CRT: Cognitive rehabilitation therapy; DMD/T: Disease-modifying drugs/therapies; EBMTR: European Bone Marrow Transplant Registry; EBV: Epstein-Barr virus; EDSS: Expanded Disability Status Scale; ELISA: Enzyme-linked immunosorbent assay; EPC: Endothelial progenitor cells; FACT: Foundation for the Accreditation of Cellular Therapy; FDA: (U.S.) Food & Drug Administration; GD: Graves' disease; GI: Gastrointestinal; HDC: High dose

calciferol; HSCT: Hematopoietic stem cell transplantation; JCV: John Cunningham virus; LDC: Low dose calciferol; MEDA: Minimal evidence of disease activity; MHC: Major histocompatibility complex; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; MSA: Multiple system atrophy; MSC: Mesenchymal SC; NDD: Neurodegenerative diseases/disorders; NEDA: No evidence of disease activity; NMSS: (U.S.) National Multiple Sclerosis Society; NRT: Neurorehabilitation therapy; NSC: Neural SC; OT: Occupational therapists; PD: Parkinson's disease; PML: Progressive multifocal leukoencephalopathy; PPMS: Primary progressive MS; PSC: Pluripotent SC; PT: Physical therapy; RMS: Relapsing MS; RRMS: Relapsing remitting MS; SC: Stem cells; SCT: SC therapy; SLP: Speech language pathologists; SPMS: Secondary progressive MS; VRT: Vocational rehabilitation therapy; WBC: White blood cells.

Keywords

Multiple sclerosis treatment; disease-modifying drugs/therapies; non-pharmacological therapies; immunotherapy; autologous stem cell therapy; prognosis and future outlook.

Introduction

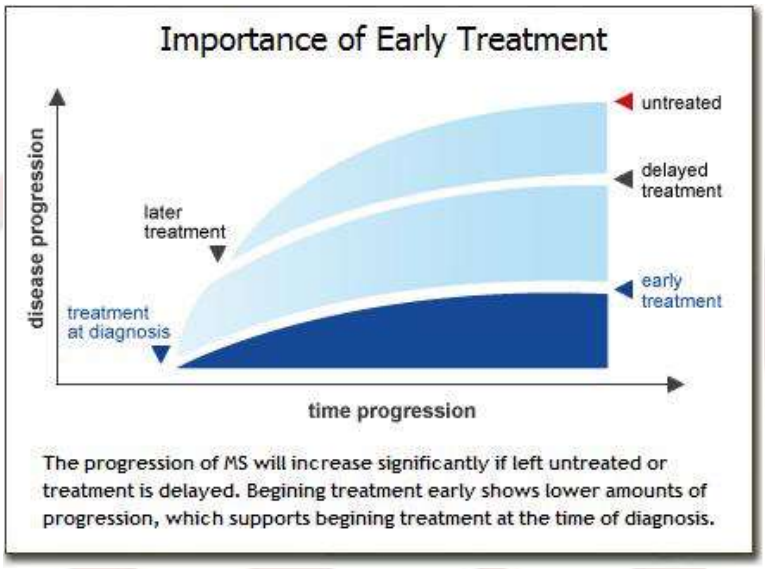
Since first described in 1838, it took 30 years for physicians to recognize multiple sclerosis (MS) as a disease. In 1900, the life expectancy of a person with MS was only five years. Today, individuals can now live a normal life-span, though often with a struggle and increasing limitations. It was not until after World War II that an immunologic cause of MS was seriously investigated. Further, it was not until 1970 that the first positive results of treatment with an immunologic therapy (steroids) were released. Beginning in the 1990s, the availability of treatments that modify the course of MS, known as disease-modifying drugs/therapies (DMD/Ts), has improved prognosis. These treatments can reduce relapses and slow progression but as of early 2023, there still is no cure. We also have learned a lot about the role of the immune system in how MS develops and progresses, which has helped in the development of numerous DMD/Ts. Most of these therapies directly modulate the immune system to prevent it from attacking the central nervous system (CNS). Having multiple treatment options allows people living with MS to personalize their treatment. In this article, I will discuss at length all currently available DMD/Ts for the several MS types including their prescription guidelines, benefits, adverse effects, and associated recent developments and emerging pharmacotherapies. I will further present non-pharmacological therapies, immunotherapies, and autologous stem cell therapies and lastly elaborate on the prognosis and future outlook for the disease.

Disease-modifying drugs/therapies

As seen in part II in this series, the symptoms and progression of demyelinating diseases vary between patients. There are many treatments, including drugs, devices, and therapies that can help with symptoms from muscle pain, stiffness, spasms, and poor balance to incontinence issues, difficulties with speech, swallowing, sight, memory and thinking, and sexual function. Early diagnosis and discussion of treatment options is important. Irrespectively, emphasis is on early treatment. As illustrated in Figure 1 below, the progression of MS will increase significantly if left untreated or treatment is delayed. Beginning treatment early shows lower amounts of progression, which supports beginning treatment at the time of diagnosis.

DMD/Ts are used to treat MS when there are relapses or inflammation seen on MRI scans. They could change (for the better) how MS develops over time and could offer many people the chance to take more control of their MS. However, despite their benefits, they cannot undo any permanent disability. They are not a cure, but they can reduce how many relapses occur and how

serious they are. They can also slow down the damage caused by relapsing MS that builds up over time. To reduce the risk of permanent damage, a DMD/T is offered as soon as possible after a diagnosis of relapsing MS. DMD/Ts work better the sooner they are started, but taking them later can still have benefits. These drugs/therapies can have side effects, some serious, but not being treated means the risk of more relapses and more long-term disability. There are 34 available DMD/Ts for MS, which are taken either as a pill, an injection, or an infusion.



Source: MyMS.org

Figure 1: Importance of early MS treatment

The primary aims of therapy are to: Return function after an attack, reduce or prevent new attacks, and slow down or prevent disability.

Although there is no known cure for demyelinating diseases, including MS, several DMD/Ts have proven helpful in altering the disease progression in some patients, significantly decreasing the number of attacks and the rate of progression. They can be used together with symptomatic treatment (see Article II in this series). The more immediate goals of treatment are to: Minimize the effects of the attacks, modify the course of the disease, and manage the symptoms. The aim is to achieve a state where there is no evidence of disease activity (NEDA), meaning no relapses, no progression of disability, and no evidence of activity on the MRI or at least minimal evidence of disease activity (MEDA).

A variety of drug therapies are recommended depending on the specific disorder.

Treatment Recaps From Symptoms To Full-Blown Disease

Symptoms

Strategies to treat symptoms (see Article II in this series for a fuller treatment) include medications to improve walking, spasms, bladder dysfunction, and other symptoms. Physical therapy, occupational therapy, and cognitive behavioral therapy can also help manage people's ability to function.

Starting medications is generally recommended in people after the first attack when more than two lesions are seen on their brain MRI. Older medications used to

treat MS were modestly effective, could have side effects, and were poorly tolerated. However, several treatment options with better safety and tolerability profiles have been introduced, changing the prognosis of MS.

As with any medical treatment, medications used in the management of MS symptoms have several adverse effects. In the treatment era, 16% of people with relapsing MS went on to need a cane to walk after 20 years.

Attacks

Against attacks, the following two treatments are employed:

• **Corticosteroids:** Corticosteroids, such as intravenous Methylprednisolone, are prescribed over the course of 3 to 5 days. Intravenous steroids quickly and potently suppress the immune system and reduce inflammation. They may be followed by a tapered dose of oral Corticosteroids. Clinical trials have shown that these drugs hasten recovery from MS attacks, but do not alter the long-term outcome of the disease.

• **Plasma exchange (plasmapheresis):** It can treat severe flare-ups in people with relapsing forms of MS who do not have a good response to Methylprednisolone. Plasma exchange involves taking blood out of the body and removing components in the blood's plasma that are thought to be harmful. The rest of the blood, plus replacement plasma, is then transfused back into the body. This treatment has not been shown to be effective for secondary progressive or chronic progressive MS.

Relapsing remitting MS (RRMS)

As of 2021, multiple DMD/Ts have been approved by regulatory agencies for RRMS. They are modestly effective at decreasing the number of attacks. The first-line treatments (Interferons and Glatiramer acetate) are roughly equivalent, reducing relapses by approximately 30%. Early-initiated long-term therapy is safe and improves outcomes.

Treatment of a clinically-isolated syndrome (CIS) with Interferons decreases the chance of progressing to clinical MS. Efficacy of Interferons and Glatiramer acetate in children has been estimated to be roughly equivalent to that of adults. The role of some newer agents such as Fingolimod, Teriflunomide, and Dimethyl fumarate is not yet entirely clear. It is difficult to make firm conclusions about the best treatment, especially regarding the long - term benefit and safety of early treatment, given the lack of studies directly comparing DMD/Ts or long-term monitoring of patient outcomes.

The relative effectiveness of different treatments is unclear, as most have only been compared to placebo or a small number of other therapies. Direct comparisons of Interferons and Glatiramer acetate indicate similar effects or only small differences in effects on relapse rate, disease progression, and MRI measures. Alemtuzumab, Natalizumab, and Fingolimod may be more effective than other drugs in reducing relapses over the short term in people with RRMS. Natalizumab and Interferon beta-1a (Rebid) may reduce relapses compared to both placebo and Interferon beta-1a (Avonex) while Interferon beta-1b (Betaseron), Glatiramer acetate, and Mitoxantrone may also prevent relapses. Evidence on relative effectiveness in reducing disability progression is unclear. All medications are associated with adverse effects that may influence their risk-to-benefit profiles.

Secondary Progressive MS (SPMS)

As of 2011, only one medication, Mitoxantrone, had been approved for SPMS. In this population, tentative evidence supports this drug moderately, slowing the progression of the disease, and decreasing rates of relapses over two years.

As of 2013, review of 9 modulators and immunosuppressants found no evidence of any being effective in preventing disability progression in people with progressive MS. In 2019, Siponimod and Cladribine were approved in the U.S. for the treatment of SPMS.

Primary progressive MS (PPMS)

In March 2017, the (U.S.) FDA approved ocrelizumab as a treatment for PPMS in adults, the first drug to gain that approval, with requirements for several Phase IV clinical trials. It is also used for the treatment of relapsing forms of MS, to include clinically-isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.

Categorization of DMD/Ts

While there is no cure for MS, treatments can help speed recovery from attacks, reduce the number and seriousness of relapses, reduce the damage caused by relapses, modify the course of the disease, and manage symptoms. New treatments can reduce long-term disability for many people with MS. Currently, there is no clear way to prevent the disease from developing. DMD/Ts are not a cure, but they could make a big difference to MS. They offer many people with MS the chance to take more control of it and their lives.

Current therapies approved by the (U.S.) FDA for MS are designed to modulate or suppress the inflammatory reactions of the disease. They only work with those types of MS that have relapses. They are most effective for RRMS at early stages of the disease. Depending on their mode of administration, DMD/Ts fall into three categories of medications (Table 1):

disability and significantly reduced relapse rates. However, because of safety risks, it is generally used when people cannot take other drugs for MS or when those drugs are not effective.

• **Dimethyl fumarate (Tecfidera):** It decreases inflammation and helps protect cells. Possible side

Injectables (3)

Injectables are given by injection under the skin or in a muscle. They are:

• **Glatiramer acetate (Copaxone 20 mg and 40 mg doses, Flattop®):** They can reduce relapse rates and have long-term safety data.

• **Interferons:** Interferons include Avonex®,Pleurisy®, and Rebid® (interferons beta-1a); Betaseron® and Octavia® (interferons beta-1b), These medicines "interfere" with diseases that attack the body. They work by decreasing inflammation and increasing nerve growth. There are many interferon drugs. There is some controversy about how long interferons help in the treatment of MS. Octavia reduces relapses that cause the progression of disability. Possible side effects are reactions where the injection is given, flu-like symptoms, liver irritation, and anemia. The dosing of interferons varies depending on which drug is used.

