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# A Review of Multiple Sclerosis Treatments: Interferon Beta, Glatiramer Acetate, Fingolimod, and Natalizumab

Ryan Golden

South Dakota State University, [ryan.golden@jacks.sdstate.edu](mailto:ryan.golden@jacks.sdstate.edu)

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# A REVIEW OF MULTIPLE SCLEROSIS TREATMENTS: INTERFERON BETA, GLATIRAMER ACETATE, FINGOLIMOD, AND NATALIZUMAB

Written by Ryan Golden

## Abstract

Multiple Sclerosis (MS) is an autoimmune disease in which the body's own immune system works to demyelinate the myelin sheaths in the central nervous system. The beginning of the review will concentrate on the history of MS while also describing how MS, the disease, differs from that of normal immune responses. The review then shifts to the four different stages of MS and how to differentiate between the stages, since the treatment options are often dependent on the stage of MS that the patient is in. The main focus of this review is to take an in depth look on four specific medications for treating MS: Interferon Beta, Glatiramer Acetate, Fingolimod, and Natalizumab. Each medication will be described along with detailing their mechanism of action, or proposed mechanism of action, and the specific stages of MS that it has been proven to help. While there is no cure for MS, these medications have been implemented to help reduce the flare-up (relapses) of the symptoms produced by this autoimmune disease. The conclusions of the review offer some insight into newer research and possible paths that researchers should consider.

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## INTRODUCTION:

Multiple Sclerosis (MS) is an autoimmune disease that effects the immune system. It can often be characterized [as a process that causes demyelination of the central nervous system](#) (1). The continual degradation of the myelin, which is important in the signaling pathways in the nervous system, can lead to disability. The interactions with the specific T-cells and the blood-brain barrier are of importance as well. While there continues to be advances in treatment to decrease the frequency of episodes of MS, there is still no cure for the disease (2). The pathological changes are initiated by extensive microglial activation which can lead to inflammatory lesions of the central nervous system (2).

[Because of the complexity of MS, and the fact that it effects each patient differently, the focus of research and treatments is to stop progression of disease, restore lost function, and ultimately to end MS for every patient](#) (3).

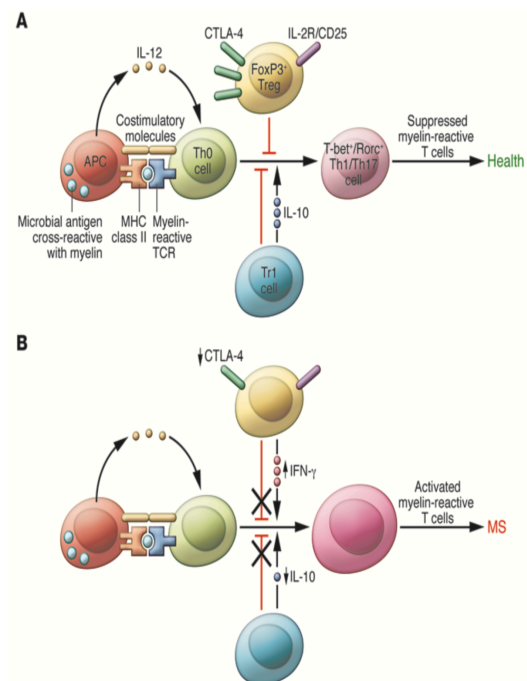
## HISTORY OF MULTIPLE SCLEROSIS

[In 1946, there was little to be known on multiple sclerosis, but this was the year in which the National Multiple Sclerosis society was founded. The following year, the National MS society sponsored their first three research projects. However, it wasn't until 1993 that the first treatment directly for MS was approved and 2010 the first oral treatment is brought to market](#) (3). [Funding continues for extended trials that continue](#)

[to provide promise for continued exploration into treatments specific to MS.](#)

## DISEASE PATHOLOGY

How multiple sclerosis effects normal cells can be a starting point to help find possible treatments. Figure 1 shows the differences in immune functions between a normal cell and a MS cell.



**Figure 1 Normal vs. MS compromised cell:** In panel A represents a normal suppression of myelin-reactive T cells, while panel B represents how myelin-reactive T cells become activated in multiple sclerosis (4).

Panel “A” [depicts an immune cell's normal reaction](#) (4). The co-stimulatory molecules along with CTLA-4 are shown to regulate or suppress myelin-reactive T cells. “B” gives a representation of how the peripheral immune regulation is damaged (4). Some main differences to note are the

increase in co-stimulatory molecules and decrease in CTLA-4. These changes lead to the activation of myelin-reactive T cells that can cross the blood-brain barrier and [initiate an inflammatory response \(4\)](#).

## STAGES OF MULTIPLE SCLEROSIS:

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Multiple Sclerosis is a disease that [can be](#) characterized by an impaired nervous system. However, it can better be broken down into four main stages: 1) Clinically Isolated Syndrome 2) Relapse-Remitting 3) Primary Progressive and 4) Secondary Progressive [\(2\)](#).