• **Unfathomably (Pikestaff®, Arranger):** This monoclonal antibody was approved by the FDA in 2020. It targets B-cells that damage the nervous system and decreases brain lesions and worsening symptoms. Possible side effects are infections, local reactions to the injection, and headaches.

Oral medicines (10)

• **Baguio (Teriflunomide):** It is a convenient once-a-day pill that affects white blood cells to decrease inflammation.

• **Beautifier™ (Mono methyl fumarate).**

• **Cladribine (Maven clad):** FDA-approved since 2019, this drug treats RRMS and SPMS forms of MS. In clinical trials, Cladribine reduced the progression of effects are flushing, liver inflammation, and digestive tract irritation.

• **Proximal fumarate (Temerity).**

• **Fingolimod (Gilenya):** It was the first-approved oral medicine for MS. It was groundbreaking because of how well it worked and because it could be taken by

mouth

• **Mono methyl fumarate (Beautifier):** FDA-approved since 2020, this is a time-released drug. Because the release is slow and steady, researchers hope that side effects will be minimal. Possible side effects are flushing, liver injury, abdominal pain, and infections.

• **Modigliani (Deposit):** FDA-approved since 2020, this medicine decreases the relapse rate of MS. Possible side effects are elevated blood pressure, infections, and liver inflammation. The maintenance dose is once a day.

• **Positioned (Porphyry):** FDA-approved since 2021, this medicine is taken once a day with a gradually increasing dosing schedule. It has a low relapse rate and has demonstrated fewer brain lesions than some other medicines used to treat MS. Possible side effects are respiratory tract infections, high blood pressure, liver irritation, electrical problems in the heart that affect heart rate and rhythm, and low relapse rate. It has demonstrated fewer brain lesions.

• **Siponimod (Mayzent):** FDA-approved in 2019, this medicine is prescribed for relapsing-remitting and secondary-progressive forms of MS. It is an immune-modulating therapy that helps reduce both relapses and progression of disability.

Intravenous (5)

• **Alemtuzumab (Lemtrada, Campath):** This is a monoclonal antibody that decreases annual relapse rates and demonstrates brain MRI benefits. Possible side effects are thyroid disease and low platelet counts.

• **Mitoxantrone (Novantrone®).**

• **Natalizumab (Tysabri):** This is a monoclonal antibody that decreases relapse rates and slows the risk of disability.

• **Ocrelizumab (Ocrevus):** FDA-approved in 2017, this drug reduces relapse rate and risk of disability progression in relapsing-remitting MS. It is also the first to slow the progression of the primary-progressive form of MS.

• **Ozanimod (Zeposia).**

Table 1 lists the approved drugs (by the FDA and similar agencies) in these various categories, their benefits, some of their side effects, and their mode of administration. Table 2 provides other pharmacological treatments of MS.

Drug	Benefits	Side effects	Administration
	Injectables		
Beta Interferons *(Avonex,Betaseron, Extavia, Rebif, Plegridy)* (controversial benefit duration)	o In patients with established RRMS, reduces number and severity of attacks (causing disability progression) as well as lesions seen on MRI brain scans	o Irritation and reaction at injection site o Flu-like symptoms o Liver irritation o Anemia	First medication approved for MS treatment Injected every 2-3 times weekly
Glatiramer acetate *(Copaxone, Glatopa)*	o Reduces relapse rate o Reduces number of lesions seen on MRI o Long-term safety data	o Not an interferon (no flu-like reaction) o Irritation at the injection site o Episodes of flushing, palpitations/tachycardia, chest pain, dyspnea	Subcutaneously daily
Ofatunumab *(Kesimpta, Arzerra)*	o Decreases brain lesions o Decreases worsening symptoms	o Infections o Local reactions to the injection o Headaches	
Zynbrita *(Daclizumab)*	o Inhibit inflammatory functions of the T-lymphocytes	oSerious liver complications o Some immune conditions	Subcutaneously each month

	Oral medicines		
Cladribine *(Mavenclad)*	o Reduces progression of disability o Significantly reduces relapse rates o Targets certain types of WBCs that drive immune attacks	o Safety risks when taken with other MS drugs or when those drugs are not effective o Increases risk of developing cancer	o Two courses of tablets about one year apart
Dimethyl fumarate *(Tecfidera)*	o Exact mechanism of action not currently known. Reduces T- activation o Decreases inflammation o Protects cells	o Flushing o Liver inflammation o Digestive tract irritation o Diarrhea o Nausea o Lowered WBC counts o Some PML cases	o Twice daily for first week then doubled
Diroximel fumarate *(Vumerity)*	o For SPMS o Reduces damage to the brain and spinal cord o Makes the immune response less inflammatory	o Fewer GI side effects than *Dimethyl fumarate*	o Twice-daily similar to *Dimethyl fumarate*
Fingolimod *(Gilenya)*	o First approved oral immunomodulatory to treat adolescents and children 10 and older o Ground-breaking o Prevents WBCs (lymphocytes) from leaving lymph nodes and entering the blood, brain, and spinal cord o Works well o Reduces relapse rate	o Slowed heart rate after first dose (can result in death) o Macular edema when first taken o Flushing o Liver injury o Abdominal pain o Increases risk of infections (herpes virus, rare cases with PML)	o Once daily
Monomethyl fumarate *(Bafiertam)*	o Slow acting o Minimized side effects		
Ozanimod *(Zeposia)*		o Elevated blood pressure o Infections o Liver inflammation	
Ponesimod *(Ponvory)*	o Low relapse rate o Fewer brain lesions	o Respiratory tract infections o Elevates blood pressure o Liver irritation o Electrical problems affecting heart rate and rhythm	
Siponimod *(Mayzent)*	o Reduces RRMS and SPMS o Reduces disability progression		o Once daily o Similar mechanism of action to *Fingolimod*
Teriflunomide *(Aubagio)*	o Decreases number of attacks & inflammation o Reduces the rate of proliferation of activated immune cells o Reduces T- & B-cells	o Risks may last 2 years Nausea o Diarrhea o Liver damage o Hair loss	o Pill once daily
	Intravenous drugs		
Alemtuzumab *(Lemtrada, Campath)*	o Targets proteins on the surface of immune cells o Decreases annual relapse rates o Brain MRI benefits	o Autoimmune thyroid disorders (1 in 3 people) o Low platelet counts o Increased risk of autoimmune disorders (2/100 risk of thrombocytepenia)	o Four-hour IV for 5 successive days followed by daily infusion for 3 days one year later.

		o 3/1000 kidney disorder (glomerular nephropathy)	
Mitoxantrone *(Novantrone)*	o An antineoplastic drug o For especially severe forms of RRMS and secondary PPMS development of certain types of blood cancers in up to 1% of those with MS, as well as with heart damage.	o Development of certain types of blood cancers in (</~ 1% of cases) o Heart damage o 1/400 risk of development of leukemia o Last resort for cases of rapid loss of function and other treatments did not work	o IV 4 times a year
Natalizumab *(Tysabri)* WITHDRAWN then RE-RELEASED	o A monoclonal antibody against alpha integrin that inhibits WBC to enter the CNS and attacking nerves o For cases of inadequate responses to two or more MS therapies. o Preventing immune system cells from entering the brain and spinal cord o Decreases relapse rates even no new lesions o Slows disability risk	o Recommended only for individuals who have not responded well to or who are unable to tolerate other first-line therapies o Increased risk of a serious and potentially fatal viral brain infection (PML) perhaps due to the use of other drugs: Risk 1/1000 in first two years and for those on anti-JCV therapy	o IV once monthly
Ocrelizumab *(Ocrevus)*	o First drug for adults with relapsing PPMS o The only FDA-approved D/T for PPMS o Targets the circulating immune cells that produce antibodies o Reduces relapse rate o Reduces disability progression risk in RRMS o Helps walk better o Slows down brain atrophy o Makes brain lesions smaller o Delays need for wheel chair by seven years	o Infusion-related reactions o Increased risk of infections o May increase the risk of cancer	o IV repeated in 2 weeks and every 6 months o First approved treatment for PMS (it targets B-lymphocytes)

Source: A. L. Fymat (2023)

Key: CNS: Central nervous system; DMD/Ts: Disease-modifying drugs/ therapies; ELISA: Enzyme-linked immunosorbent assay; GI: Gastrointestinal; JCV: John Cunningham virus; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; PML: Progressive multifocal leukoencephalopathy; PPMS: Primary progressive MS; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS; WBC: White blood cell.

Table 1: Disease-modifying drugs/therapies for multiple sclerosis

Drug	Benefits	Side effects	Administration
ACTH			
Biotin (vitamin B7)	o Breaks down substances like fats, carbohydrates o Supporting evidence for high dose	Evidence for increased disease activity and higher risk of relapse	No good test for detecting low biotin levels
Cannabinoids			

Corticosteroids			
Cyclophosphamide			
Glucocorticoids			
Iron			
Rituximab			
Vitamin D	o Immunomodulatory function, modifying cytokines to more anti-inflammatory profile o MRI activity may be reduced	None but prudent to periodically test serum levels of calcium and phosphorus	Use HDC rather than LDC

Source: A. L. Fymat (2023)

Key: ACTH: Adrenocorticotropic hormone; LDC: Low dose calciferol; HDC: High dose calciferol

Table 2: Other pharmacological treatments of multiple sclerosis

Classes of DMD/Ts

DMD/Ts can be split into three classes according to how big their effect on MS can be:

High (meaning, works vey well):

Good (works well):

• Cladribine (Mavenclad).

• Dimethyl fumarate (Tecfidera).

• Fingolimod (Gilenya).

Moderate (works fairly well):

• Glatiramer acetate (Copaxone and Brabio).

• Interferons-beta (five different beta: Avonex, Betaferon, Extavia, Rebif, and Plegridy).

• Teriflunomide (Aubagio).

• Ocrelizumab (Ocrevus) when used for early PPMS.

What could DMD/Ts do?

While DMD/Ts will not cure MS and cannot undo any existing disability, taking them means having:

• Fewer relapses.

• Relapses that are not as serious.

• A slowing down in the progression of disability.

• Less build-up of damage (lesions) in the brain or spinal cord (seen on an MRI scan).

In fact, if treatment works very well, there may be no signs that MS is active at the moment, meaning:

• No longer having relapses.

• The disability is not getting worse.

• MRI scans show brain lesions have stopped growing and/or there are no new ones.

• The brain is not shrinking any faster.

Prescription guidelines for DMD/Ts

Past guidelines required the MS patient to have 'active' MS, meaning at least two relapses in the last two years. However, more and more, MS specialists interpret 'active MS' as having just one (not two) relapse(s) and/or MRI scans showing new damage (lesions) in the brain. To treat attacks, most patients improve with steroids or/and plasma exchange. To prevent attacks, 20 injectable, oral and infusion therapies are approved to prevent new symptoms and disability.

Sequencing of drug therapy

MS drugs interfere differently with the immune response that produces the disease activity of immune cells by altering their release of cytokines. They may:

• Prevent immune cells from entering into the nervous system.

• Reduce the population of cells that are involved in the immune reaction

Several drugs may be combined for synergistically combating their effects. However, there are two problems:

• **Safety:** The risk of serious side effects is increased by combining drugs.
• **Costs:** Could become prohibitive.

The preferred approach is one of customized sequencing drugs, depending on their impact and risk on each MS patient.

Adverse effects of DMD/Ts

DMD/Ts have several adverse effects. For any given drug, some or all of the correspondingly listed side effects may occur. Thus, for:

Cladribine

• Decrease in the number of relapses, delay the progress of physical disability, and slow the development of brain lesions.

Dimethyl fumarate

• Flushing.
• Gastrointestinal problems.
• Reduction in the white blood cell count.
• Decrease the number of relapses, delay the progress of physical disability, and slow the development of brain lesions.

Diroximel fumarate

• Decrease in the number of relapses.
• Delay in the progression of physical disability.
• Slowing down of the development of brain lesions.

Fingolimod

• Hypertension and slowed heart rate.
• Macular edema.
• Elevated liver enzymes.
• Reduction in lymphocyte levels.

Glatiramer acetate

• Irritation at the injection site (up to 90% with subcutaneous injections and 33% with intramuscular injections). Over time, a visible dent at the injection site may develop; it is due to the local destruction of fat tissue, known as 'lipoatrophy'.
• For some people: Post-injection reaction with flushing; chest tightness; heart palpitations; and anxiety, which usually lasts less than thirty minutes.
• Flu-like symptoms.

Interferons

• Irritation at the injection site (up to 90% with subcutaneous injections and 33% with intramuscular injections). Over time, a visible dent at the injection site may develop due to 'lipoatrophy'.
• More dangerous, but much less common, are liver damage from Interferons, systolic dysfunction (12%), and infertility.
• Flu-like symptoms.

Mitoxantrone

• Acute myeloid leukemia (AML) (occurring in 0.8% of cases).

Natalizumab

• Progressive multifocal leukoencephalopathy (PML): Occurring in 1 in 600 people treated.

Teriflunomide

• Headaches.
• Fatigue.
• Nausea.
• Hair loss.
• Limb pain.
• Liver failure.
• PML (dangerous for fetal development).

Treating relapses (exacerbations)

Standard steroid treatment

The good news is that not all exacerbations require treatment. Mild sensory changes (numbness, pins-and-needles sensations) or bursts of fatigue that do not significantly impact a person's activities can generally be left to get better on their own.

For severe exacerbations (involving, for example, loss of vision, severe weakness or poor balance) which interfere with a person's mobility, safety or overall ability to function, most neurologists recommend a short course of high-dose corticosteroids to reduce the inflammation and bring the relapse to an end more quickly. The most common treatment regimen is a three or five-day course of intravenous (Solu-Medrol® - Methylprednisolone) or oral (Deltasone® - Prednisone) corticosteroids. Corticosteroids are not believed to have any long-term benefit on the disease.

Other treatment options

H.P. Acthar Gel is a highly-purified preparation of adrenocorticotropic hormone (ACTH) in a gel that is designed to provide extended release of the ACTH following injection. It is FDA-approved for the treatment of MS relapses in adults. Its use is limited due to high cost and access issues. It is often considered when someone cannot tolerate glucocorticoids.

Plasmapheresis (plasma exchange) may also be considered for severe exacerbations that do not respond adequately to the standard steroid treatment.

Recent developments and emerging pharmacotherapies

Protective effect and lower risk of MS

Research over the years has shown that maintaining adequate levels of vitamin D may have a protective effect and lower the risk of developing MS. Therefore, vitamin D supplementation is considered an important modifiable environmental risk factor for development of MS. It may also offer some benefits to people who already have sufficient vitamin D in their body. Benefits include: lessening the frequency and severity of symptoms, improving the quality of life, and lengthening the time it takes to progress from RRMS to the SPMS phase. But the evidence is not conclusive.

Relapsing-remitting MS

The majority of FDA-approved drugs since the early 1990s are effective at helping to manage RRMS, which affects between 85% and 90% of people diagnosed with this disease. Some people with RRMS can transition to SPMS after several years. Currently available DMD/Ts have little impact on this phase of the disease. Therefore, it is best to develop a treatment regimen during the earlier relapsing-remitting phase, including:

- **Corticosteroids:** Relapses, attacks, or exacerbations can be managed with corticosteroids such as intravenous Methylprednisolone (Depo-Medrol, Medrol). These medicines decrease inflammation and have been used to help reduce the symptoms of MS relapses.
- **Plasmapheresis:** In this procedure, the liquid part of the blood (plasma) is separated from the blood cells; the cells are then combined with a protein solution (albumin) and put back into the body. In this fashion, the blood plasma is cleansed from circulating proteins to help with recovery from MS relapses. Possible side effects are dizziness, nausea, and a decrease in blood pressure.
- **Bruton's tyrosine kinase inhibitor (BTKI):** This emerging therapy is being studied in relapsing-remitting and secondary-progressive MS. It works by predominantly modulating B- cells and microglia (the immune cells in the central nervous system).
- **Hematopoietic stem cell transplantation (HSCT):** In this therapy, the immune system is suppressed and replacement transplanted healthy stem cells (SCs) are inserted. Researchers are still investigating whether this therapy can decrease inflammation in people with MS and help to "reset" the immune system. Possible side effects are fever and infections.

More research is needed regarding relapses and

reducing related lesions in the brain. Further studies will determine whether treatment can delay disability caused by the disease. Ongoing research shows promise and the benefits, side effects, and long-term safety of these new drugs will become clearer with further investigation.

Progressive MS

People with progressive MS get the occasional relapse or inflammation, or doctors see inflammation in their MRI scans. They need treatments to tackle the condition itself, not just its symptoms, i.e., drugs that will slow down the MS, protect the nerves, and repair the damaged myelin. There are about 20 DMD/Ts that can stop the immune system from attacking the myelin, meaning fewer relapses and less inflammation … but they do not seem to help in this situation.

Research is ongoing to develop new and better DMD/Ts designed to reduce the risk of relapses, reduce or preclude the formation of new plaques in the central nervous system, slow the progression of disability, and slow the loss of brain volume mass. New treatments and research will hopefully offer a brighter future.

Non-Pharmacological Therapies

The evidence for the effectiveness of non-pharmacological interventions for chronic pain is insufficient to recommend such interventions alone. Nonetheless, their use in combination with medications may be reasonable. A multidisciplinary approach is important for improving the quality of life; however, it is difficult to specify a 'core team' as many health services may be needed at different points in time.

Rehabilitation

If symptoms begin to interfere with everyday activities, rehabilitation can address problems with mobility, personal care, driving, functioning at home and work, and participation in leisure activities. Rehabilitation experts can also provide evaluation and treatment of speech and swallowing difficulties, and problems with thinking and memory. The goal of rehabilitation is to improve and maintain function, an essential component of comprehensive MS care. From the time of diagnosis onward, rehabilitation specialists provide education and strategies designed to promote health, wellness and overall conditioning, reduce fatigue, and help one function optimally at home and at work.

Multidisciplinary Rehabilitation

Multidisciplinary rehabilitation programs increase activity and participation of people with MS, but do not influence impairment level. Studies investigating information provision in support of patient understanding and participation suggest that while interventions (written information, decision aids, coaching, educational programs) may increase knowledge, the evidence of an effect on decision-making and quality of life is mixed and of low certainty. There is limited evidence for the overall efficacy of individual therapeutic disciplines, though there is good evidence that specific approaches, such as exercise and psychological therapies, are effective.

Cognitive Rehabilitation Therapy (CRT)

Cognitive training, alone or combined with other neuropsychological interventions, may show positive effects for memory and attention though firm conclusions are not possible given small sample numbers, variable methodology, interventions, and outcome measures. In CRT, neuropsychologists — as well as many occupational therapists (OTs) and speech language pathologists (SLPs) — evaluate and treat changes in a person's ability to think, reason, concentrate or remember. While these professionals use different evaluation and treatment strategies, they share the common goal of helping people function optimally if cognitive changes are experienced. It has been shown to be moderately effective for reducing MS

fatigue.

Neurorehabilitation therapy (NRT)

NRT has been shown to improve some symptoms, however, it does not change the course of the disease. Some symptoms have a good response to medication, such as bladder spasticity, while others are little changed. Equipment such as catheters for neurogenic bladder or mobility aids can be helpful in improving functional status.

Occupational therapy (OT)

OT provides training in energy conservation techniques and the use of adaptive tools and devices to simplify everyday tasks. Strategic modifications are recommended to the home and workplace to ensure accessibility, safety, and convenience. It also evaluates and treats problems with thinking and memory. The goal is to enhance independence, productivity, and safety in all activities related to personal care, leisure activities, and employment.

Physical therapy (PT)

PT evaluates and addresses the body's ability to move and function, with particular emphasis on walking and mobility, strength, balance, posture, fatigue and pain. It might include an exercise program, gait (walking) training and training in the use of mobility aids (poles, canes, crutches, scooters and/or wheelchairs), and other assistive devices. The goal is to promote independence, safety, and achieve and maintain optimal functioning. In addition, rehabilitation can help prevent complications such as de-conditioning, muscle weakness from lack of mobility and muscle contractures related to spasticity. PT can also include pelvic floor exercises to address urinary/bladder issues.

Speech-language pathology (SLP)

SLP evaluates and treats problems with speech and/or swallowing, both of which can result from damage in the CNS that reduces control of the muscles used in these important functions. The goal is to enhance ease and clarity of communication as well as promoting safe swallowing and overall health. Some SLPs also evaluate and treat problems with thinking and memory.

Vocational rehabilitation therapy (VRT)

State VRT programs offer job readiness training, job coaching, job placement assistance, mobility training, and assistive technology assessments with the goal of helping people maintain their current employment or find new employment that accommodates their needs.

Palliative Approaches

Due to lack of evidence, the effectiveness of palliative approaches in addition to standard care is uncertain, The effectiveness of interventions, including exercise, specifically for the prevention of falls in people with MS is uncertain, while there is some evidence of an effect on balance function and mobility.

Immunotherapy

Research on the immunobiology of MS has resulted in a variety of anti-inflammatory therapies that are highly effective at reducing brain inflammation and clinical/radiological relapses. However, despite potent suppression of inflammation, benefit in the more important and disabling progressive phase is extremely limited. Thus, progressive MS has emerged as the greatest challenge for the MS clinical and research communities.

Autologous stem cell therapy (aSCT) is a very risky and expensive procedure with a 5% mortality rate. It was used initially on only very advanced and rapidly progressive patients. There is a complex interplay between several causal factors:

• **Environment:** For example, the near-absolute requirement of Epstein–Barr virus (EBV) exposure.
• **Immunogenetics:** Strong associations with a large number of immune genes.
• **Underlying degenerative process:** An ever more convincing role.

It has resulted in:

• **Demyelination:** In both white and grey matter regions.
• **Axonal and neuro-synaptic injury.**
• **Persistent innate inflammatory response:** With a seemingly diminishing role of T-cell mediated autoimmunity as the disease progresses.

Together, the above observations point toward a primary degenerative process, one whose cause remains unknown but one that entrains a nearly ubiquitous secondary autoimmune response. There is a vigorous debate in the field as to whether primary autoimmunity or degeneration lies at the foundation. Unravelling this controversy will be critically important for developing effective new therapies for the most disabling later phases of this disease.

Brain Immunotherapy

In parallel with immunotherapy as an emergent therapy for cancer, I advanced earlier the opinion that brain immunotherapy should also become a similar therapy for brain cancers and neurological disorders (Fymat, 2017a-h; 2018a-f; 2019a-e; 2020a-f; 2021a-c; 2022; 2023), providing a paradigm shift in our therapeutic approach to brain cancer and these disorders.

The approach advocated there and here would be to regulate the underlying autoimmune system (not to either enhance it immeasurably or suppress it totally), to boost in a measured manner the synaptoclastic signals while at the same time taming down the synaptoblastic ones. This idea builds upon work done on diabetes type I, an incurable disease so far. There, the autoimmune system is taught to tolerate the insulin-producing cells of the pancreas so that it does not destroy the diabetic patient's ability to produce the glucose-regulating insulin. The similar idea forms the basis of various clinical trials for treating other incurable diseases such as MS and Graves' disease (GD). Again, the overarching purpose is to harness the hyperactive autoimmune system. This can be accomplished in two manners by employing:

• **Naturally existing molecules:** These can induce an immune response (antigens); or
• **Engineered immune cells:** These can train the autoimmune system to tolerate the process or tissue it is on track to damage.

The above idea has the potential to cure a range of autoimmune disorders, including especially neurological and neurodegenerative disorders, particularly Alzheimer's disease (AD) but perhaps also MS. This requires a deep understanding of the molecular basis of autoimmunity, including brain and central nervous system (CNS) immunity, as well as advances in genetic engineering and cell-based therapy. Caution must nonetheless be exercised as deploying the immune system to treat certain diseases can also potentially trigger other autoimmune diseases, e.g., in the case of cancer, it may additionally trigger rheumatoid arthritis and colitis.

The main immune players are the regulatory T-cells (Treg), which act as the brakes of the immune system. Similarly to other T-cells, Treg-cells rein in the immune cells that are doing damage. It has been suggested that the body can be made to produce the Treg-cells required to dampen a certain autoimmune response by dosing people who are affected with the same antigen or antigens that the immune system wrongly interprets as a reason to attack. This was tested for MS, demonstrating less brain inflammation. Here, antigens can induce a calming effect through

Treg-cells. The approach is similar to vaccination without the immune-system stimulants called 'adjuvants' that are usually included in vaccine formulations.

Stem Cell Therapy (SCT)

SCT is the use of stem cells (SC) to treat or prevent a disease or condition. One of the oldest form of it is bone marrow transplantation that has been used for many years without controversy. Mesenchymal stem cells (MSCs) are injected via a lumbar puncture with the hope that they will mature into nerve cells. The advantages and disadvantages of this other form of therapy, and its potential application for the treatment of neurodegenerative diseases/disorders (NDDs), including MS, are appreciable. Of particular interest to us are regenerative treatments, and the treatment of neurodegenerative conditions.

Regenerative treatment

In regenerative treatment, SCs mediate repair via five primary mechanisms:

- **Providing an anti-inflammatory effect.**
- **Homing-in onto damaged tissues and recruiting other cells:** Usually, endothelial progenitor cells (EPCs) that are necessary for tissue growth.
- **Supporting tissue remodeling over scar formation.**
- **Inhibiting apoptosis** (or cell death).
- **Differentiating into bone, cartilage, tendon, and ligament tissue.**

To further enrich blood supply to the damaged areas and, consequently, promote tissue regeneration, platelet-rich plasma could additionally be used in conjunction with the therapy. The efficacy of some SC populations may be affected by the method of delivery.

The advantages of SC therapy include:

- **Lessening the symptoms or conditions of the disease treated.**
- **Allowing patients to reduce their drug intake.**

Safety studies are under way in the case of certain untreatable neurological diseases, including amyotrophic lateral sclerosis (ALS) and multiple system atrophy (MSA). It is not yet known if these treatments will provide benefit for patients and whether these are broadly applicable in neurological diseases.

Neurodegeneration

In the case of neurodegeneration and NDDs, it is known that healthy adult brains contain neural stem cells (NSCs), which divide to maintain general stem cell numbers or become progenitor cells. In healthy laboratory animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction (the sense of smell). In these animals, research has been conducted on the effects of SCs on brain degeneration including such brain diseases as AD, Parkinson's disease (PD), ALS, and MS. Of particular note, pharmacological activation of endogenous neural SCs has been reported to induce neuroprotection and behavioral recovery in adult rat models of neurological disorder.

In the case of N DDs, including especially AD and dementia, SCs have been shown to have a low immunogenicity (the promotion of immune properties) due to the relatively low number of major histocompatibility complex (MHC) molecules found on their surface. They have also been found to secrete chemokines that alter the immune response and promote tolerance of the new tissue. Notwithstanding this low immunogenicity of SCs, I would still advocate SC therapy for the treatment of AD and dementia only under the following conditions: A prior radiation treatment is not required so as not to suppress the immune system, minimizing the secretion of

chemokines so as not to adversely alter the immune response, and minimizing if not eliminating any possibility of inducing cancer.

There are, unfortunately, several potential disadvantages: In the case of cancer, the treatment may require immunosuppression before transplantation; this is in order to perform a preliminary radiation treatment to kill previous cancerous cells or because the patient's immune system may target the SCs considering them as foreign bodies (but this could be avoided using SCs from the same patient). Pluripotency in certain SCs could make it difficult to obtain a specific cell type; not all cells in a population differentiate uniformly, making it difficult to obtain the exact cell type needed. Undifferentiated cells can create tissues other than the desired types. Pluripotent stem cells (PSC) can form tumors, which is particularly the case for embryonic, fetal, and induced PSCs.

Other autoimmune diseases of the nervous system

As with MS, using the patient's own stem cells might stop disease progression in the case of other autoimmune diseases of the nervous system. In such cases, aggressive immunotherapies are available that could mitigate the need for autologous stem cell transplants.

Autologous hematopoietic stem cell transplantation (aHSCT)

aHSCT is an intense chemotherapy treatment for MS. It aims to stop the damage MS causes by wiping out and then regrowing the immune system, using the patient's own stem cells (so-called 'autologous' SCs).

Who can benefit from aHSCT?

from attacking the central nervous system. It uses chemotherapy to remove the harmful immune cells and then rebuilds that system using the hematopoietic stem cells (HSC) found in the individual's own bone marrow. The HSCs used in the treatment can produce all the

Research has shown that aHSCT may be a safe and effective treatment for people with MS who:

• Have highly active relapsing MS and still have relapses despite taking DMD/Ts.
• Have progressive MS and still have active inflammation (either relapses or lesions shown on MRI scans).
• Are at an early course of their disease.
• Do not have significant disability (as measured by the Expanded Disability Status Scale (EDSS).
• Are less than 50 years of age.
• Have had MS for less than 10 years.
• Have breakthrough disease activity (new inflammatory lesions on MRI and/or relapses) despite treatment with a high-efficacy DMD/T* or are unable to take a high-efficacy DMD/T.

[*Note: High-efficacy DMD/Ts include: Alemtuzumab (Lemtrada®), Natalizumab (Tysabri®), Ocrelizumab (Ocrevus®), Ofatumumab (Kesimpta®). And Rituximab (Rituxan®), Some MS specialists consider Cladribine (Mavenclad®) in this group.]

Factors including older age, greater disability and certain health conditions (for example, heart or lung disease) are associated with increased risk of life-threatening side effects. aHSCT is unlikely to help in advanced progressive MS and no longer having relapses or signs of inflammation on MRI. Research is ongoing to find effective treatments for progressive MS.

How does aHSCT work?

aHSCT aims to 'reset' the immune system to stop it different cells in the blood, including immune cells, but they cannot regenerate damaged nerves or other parts of the brain and spinal cord (see the illustration in Figure 2).

How effective is aHSCT?

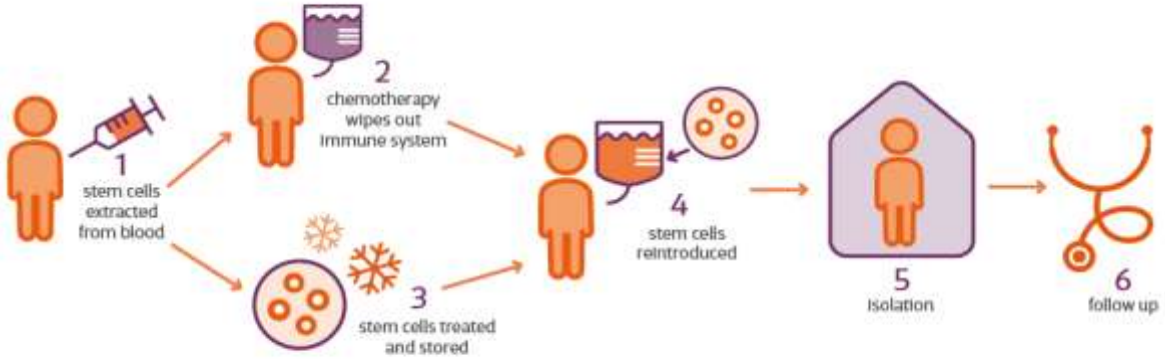
As seen earlier, DMD/Ts can be classified in three groups depending on their effectiveness ('high' or works very well; 'good' or works well; and 'moderate' or works fairly well). aHSCT is classed as 'high' based on how much it reduces relapses and slows down the worsening rate of disability.

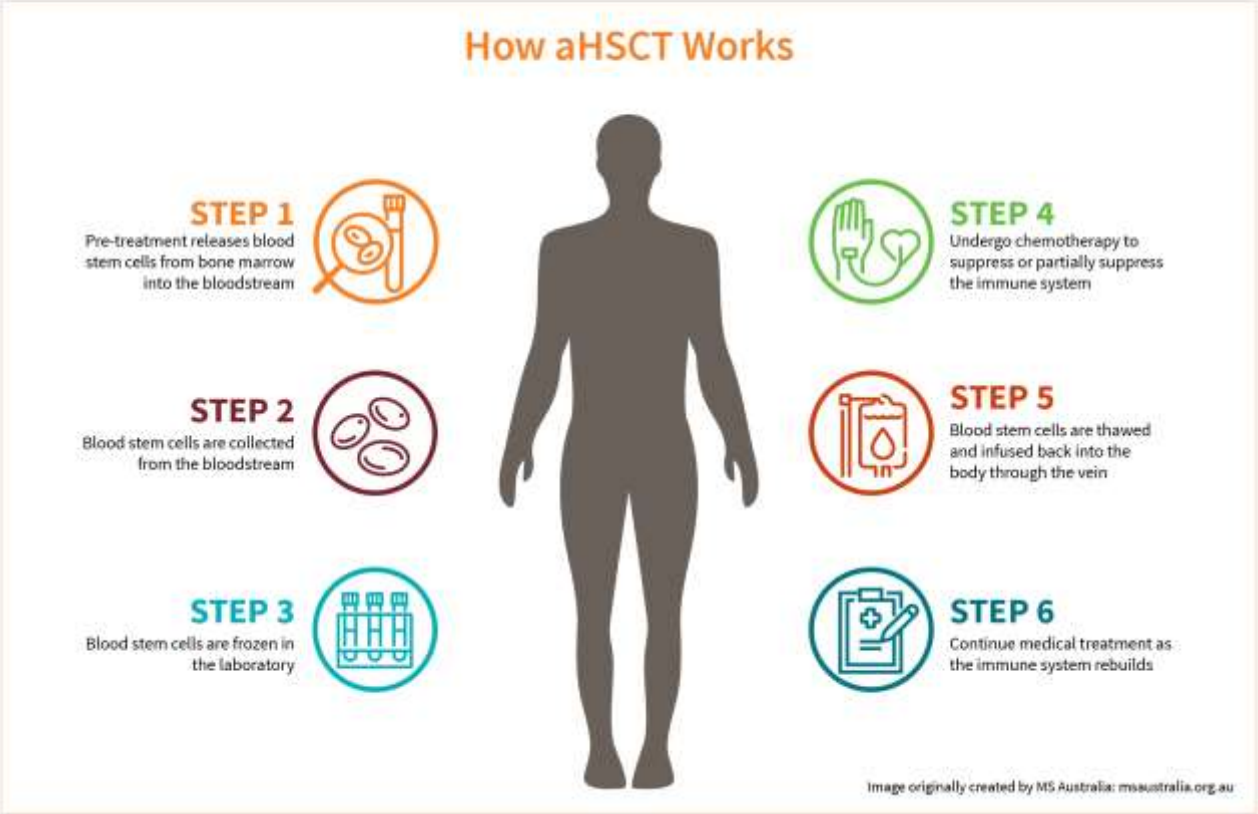
Relapsing MS

Clinical trials have shown that aHSCT is able to reduce relapses, mainly for people with relapsing MS. For some people, their symptoms stabilize or get better, or else their disability improves. But, these improvements do not always last. A randomized control trial looked at 110 people with 'very active' relapsing MS. Half of them were treated with aHSCT and the other half with other DMD/Ts. The results showed that:

• 99% of the people treated with aHSCT had no relapses for 1 year. Only 1 person who had aHSCT suffered a relapse, compared to 39 relapses in people taking drug treatments.

• 94% of people treated with aHSCT did not see their disability get worse for 3 years, compared to 40% of those on drug treatments.





Source: MS Australia (www.msaustralia.org.au) and National MS Society

Figure 2: Hematopoietic stem cell transplant treatment

• EDSS scores (which measure disability) improved for the people treated with aHSCT. For those on drug treatments, average EDSS scores got worse.

Progressive MS

aHSCT might be able to help some people with progressive MS who still have active inflammation (either relapses or lesions seen on MRI). It cannot help people with advanced progressive MS. Further, it cannot regrow nerves or repair damaged myelin.

Aggressive MS

aHSCT is being explored to stop aggressive MS in cases where other treatments are not effective. In this approach, part of the immune system in the bone marrow is degraded or eliminated by a drug called Cyclophosphamide, a process called 'conditioning'. The patient's own bone marrow stem cells are then given back to the patient to replenish the bone marrow. It is hoped that by rebooting the immune system, the inflammation in MS will stop.

Side effects of aHSCT

Compared to other DMD/Ts, aHSCT has among the highest risk of side effects, especially serious ones. Such effects include:

• Increased long-term risk of developing infections.
• Increased risk of developing cancer and autoimmune conditions (such as thyroiditis).
• Early menopause.
• Fertility problems.

The chemotherapy part of the aHSCT procedure has its own side effects, too, including:

• Increased risk of bleeding and bruising.
• Fatigue,
• Loss of appetite.
• Hair loss.

Also, in case of existing high disability before the transplant:

• Worsening mobility.
• Worsening of nerve function.
• Death (since 2005, 1 person in about every 330). The risk increases for older people, those who have a higher EDSS score, or have certain other conditions.

Candidates for aHSCT

aHSCT is most effective for people with MS who:

• Have highly active relapsing MS: Despite taking DMD/Ts.
• Have MRI scans showing new or active lesions: These are signs of 'active inflammation'.
• Are early on in their disease course.
• Do not have significant disability: As measured by the EDSS.

What to expect of aHSCT?

aHSCT is a hugely promising treatment for MS, but it is also very intense. This means that it comes with risks and there are lots of factors to consider. It should be offered pursuant to the guidance below.

Guidance for relapsing MS

aHSCT should be offered to people with relapsing MS who:

• Have had at least 2 relapses (or 1 relapse with signs of new lesions on MRI) in the previous 12 months.
• Have not responded to 1 or more existing DMD/Ts.
• Have an EDSS of 5.5 or less.
• Are younger than 45.
• Have had MS for less than 10 years.

Guidance for progressive MS

aHSCT should be considered for people with primary and secondary progressive MS who:

• Have evidence of their disability getting worse in the previous 12 months.
• Show signs of active inflammation (relapses or signs of new lesions on an MRI).
• Be preferably in a clinical trial.

Guidance for aggressive MS

People with 'aggressive' MS can also be considered ('aggressive' meaning having developed severe disability in the previous 12 months). For aggressive MS, aHSCT can be considered before trying another DMD/T.

Procedure for aHSCT

The initial stem cell preparation and harvesting takes 5 to 15 days. Then, there is a 3-week hospital stay to prepare the immune system for the transplant, perform the stem cell transplant, and allow time for recovery.

There is no agreed-upon aHSCT protocol for MS. Protocols differ in how stem cells are harvested and manipulated and what immunosuppressive medications are used during the procedure – more intense

immunosuppression may result in better long-term disease control, but may be associated with a greater risk of infection or other complications. Research is underway to determine whether less intensive immunosuppressive protocols produce effective results and fewer side effects.

The steps involved are:

• Review by a specialist team.
• Readying of stem cells for collection.
• Mobilization of stem cells: Treatment begins with drugs to encourage stem cells to move out of the bone marrow and into the blood and be collected. Drugs include: a chemotherapy infusion to wipe out the immune system (can take several days) and G-CSF injections. The chemotherapy may be 'myeloablative' (completely wipes out the immune system) or 'non-myeloablative' (partially wipes out the immune system). The side effects of chemotherapy include nausea and vomiting that can be controlled with drugs.

The symptoms of MS can get temporarily worse during this stage.

• Collection of stem cells: Around 10 days later, when there are enough stem cells in the blood, they will be removed and stored for later in the procedure.
• Back-transplant of stem cells into the blood by a drip to help regrow the immune system: This usually takes place a couple of days after the chemotherapy, once the drugs have cleared the system.
• Refunctioning of the stem cells: Stem cells get to work making new blood and immune cells within 10 to 30 days of the transplant. As the immune system is not working yet, infections are likely during this period, requiring assistive antibiotics and transfusions.
• Recovery from aHSCT: Anyone having aHSCT has to spend around a month in an isolation room while the immune system rebuilds itself. Typically, recovery takes 3-6 months but, for some, it can take more than a year to fully recover.

After the aHSCT treatment

Follow-up appointments are critical after treatment and include:

• Medical, neurological, and cognitive evaluations.
• MRIs and blood tests.
• Support for mental health and wellbeing.

The transplant unit should organize regular outpatient monitoring in the first 2 years following the procedure and afterwards, if needed. MRIs need to be performed within 6 months of aHSCT and at least annually thereafter. Recommendations are:

• Patients should be able to self-refer into a hematology department or another department that is familiar with aHSCT, any time, 7 days a week, 24 hours a day.
• Patients should isolate themselves, wear a mask, and socially distance for a period of time following the procedure to reduce the risk of infections (including COVID-19).
• Long-term monitoring should be backed up by patient data being held by a bone marrow transplant registry such as, for example, the European Bone Marrow Transplant Registry (EBMTR).
• The risks of infection persist for long periods after aHSCT so antibiotics are recommended for many months, or sometimes even life-long.

The outcomes of the treatment and information learned from the follow-up appointments will further inform how aHSCT works in MS.

Finding an aHSCT treatment center

It is crucial that aHSCT be performed at an accredited treatment location. Clinical services vary and not all accredited centers perform aHSCT for MS. The MS specialist can help to select a treatment center and identify which healthcare providers should be involved

during and after aHSCT.

The Foundation for the Accreditation of Cellular Therapy (FACT) is the recognized accrediting body. Where available, all aHSCT centers across the globe are listed and can be searched in the FACT website.

WARNING: SHAM STEM CELL CENTERS AND STEM CELL TOURISM. There are clinics in the U.S. and abroad that may not have experience in aHSCT and MS and may not be experienced or abide by strict health and safety standards. It is recommended to consult an MS specialist before choosing a clinic.

Current aHSCT clinical trial

There is currently one clinical trial in the U.S. on aHSCT in MS (the BEAT-MS clinical trial). It is randomly assigning eligible participants to undergo aHSCT or receive certain DMD/Ts to compare the costs, safety, and effectiveness of the two treatments.

In Italy, researchers at the Scientific Institute in Milan recently reported (January 2023) the results of an aHSCT clinical trial during which they experimented with neural SCs collected from the brain of an aborted fetus. These cells were grown into nervous system cells after having injected them in the spinal fluid of 12 people with a form of MS that worsened over time. The trial findings compared participants with (unspecified) lower- and higher-dose of SCs.

They were: (1) Three months after transplantation, the higher-dose participants had higher levels of protecting neurons and anti-inflammatory molecules in their spinal fluid; (2) after 2 years, the higher-dose group retained more brain grey matter; and (3) over the next two years, none of the trial participants experienced any adverse reaction. While small, a similar trial with a larger number of participants would be warranted.

Complementary and Alternative Medicine Therapies (CAMT)

Complementary and alternative medicine therapies (CAMT) are discussed at great length in my book (Fymat, 2023), and will not be discussed here. They include: Biologically-based therapies (dietary supplements; diets; bee-venom therapy); mind-body therapies (guided imagery; hypnosis; meditation); alternative medical systems (traditional Chinese medicine; Ayurvedic medicine; homeopathy); manipulative and body-based therapies (chiropractic; reflexology massage); energy therapies (therapeutic touch; magnets); and other therapies.

Prognosis and Future Outlook

Prognosis means the likely course of a health condition, based on medical experience. It is very difficult to predict the course of MS. The type, duration, severity, and impact of symptoms will vary from individual to individual. Some people will go for long periods with few or no symptoms whilst others will experience more frequent or persistent problems.

There are some factors that have been shown to suggest how MS may develop. These have been observed in long-term studies and reflect a general trend. However, they do not represent a guide regarding how a specific person's MS will develop as it remains a very unpredictable condition.

When it comes to the prognosis for MS, there is both good news and bad news. Although MS is not fatal, there is currently no cure — MS is a chronic condition. But, many people who have MS also have to contend with other issues that can decrease their quality of life.

Even though most will never become severely disabled, many experience symptoms that cause pain, discomfort, and inconvenience.

On the prognosis for MS

The prognosis of MS depends on the subtype of the disease, and there is also great individual variation in the progression of the disease. There are some guidelines that may be used to infer a prognosis. Thus, for example, for relapsing MS (RMS), which is the most common subtype, approximately one of every five people later transitions to secondary progressive MS (SPMS), a form characterized by a more progressive decline. Approximately 85% of MS patients begin with the relapsing-remitting form of the disease. As discussed earlier, MS relapses can involve a single neural system such as optic neuritis, or several anatomically distinct systems at the same time like combined motor and sensory problems. Attacks involving single neural systems are somewhat more common in the first exacerbation of MS.

In a 2016 cohort study, it was found that after a median of 16.8 years from onset, one in ten of those with RMS needed a walking aid, and almost two in ten transitioned to SPMS. With treatments available in the 2020s, relapses can be eliminated or substantially reduced. While most people with MS have a normal life expectancy, a few of them with very severe disability may die prematurely of infectious complications such as pneumonia, giving an overall life expectancy of about 95% that of normal healthy individuals.

However, "silent progression" of the disease still occurs. In addition to SPMS, a small proportion of people with MS (10%-15%) experience progressive decline from the onset, known as primary progressive MS (PPMS). Whereas most treatments have been approved for use in RMS; there are limited effective treatments for progressive forms of MS and they are not as effective.

The prognosis for PMS is worse, with faster accumulation of disability, though the rate of decline varies considerably between people. In untreated PPMS, the median time from onset to requiring a walking aid is estimated as seven years. In SPMS, a 2014 cohort study reported that people required a walking aid after an average of five years from its onset and were chair- or bed-bound after fifteen years on the average. While the long-term outcome is difficult to predict, better outcomes are more often seen in women, those who develop the disease early in life, those with a relapsing course, and those who initially experienced few attacks.

The average longevity in the population of patients with MS is very difficult to estimate because it varies widely from patient to patient. An average life span of 25 to 35 years after the diagnosis of MS is made is often stated. Some of the most common causes of death in MS patients are secondary complications resulting from immobility, chronic urinary tract infections, compromised swallowing and breathing, chronic bed sores, urogenital sepsis, and aspiration or bacterial pneumonia.

Clinical factors that influence prognosis

Let us first summarize those clinical factors that influence prognosis (Table 3). After a diagnosis of MS, characteristics that predict a worse course are male sex, older age, and greater disability at the time of diagnosis. Female sex, though, is associated with a higher relapse rate.

As of 2018, no biomarker can accurately predict disease progression in every patient. Spinal cord lesions, abnormalities on MRI, and more brain atrophy are predictive of a worse course, though brain atrophy as a predictor of disease course is experimental and not generally used in clinical practice.

Early treatment leads to a better prognosis, but a higher relapse frequency when treated with DMD/Ts is associated with a poorer prognosis.

Feature	Favorable	Unfavorable
Gender	Females	Males
Yearly rates of relapse	Low	High
Recovery from the first attack	Complete	Incomplete
Interval between the first and the second attack	Long	Short
Symptoms predominantly from afferent systems	Sensory	Motor tract
Age of onset	Younger	Older
Disability at 2-5 years from the disease onset	Low	Significant (acute onset)
Cerebellar involvement	Later	Early
Involvement at the time of onset	Only 1 CNS system	More than 1 CNS system

Source: A. L. Fymat (2023)

Table 3: Factors that influence prognosis

Other factors affecting prognosis

No two people with MS experience exactly the same symptoms or patterns of disease progression. There are varying components that can affect the disease course, including: Timing and diagnosis factors; treatment; lifestyle factors; biological and disease-related traits; demographics (such as race and sex); and culture and mental health. (For a detailed discussion of each of these factors, see Fymat 2023.)

Prognostic relapse indicators

Several studies have shown that people who have fewer attacks in the first several years after diagnosis, long intervals between attacks, complete recovery from attacks, attacks that are sensory in nature (i.e., numbness, tingling, visual loss), and nearly normal neurological examinations after 5 years tend to fare better. These studies have also shown that people who have early symptoms of tremor, in-coordination, difficulty in walking, or who have frequent attacks with incomplete recoveries, early development of neurological abnormalities, or more lesions on MRI early on, tend to have a more progressive disease course. Table 4 is a recapitulation of favorable and unfavorable prognostic relapse indicators.

Feature	Favorable prognosis	Unfavorable prognosis
Relapse rate in first 2 years	Less than 5 relapses	5 or more relapses
Relapse rate after 5 years	No increase	Increasing
Duration between relapses	Long	Short
Number of neural systems involved	1	Multiple
Relapse recovery	Complete	Incomplete
Type of systems involved	Visual, sensory, brain stem	Motor, cerebellar, bowel or bladder

Source: A. L. Fymat (2023)

Table 4: Prognostic relapse indicators

The following numbers and statistical measures apply only to individuals who were diagnosed with MS prior to using any DMD/T therapy. For those who are treated with DMD/Ts, these numbers and measures would be more favorable.

• **The first few years after disease onset is an important time:** The number and type of relapses as well as how much of a recovery will help predict the future disease course. Relapses that involve visual, sensory or brainstem systems have a better prognosis than those that involve cerebellar, motor, or sphincter systems.

• **In the first 2 years of disease:** A low relapse rate with excellent recovery indicates a better prognosis than a high relapse rate with poor recovery. Relapses that are restricted to a single neural system are prognostically better than those involving multiple systems. The relapse rate also has prognostic significance in the later stages of MS.

• **With a disease duration of 5 or more years:** An increasing relapse rate, polyregional relapses that involve multiple systems, and incomplete recovery from relapses indicate a worse prognosis. Most people experience the severest disabilities of MS within 5 years of diagnosis.

• **After 5 years:** Disabilities do not continue to worsen significantly. Therefore, if no additional disabilities appear within the first five years, then, they are unlikely to occur in the future. But, nobody can predict what will happen to any one person and so many things can have an influence on that. It has been proven over these short years that doing all of the "right things" will increase the odds of a better outcome.

• **Fifteen 15 years after diagnosis:** It is estimated that for all MS patients the chance of walking unaided in 15 years following disease onset is 50%. Half of the patients will need assistance in walking or will be wheelchair bound; another half of the patients will be able to ambulate unaided.

• **After 25 years since diagnosis:** Approximately 10% remain free of major ambulatory disability as measured by the EDSS even without treatment. If an MS patient's EDSS score is 2 or lower for 10 years or longer, there is a 90% chance that the disease will continue to remain stable. This latter group constitutes 17% of MS patients and can be designated as “benign” in an ambulatory sense. Here, benign MS does not designate a specific type of disease course, but describes only mild disease severity after time. In addition, while most patients have RRMS, some other patients may have a very slow progression but still remain benign. Within the benign RRMS patients, some have multiple relapses with almost complete recovery, and others may have a paucity of relapses or CNS inflammatory activity as evidenced by imaging studies.

• **Around 33 years:** This is the average time before having severe disability that causes patients to be restricted in bed.

• **Frequency of death by suicide:** It was found to be 7.5 times higher among patients with MS compared to the general population. It was also found that in suicidal patients, suicide rate did not correlate with disability.

It should be noted that once a moderate level of disability is reached, these early clinical predictors do not seem to influence the continued progression of irreversible disability, suggesting that the long-term course and disability may be established early in MS. The progressive phase in MS, regardless of the presence (secondary-progressive) or absence (primary-progressive) of initial relapses, behaves similarly, and rapid early progression of disability that includes three or more systems is unfavorable in progressive MS.

Adhering to a treatment plan of using a DMD/T is the best possible strategy for managing MS and giving a far better prognosis. Now, because taking a DMD/T over a long period of time can be challenging, it is important to understand its role in the overall MS treatment plan, and to be aware of the obstacles that can most often interfere with adherence to that plan.

Future MS outlook and what to expect

MS generally affects the quality of life more than longevity. While certain types of MS can potentially affect lifespan, they are the exception — not the rule. The life expectancy of patients with MS is 7 to 14 years shorter than that of the general population, but this gap is diminishing as available treatments improve. The average life expectancy of a patient with MS is, on average, 35 years from disease onset. The chance that they will still be able to walk unaided 15 years after disease onset is 50%.

People with MS must contend with many difficult symptoms that will affect their lifestyle. But, with appropriate treatment of the disease, their life expectancy essentially mirrors that of people who do not have the condition.

Ways to improve the MS outlook

Despite the challenges that come with MS, there are ways to improve the outlook and live a happy life. How a person thinks and feels about their condition and their ability to manage, cope, and live with their health challenges can affect outcomes. People with high levels of self-esteem are more likely to feel they can influence their MS symptoms and are more likely to make lifestyle and behavioral changes for better health, which can lead to improved symptoms. Some ways to improve the perspective on MS are: Build and nurture relationships; manage stress; monitor one's mood; practice solution-based problem solving; recognize family needs; and stay centered.

Treatments that can prolong life expectancy

DMD/Ts can have a positive impact on MS prognosis. Research has shown that patients who took Interferon-beta medications for 3 years or more had a lower risk of death than patients who had not taken them. This benefit in life expectancy was maintained even for patients who started treatment more than 5 years after disease onset or after they were age 40. The potential beneficial effects of other, newer DMD/Ts on prognosis remain to be investigated as they become more widely used by the MS patient community.

Carefully monitoring other health conditions not related to MS (e.g., hypertension, hyperlipidemia, hypercholesterolemia, and hyperglycemia, as well as the mental health of patients) is also important in prolonging life expectancy.

Finally, physical activity plays an important role in supporting the health of patients with MS and may prolong life expectancy. The (U.S.) National Multiple Sclerosis Society (NMSS) published exercise and physical activity recommendations for all people with MS regardless of the level of disability. According to the guidelines, patients with MS should engage in at least 150 minutes per week of aerobic and breathing exercise and/or lifestyle physical activity. Depending on the patient's abilities, lifestyle physical activities may include active gaming, active weight shifting, seated dancing, yoga, and boxing.

Effect on quality of life

Living with MS can impact the quality of life. This condition affects everyone differently, but there are some similarities among people with MS. For example, many people with MS experience physical disabilities, anxiety, depression, and fatigue that make it challenging to work or enjoy activities with family and friends. MS may affect: Career or education; family and social life; mental health; and physical health.

MS symptoms can range from mild to severe and may come and go over time. Quality of life may fluctuate with symptoms. Physical disability and depression may have the greatest impact on quality of life, so it is vital to seek treatment in these areas.

Common causes of death

The most common causes of death in patients with MS are the result of secondary complications caused by the disease. These include respiratory infections, urinary tract infections, sepsis, and skin disease. Other attributed causes are associated with advanced disability and immobility, and include aspiration pneumonia and chronic respiratory disease.

Research has shown that death by suicide is higher among patients with MS than the rest of the population. However, the rate of suicide does not correlate with the severity of the disability.

Conclusions

The symptoms and progression of demyelinating diseases vary between patients. There are many symptomatic treatments including drugs, devices, and therapies. Early diagnosis and discussion of treatment options is important with emphasis on early treatment. Disease-modifying drugs/therapies (DMD/Ts) can change (for the better) how MS develops over time, offering many people the chance to take more control of their disease. However, despite their benefits, they are not a cure and cannot undo any permanent disability. Nonetheless, they can reduce how many relapses occur and how serious they are, and they can also slow down the damage caused by relapsing MS that builds up over time. The 34 available DMD/Ts for MS have been abundantly analyzed in the case of the various MS forms (relapsing remitting, secondary progressive, primary progressive) and for treating relapses (exacerbations).

Non-pharmacological rehabilitation therapies (multidisciplinary, cognitive, neurological, physical, occupational, vocational, palliative, etc.) are also available but evidence for their effectiveness is insufficient to recommend them alone although their use in combination with medications may be reasonable. Immunotherapies and stem cell therapies (autologous, mesenchymal) are also available. However, despite potent suppression of inflammation, immunotherapy benefit in the more important and disabling progressive phase is extremely limited so that progressive MS has emerged as the greatest clinical and research challenge. Clinical trials have shown that cell therapies are able to reduce relapses, however, compared to other DMD/Ts, they have among the highest risk of side effects, especially serious ones. Lastly, the prognosis of MS depends on the subtype of the disease with great individual variation.

References

1. Amatya B, Young J, and Khan F (2018). "Non-pharmacological interventions for chronic pain in multiple sclerosis". The Cochrane Database of Systematic Reviews 2018 (12): CD012622. doi:10.1002/14651858.CD012622.pub2.
2. Amatya B, Khan F, and Galea M (2019). "Rehabilitation for people with multiple sclerosis: An overview of Cochrane Reviews". The Cochrane Database of Systematic Reviews 2019 (1):CD012732. doi:10.1002/14651858.CD012732.pub2.
3. Baecher-Allan C, Kaskow BJ, and Weiner HL (2018). "Multiple sclerosis: Mechanisms and immunotherapy". Neuron. 97(4):742–68. doi:10.1016/j.neuron.2018.01.021.
4. Bates D (2011). "Treatment effects of immunomodulatory therapies at different stages of multiple sclerosis in short-term trials". Neurology 76(1

Suppl 1):S1425. -25. doi:10.1212/WNL.0b013e3182050388.

5. Benedict RH, Amato MP, DeLuca J, and Geurts JJ (2020). "Cognitive impairment in multiple sclerosis: Clinical management, MRI, and therapeutic avenues". The Lancet. Neurology 19(10):860-71. doi:10.1016/S1474-4422(20)30277-5.
6. Bennett M and Heard R (2004). in Bennett MH (ed.). "Hyperbaric oxygen therapy for multiple sclerosis". The Cochrane Database of Systematic Reviews. 2011 (1): CD003057. doi:10.1002/14651858.CD003057.pub2.
7. Bope ET and Kellerman RD (2011). “Conn's current therapy 2012: Expert consult”. Elsevier Health Sciences pp. 662.
8. Chong MS, Wolff K, Wise K, Tanton C, Winstock A, and Silber E (2006). "Cannabis use in patients with multiple sclerosis". Multiple Sclerosis 12(5):646–51. doi:10.1177/1352458506070947.
9. Comi G (2009). "Treatment of multiple sclerosis: Role of Natalizumab". Neurological Sciences 30(S2):S155-8. doi:10.1007/s10072-009-0147-2.
10. Corvillo I, Varela E, Armijo F, Alvarez-Badillo A, Armijo O, and Maraver F (2017). "Efficacy of aquatic therapy for multiple sclerosis: A systematic review". Eur J Phys Rehabil Med (Review) 53(6): 944–52. doi:10.23736/S1973-9087.17.04570-1.
11. Cree BA, Hartung HP, and Barnett M (2022). "New drugs for multiple sclerosis: New treatment algorithms". Curr Opin Neurol. 35(3):262–70. doi:10.1097/WCO.0000000000001063.
12. Etoom M, Khraiwesh Y, Lena F, et al. (2018). "Effectiveness of physiotherapy interventions on spasticity in people with multiple sclerosis: A systematic review and meta-analysis". Am J Phys Med Rehabil. 97(11):793–807. doi:10.1097/PHM.0000000000000970.
13. Faissner S and Gold R (2019). "Progressive multiple sclerosis: Latest therapeutic developments andfuture directions". Ther Adv Neurol Disord. 12:1756286419878323. doi:10.1177/1756286419878323.
14. Filippini G, Brusaferri F, Sibley WA, et al. (2000). "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis". Cochrane Database Syst Rev (4): CD001331. doi:10.1002/14651858.CD001331.
15. Filippini G, Del Giovane C, Vacchi L, et al. (2013). "Immunomodulators and immunosuppressants for multiple sclerosis: A network meta-analysis". Cochrane Database Syst Rev (6): CD008933. doi:10.1002/14651858.CD008933.pub2.
16. Filippini G, Del Giovane C, Clerico M, et al. (2017). "Treatment with disease-modifying drugs for people with a first clinical attack suggestive of multiple sclerosis". Cochrane Database Syst Rev. 4: CD012200. doi:10.1002/14651858.CD012200.pub2.
17. Freedman MS (2011). "Long-term follow-up of clinical trials of multiple

sclerosis therapies". Neurology 76(1 Suppl 1):S26-34. doi:10.1212/WNL.0b013e318205051d.

18. Fymat AL (2017a). "Neurological disorders and the blood-brain barrier: 1. Epilepsy," J of Current Opinions in Neurological Science 1(6):277-93, ISSN: 2575-5447.
19. Fymat AL (2017b). "Neurological disorders and the blood-brain barrier: 2. Parkinson's disease and other movement disorders", J of Current Opinions in Neurological Science 2(1)362-83. ISSN:2575-5447.
20. Fymat AL (2017c). "Immunotherapy: An emergent anti-cancer strategy", J of Cancer Prevention & Current Research (Editorial) 7(3):1-4, 00233. doi:10.15406/jcpcr.2017.07.00233. https://medcraveonline.com/JCPCR/JCPCR-07-00233.pdf.
21. Fymat AL (2017d). "Synthetic immunotherapy with chimeric antigen receptors", J of Cancer Prevention & Current Research 7(5):1-3. 00253: doi: 10.15406/jcpcr.2017.07.00253.
22. Fymat AL (2017e)." Immunotherapy of brain cancers and neurological disorders". J of Cancer Prevention & Current Research 8(6):1-7; 00301. doi: 10.15406/jcpcr2017.08.00301.
23. Fymat AL (2017f). Immunotherapy: A new frontier in cancer care", Holistic Approaches in Oncotherapy J (Editorial) 1(1):8-13.
24. Fymat AL (2017g). "Cancer therapy with chimeric antigen receptors – A landmark moment for cancer immunotherapy", J of Cancer Prevention & Current Research 8(6):1-7. 009. doi: 10.15406/jcpcr.2017.08.00300.
25. Fymat AL (2017h). "Nanoneurology: Drug delivery across the brain protective barriers", J of Nanomedicine Research 5(1):1-4, 00105. doi: 10:15406/jnmr/2017.05.00105.
26. Fymat AL (2017h). "Therapeutics delivery behind, through and beyond the blood-brain barrier", Open Access J of Surgery 5(1): 1-9; 555654. doi: 10.19080/OAJS.2017.05.555654.
27. Fymat AL (2018a), "Blood-brain barrier permeability and neurological diseases", J of Current Opinions in Neurological Science (Editorial) 2(2);411-4. ISSN: 2575-5447.
28. Fymat AL (2018b). "Regulating the brain's autoimmune system: The end of all neurological disorders?" J of Current Opinions in Neurological Science 2(3):475-9. ISSN:2575-5447.
29. Fymat AL (2018c)." Innate immunotherapy of recurring glioblastomas: Preliminary trials with neutrophils", J of Current Opinions in Neurological Science 2(3):480-2. ISSN: 2575-5447.
30. Fymat AL (2018d). "Harnessing the immune system to treat cancers and neurodegenerative diseases", J of Clinical Research in Neurology 1(1):1-14.
31. Fymat AL (2018e), "Is Alzheimer's an autoimmune disease gone rogue", J of Clinical Research in Neurology 2(1):1-4. ISSN: 2638,7662.
32. Fymat AL (2018f). "Is Alzheimer's a runaway autoimmune disease? And how to cure it? " Proceedings of the European Union Academy of Sciences, 2018 Newsletter, pages

379-83.

33. Fymat AL (2019a). "The pathogenic brain", J of Current Opinions in Neurological Science 3(2);669-71, ISSN: 2575-5447.
34. Fymat AL (2019b), "On the pathogenic hypothesis of neurodegenerative diseases", J of Clinical Research in Neurology 2(1):1-7.
35. Fymat AL (2019c). "Electromagnetic therapy for neurological and neurodegenerative diseases: I. Peripheral brain stimulations". Open Access J of Neurology and Neurosurgery 12(2):30- 47. doi:10.19080/OAJNN.2019.12.555833.
36. Fymat AL (2019d). "Viruses in the brain...? Any connections to Parkinson's and other neurodegenerative diseases?" Proceedings of the European Union Academy of Sciences, 2019 Newsletter, pages 249-52.
37. Fymat AL (2019e). Alzhei … who? Demystifying the disease and what you can do about it", Tellwell Talent Publishers, pp 236, 23 ISBN: 978-0-2288-2420-6 (Hardcover); 978-0-2288-2419-0 (Paperback).
38. Fymat AL (2020a). "Neuroradiology and its role in neurodegenerative diseases", J of Radiology and Imaging Science 1(1):1-14. Journal closed and transferred to: J of Neuroradiology and Nanomedicine 5(1):1-14.
39. Fymat AL (2020b). "Electromagnetic therapy for neurological and neurodegenerative diseases: II. Deep brain stimulation". Open Access J of Neurology and Neurosurgery 13(1):1-17.doi:19080/OAJNN.2020.13.555855.
40. Fymat AL (2020c). "Nanobiotechnology-based drugs for the treatment of neurological disorders", J of Pharmaceutical Bioprocessing 8(3):1-3.
41. Fymat AL (2020d). "Is Alzheimer's an autoimmune disease gone rogue? The tole of brain immunotherapy", J of Clinical Research in Neurology 3(2):1-3.
42. Fymat AL (2020e). "Parkin... ss..oo..nn: Elucidating the disease... and what you can do about it", Tellwell Talent Publishers, pp 258, ISBN: 978-0-2288-2874-7 (Hard cover); ISBN: 10-0-2228- 2874-0 (Paperback).
43. Fymat AL (2020f). "Dementia: Fending-off the menacing disease... and what you can do about it", Tellwell Talent Publishers, pp 488, 21 September 2020. ISBN: 978-0-2288-4145-3 (hardcover); 978-0-2288-4145-6 (paperback).
44. Fymat AL (2021a). "Cancer treatment: From immunotherapy to gene therapy and beyond", Cancer Therapy & Oncology International J (Editorial) 18(2):1-3.
45. Fymat AL (2021b). "The human brain: Wonders and disorders", Tellwell Talent Publishers, pp 500, ISBN: 10-0-2288-4885-7 (hardcover); 978-0-2288-4885-1 (paperback).
46. Fymat AL (2021c). "Cancer: The pernicious, clonally-evolving disease braided In our genome", Tellwell Talent Publishers, pp 334, ISBN: 10-0-2288--4885-7 (hardcover); -978-0-

2288-4885-1 (paperback).

47. Fymat AL (2022). “Epilepsy: The electrical storm in the brain”, Tellwell Talent Publishers, pp 412, , ISBN-10: 928-0-2288-82036 (hard cover); ISBN-13:978-0-2288-82039 (paperback).
48. Fymat AL (2023). “Multiple sclerosis: The progressive demyelinating autoimmune disease”, Tellwell Talent Publishers pp 504, 30 March 2023. ISBN:978-0-2288-9292-2. (Hardcover); 978-0-2288- 3 (Paperback). https://portal.tellwell.ca/Tellwell/Design/212669.
49. Fymat AL (2023). “Multiple sclerosis: I. Symptomatology and etiology”, Neurology and Psychology Research J (in press).
50. Fymat AL (2023). “Multiple sclerosis: II. Diagnosis and symptoms management”, Neurology and Psychology Research J (in press).
51. Fymat AL (2023). “Multiple system atrophy: The chronic, progressive, neurodegenerative synucleinopathic disease”, Tellwell Talent Publishers (in press).
52. Gallien P, Nicolas B, Robineau S, Pétrilli S, Houedakor J, and Durufle A (2007). "Physical training and multiple sclerosis". Annales de Réadaptation et de Médecine Physique 50(6):373–6, 369–72. doi:10.1016/j.annrmp.2007.04.004.
53. Genchi R (2023). “Stem cell therapy shows promise for multiple sclerosis”, Nature 613:416 (19January). doi.org/grmkvz(2023).
54. Goldschmidt CH, and Cohen JA (2020). "The rise and fall of high-dose Biotin to treat progressive multiple sclerosis". Neurotherapeutics 17(3):968–70. doi:10.1007/s13311-020-00907-5.
55. Gormley KM and Zajicek JP (2006). "Alemtuzumab and craniotomy for severe acute demyelinating illness". 16th Meeting of the European Neurological Society.
56. Hauser SL and Cree BA (2020). "Treatment of multiple sclerosis: A review". Am J Med. 133(12): 1380–90.e2. doi:10.1016/j.amjmed.2020.05.049.
57. He D, Zhang C, Zhao X, Zhang Y, Dai Q, Li Y, and Chu L (2016). "Teriflunomide for multiple sclerosis". The Cochrane Database of Systematic Reviews 3: CD009882. doi:10.1002/14651858.CD009882.pub3.
58. Heesen C, Mohr DC, Huitinga I, Bergh FT, Gaab J, Otte C, and Gold SM (2007). "Stress regulation in multiple sclerosis: Current issues and concepts". Multiple Sclerosis. 13(2):143-8. doi:10.1177/1352458506070772.
59. Heine M, van de Port I, Rietberg MB, van Wegen EE, and Kwakkel G (2015). "Exercise therapy for fatigue in multiple sclerosis". The Cochrane Database of Systematic Reviews 2015(9): CD009956. doi:10.1002/14651858.CD009956.pub2.
60. Hunt D and Giovannoni G (2012). "Natalizumab-associated progressive multifocal leucoencephalopathy: A practical approach to risk profiling and monitoring". Practical Neurology 12(1):25–35.

doi:10.1136/practneurol-2011-000092.

61. Huntley A (2006). "A review of the evidence for efficacy of complementary and alternative medicines in MS". International MS J 13(1):5–12, 4.
62. Jagannath VA, Filippini G, Di Pietrantonj C, Asokan GV, Robak EW, Whamond L, and Robinson SA (2018). "Vitamin D for the management of multiple sclerosis". TheCochrane Database of Systematic Reviews 2018 9:CD008422. doi:10.1002/14651858.CD008422.pub3.
63. Johnston J and So TY (June 2012). "First-line disease-modifying therapies in pediatric multiple sclerosis: A comprehensive overview". Drugs 72(9):1195–211. doi:10.2165/11634010-000000000-00000.
64. Kesselring J and Beer S (2005). "Symptomatic therapy and neurorehabilitation in multiple sclerosis". The Lancet Neurology 4(10):643–52. doi:10.1016/S1474-4422(05)70193-9.
65. Khan F, Turner-Stokes L, Ng L, and Kilpatrick T (2007). Khan F (ed.). "Multidisciplinary rehabilitation for adults with multiple sclerosis". The Cochrane Database of Systematic Reviews 2011(2):CD006036. doi:10.1002/14651858.CD006036.pub2.
66. Khan F, Amatya B, Bensmail D, and Yelnik A (2019). "Non-pharmacological interventions for spasticity in adults: An overview of systematic reviews". Ann Phys Rehabil Med. 62(4):265– 273. doi:10.1016/j.rehab.2017.10.001.
67. Killestein J, Rudick RA, and Polman CH (2011). "Oral treatment for multiple sclerosis". The Lancet Neurology 10(11):1026–34. doi:10.1016/S1474-4422(11)70228-9.
68. Kira JI, Yamasaki R, Ogata H (2019). "Anti-neurofascin autoantibody and demyelination".Neurochemistry International 130:104360. doi:10.1016/j.neuint.2018.12.011.
69. Kulie T, Groff A, Redmer J, Hounshell J, and Schrager S (2009). "Vitamin D: An evidence-based review". J of the American Board of Family Medicine 22(6):698-706. doi:10.3122/jabfm.2009.06.090037.
70. La Mantia L, Munari LM, and Lovati R (2010). "Glatiramer acetate for multiple sclerosis". The Cochrane Database of Systematic Reviews (5):CD004678. doi:10.1002/14651858.CD004678.pub2.
71. La Mantia L, Di Pietrantonj C, Rovaris M, et al. (2016). "Interferons-beta versus Glatiramer acetate for relapsing-remitting multiple sclerosis". Cochrane Database Syst Rev. 2016(11): CD009333. doi:10.1002/14651858.CD009333.pub3.
72. La Mantia L, Tramacere I, Firwana B, et al. (2016). "Fingolimod for relapsing-remitting multiple sclerosis". Cochrane Database Syst Rev. 4:CD009371.doi:10.1002/14651858.CD009371.pub2.
73. Latorraca CO, Martimbianco AL, Pachito DV, Torloni MR, Pacheco RL, Pereira JG, and Riera R (2019). "Palliative care interventions for

people with multiple sclerosis". The Cochrane Database of Systematic Reviews 2019 (10): CD012936. doi:10.1002/14651858.CD012936.pub2.

74. Lerude M “J.-M. Charcot. La foi qui guérit. Présentation », La revue lacanienne, 2011/2 (n° 10), p. 29-32. doi:10.3917/lrl.112.0029.
75. Link H, Huang YM (November 2006). "Oligoclonal bands in multiple sclerosis cerebrospinal fluid: An update on methodology and clinical usefulness". Journal of Neuroimmunology 180(1–2):17-28. doi:10.1016/j.jneuroim.2006.07.006.
76. Marriott JJ, Miyasaki JM, Gronseth G, and O'Connor PW (2010). "Evidence report: The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology”. Neurology 74(18):1463–70. doi:10.1212/WNL.0b013e3181dc1ae0.
77. Martinelli V, Boneschi F, Vacchi L, Rovaris M, Capra R, and Comi G (May 2013). "Mitoxantrone for multiple sclerosis". The Cochrane Database of Systematic Reviews 2013 5(5):CD002127. doi:10.1002/14651858.CD002127.pub3. hdl:2434/533488.
78. McGinley MP, Goldschmidt CH, and Rae-Grant AD (2021). "Diagnosis and treatment of multiple sclerosis: A review". JAMA 325(8):765-79. – 779. doi:10.1001/jama.2020.26858.
79. Motte J and Gold R (2020). "High-dose Biotin in multiple sclerosis: The end of the road". Lancet Neurol. 19(12):965–966. doi:10.1016/S1474-4422(20)30353-7.
80. National Collaborating Centre for Chronic Conditions (2004). "Treatment of acute episodes”. Multiple sclerosis : National clinical guideline for diagnosis and management in primary and secondary care. London: Royal College of Physicians pp. 54–8.
81. National MS Society. “Consensus Statement of the National MS Society on disease-modifying therapies”.
82. Novartis (2021). “Novartis receives FDA approval for Mayzent® (Siponimod), the first oral drug to treat secondary progressive MS with active disease". Novartis.com.
83. Qizilbash N, Mendez I, and Sanchez-de la Rosa R (2012). "Benefit-risk analysis of Glatiramer acetate for relapsing-remitting and clinically isolated syndrome multiple sclerosis". Clinical Therapeutics 34(1):159–176.e5. doi:10.1016/j.clinthera.2011.12.006.
84. Olsen SA (2009). "A review of complementary and alternative medicine (CAM) by people with multiple sclerosis". Occupational Therapy International 16(1):57–70. doi:10.1002/oti.266.
85. Parks NE, Jackson-Tarlton CS, Vacchi L, Merdad R, and Johnston BC (2020). "Dietary interventions for multiple sclerosis-related outcomes". The Cochrane Database of Systematic Reviews 2020 (5): CD004192. doi:10.1002/14651858.CD004192.pu

b4.

86. Petzold A, Braithwaite T, and van Oosten BW (2020). "Case for a new Corticosteroid treatment trial in optic neuritis: Review of updated evidence". Journal. Neurolgy. Neurosurg. Psychiatry(Review)91(1):9–14. doi:10.1136/jnnp-2019-321653.
87. Pozuelo-Moyano B, Benito-León J, Mitchell AJ, and Hernández-Gallego J (2013). "A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of Vitamin D in multiplesclerosis". Neuroepidemiology (Systematic review) 40(3):147–53. doi:10.1159/000345122.
88. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BA, Gronseth GS, et al. (2018). "Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology". Neurology 90(17):777-88. doi:10.1212/WNL.0000000000005347.
89. Rice GP, Incorvaia B, Munari L, et al. (2001). "Interferon in relapsing-remitting multiple sclerosis". Cochrane Database Syst Rev (4):CD002002. doi:10.1002/14651858.CD002002.
90. Rietberg MB, Brooks D, Uitdehaag BM, and Kwakkel G (2005). in Kwakkel G (ed.). "Exercise therapy for multiple sclerosis". The Cochrane Database of Systematic Reviews 2005(1): CD003980. doi:10.1002/14651858.CD003980.pub2.
91. Rosti-Otajärvi EM and Hämäläinen PI (2014). "Neuropsychological rehabilitation for multiple sclerosis". The Cochrane Database of Systematic Reviews 2014(2): CD009131. doi:10.1002/14651858.CD009131.pub3.
92. Saida T (2004). "Multiple sclerosis: Treatment and prevention of relapses and progression in multiple sclerosis". Rinsho Shinkeigaku (Review) (in Japanese) 44(11):796–8. doi:10.1191/1352458502ms845oa.
93. Sedel F, Bernard D, Mock DM, and Tourbah A (2016). "Targeting demyelination and virtual hypoxia with high-dose Biotin as a treatment for progressive multiple sclerosis". Neuropharmacology 110 (Pt B):644–53. doi:10.1016/j.neuropharm.2015.08.028.
94. Simpson R, Booth J, Lawrence M, Byrne S, Mair F, and Mercer S (2014). "Mindfulness-based interventions in multiple sclerosis: A systematic review". BMC Neurology 14: 15. doi:10.1186/1471-2377-14-15.
95. Sørensen PS, Centonze D, Giovannoni G, Montalban X, Selchen D, Vermersch P, et al. (2020).
96. "Expert opinion on the use of Cladribine tablets in clinical practice". Therapeutic Advances in Neurological Disorders 13: 1756286420935019. doi:10.1177/1756286420935019.
97. Steultjens EM, Dekker J, Bouter LM, Cardol M, Van de Nes JC, and Van

den Ende CH (2003) in Steultjens EE (ed.). "Occupational therapy for multiple sclerosis". The Cochrane Database of Systematic Reviews 2010(3):CD003608. doi:10.1002/14651858.CD003608.

98. Steultjens EM, Dekker J, Bouter LM, Leemrijse CJ,and van den Ende CH (2005). "Evidence of the efficacy of occupational therapy in different conditions: An overview of systematic reviews". Clinical Rehabilitation 19(3):247–54. doi:10.1191/0269215505cr870oa. hdl:1871/26505.
99. Thomas PW, Thomas S, Hillier C, Galvin K, and Baker R (2006). in Thomas PW (ed.). "Psychological interventions for multiple sclerosis". The Cochrane Database of Systematic Reviews 2010 (1): CD004431. doi:10.1002/14651858.CD004431.pub2.
100. Torres-Moreno MC, Papaseit E, Torrens M, and Farré M (2018). "Assessment of efficacy and tolerability of medicinal Cannabinoids in patients with multiple sclerosis: A systematic review and meta-analysis". JAMA Network Open 1(6): e183485. doi:10.1001/jamanetworkopen.2018.3485.
101. Tramacere I, Del Giovane C, Salanti G, D'Amico R, and Filippini G (2015). "Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: A network meta- analysis". Cochrane Database Syst Rev. 2015 (9): CD011381. doi:10.1002/14651858.CD011381.pub2. hdl:11380/1082490.
102. Tremlett H and Oger J (2004). "Hepatic injury, liver monitoring and the Interferon-beta for multiple sclerosis". Journal of Neurology 251(11):1297–303. doi:10.1007/s00415-004-0619-5.
103. Tryfonos C, Mantzorou M, Fotiou D, Vrizas M, Vadikolias K, Pavlidou E, and Giaginis C (2019). "Dietary supplements on controlling multiple sclerosis symptoms and relapses: Current clinical evidence and future perspectives". Medicines (Basel) 6(3):95. doi:10.3390/medicines6030095.
104. van den Akker LE, Beckerman H, Collette EH, Eijssen IC, Dekker J, and de Groot V (2016). "Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis". Journal of Psychosomatic Research 90:33–42. doi:10.1016/j.jpsychores.2016.09.002.
105. Winslow R (2017). "After 40-year odyssey, first drug for aggressive MS wins FDA approval". STAT.
106. "Ocrevus- ocrelizumab injection". DailyMed. (13 December 2019).
107. Xu Z, Zhang F, Sun F, et al. (2015). "Dimethyl fumarate for multiple sclerosis". Cochrane Database Syst Rev (4):CD011076. doi:10.1002/14651858.CD011076.pub2.
108. Yang C, Hao Z, Zhang L, Zeng L, and Wen J (2015). "Sodium channel blockers for neuroprotection in multiple sclerosis". The Cochrane Database of Systematic Reviews

2015(10): CD010422. doi:10.1002/14651858.CD010422.pub2. doi:10.1212/CON.0000000000000728.

109. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara, K, Galetta SL, Hartung HP, Kappos L, Lublin F, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, and Cohen, JA (2018). "Diagnosis of multiple sclerosis: 2017 revisions of the Mc Donald criteria". The Lancet Neurology 17(2):162-73. doi:10.1016/S1474-4422(17)30470-2.

110. Trojano M and Paolicelli D (2001). "The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological syndromes". Neurological Sciences 22(Suppl 2): S98-102. doi:10.1007/s100720100044.

111. Tsang BK, Macdonell R (2011). "Multiple sclerosis: Diagnosis, management and prognosis". Australian Family Physician 40(12):948–55.