Clinical signs can often provide grounds to make a diagnosis of MS, magnetic resonance imaging (MRI), is an important method to support these findings [\(5\)](#). There is a set of criteria that [must be](#) met in order to provide the [clinical](#) diagnosis of multiple sclerosis. This is referred to as the “McDonald Criteria” by the International Panel on Diagnosis of MS [\(5\)](#). The McDonald Criteria was originally written in 2001, but with the latest revisions coming in 2013 [\(5\)](#). The McDonald Criteria contains the guidelines as to the different stages of MS and how to classify the patient’s stage based on the presenting conditions. It is important for the panel to continually look at revisions as the technology and research in MS advances.

## CLINICALLY ISOLATED SYNDROME

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Clinically isolated syndrome [often refers to](#) the first step in multiple sclerosis. This stage is a change in 2013 from the previous stages listed in McDonald’s Criteria [\(6\)](#). It is known to be an acute onset of demyelination located in the central nervous system [\(7\)](#). This syndrome is found in approximately 90 percent of initial presentations of MS and has become a key diagnosis tool for early detection of MS [\(7\)](#).

There continues to be more research on the importance of early diagnosis [and how it correlates to](#) the clinical course of MS. As a result, a recent study [by Kavaliunas, A. et. al in 2017](#), worked to see the correlation of early treatment initiation and time line of disability.

The study included 639 patients that were diagnosed with MS from 2001 to 2007. The study followed up with patients in 99 months as the median amount of time [\(8\)](#). The aim of the study was to find the relationship of time of treatment to an irreversible score of 4 on the Expanded Disability Status Scale (EDSS).

EDSS is a score 0-10 that is given as a determinant of the progression or stage that is the MS is inhibiting on the patient’s body. On this scale, a 0 would indicate that the neurological exam is normal whereas a 10 would indicate death due to MS [\(9\)](#). Signs of disability begin to show up at a EDSS score of 2. The before mentioned study from 2017 found that patients who

started their treatment later had a greater risk of reaching EDSS 4, which was found to increase by 7.4 percent for every year in which they delayed the initiation of treatment (8). It was concluded that early treatment initiation had a positive correlation ( $p < 0.001$ ) with a better clinical outcome (8).

The before mentioned study is just one reason as to the importance of having the diagnostic ability to discover MS in the early stages. This can then give specialists the opportunity to monitor someone who may be at risk for developing multiple sclerosis.

#### RELAPSE-REMITTING MULTIPLE SCLEROSIS

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[Relapse-Remitting Multiple Sclerosis](#) is defined as an occurrence, recurrence, or possible worsening of neurological dysfunction that lasts more than 24 hours (10). Of these dysfunctions, they must become stabilized or resolved either partially or completely after that time (10).

Relapse-Remitting Multiple Sclerosis (RRMS) can be defined as having clearly defined disease relapses that follow with either a full recovery or with partial recovery (11). It is between these relapses that there is a period that lacks progression of the disease, i.e. remitting (11).

This stage carries some defining elements to RRMS. The episode of relapse is dependent on the worsening of neurological function but must also have

stability between attacks. A dissociation has not been found within the disease between patients that fully recover and those that only partially recover (11).

#### PRIMARY-PROGRESSIVE MULTIPLE SCLEROSIS

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Primary-Progressive Multiple Sclerosis (PPMS) is defined as the disease progression from the onset of initial MS with occasional plateaus and also having temporary improvements that are minor (11). The essential point to this stage of MS is that it is characterized by an almost continuous, but gradual worsening baseline conditions of MS with minor improvements to conditions, but no distinct relapses (11).

While RRMS does not have a continual increase in disability, PPMS has the increase in disability as time increases. The plateaus of minor improvement may or may not be seen in the patient, however it is more likely than not that plateaus will be seen (11).

#### SECONDARY-PROGRESSIVE MULTIPLE SCLEROSIS

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Secondary-Progressive Multiple Sclerosis (SPMS) can be defined as RRMS as the initial course of disease, but is followed by progression that may or may not have relapses, minor remissions, or plateaus (11). It can be thought about that SPMS is the longitudinal outcome of [some, but not all](#) RRMS.

The distinguishing characteristic from RRMS and SPMS is the worsening of baseline conditions from one stage to the other (11).

All four of the above stages can be diagnosed by clinical symptoms, but a MRI can give more accurate baseline information. [The purpose of the MRI is to find evidence of brain and spinal lesion. Lesions can be seen due to the contrast that is injected. MRI was first used as a diagnostic tool in 1981 \(3\).](#)

## TREATMENTS OF MULTIPLE SCLEROSIS

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In, 1993 the list of licensed multiple sclerosis treatments was zero, but as of March, 2017, 15 approved [treatments](#) exist. As stated earlier, there are no known cures for MS, but rather treatments that can provide temporary improvements or decrease in symptoms.

The aim for most treatments is to help with symptoms to improve the quality of everyday life. The following is [a subset](#) of the growing list of disease-modifying treatments for multiple sclerosis.

### INTERFERON BETA

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#### WHAT IS INTERFERON BETA?

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Interferon beta is polypeptide that is produced by fibroblasts in the body. This polypeptide has anti-inflammatory effects because of its inhibition of T-lymphocyte proliferation (12). Only recombinant forms

of interferon beta are given for MS treatment, interferon beta-1a and interferon beta-1b. Interferon beta-1a is given in doses of either 30 micrograms intramuscularly once a week or subcutaneously with doses of either 22 or 44 micrograms, while interferon beta-1b is administered at a dose of 250 micrograms subcutaneously every other day (12).

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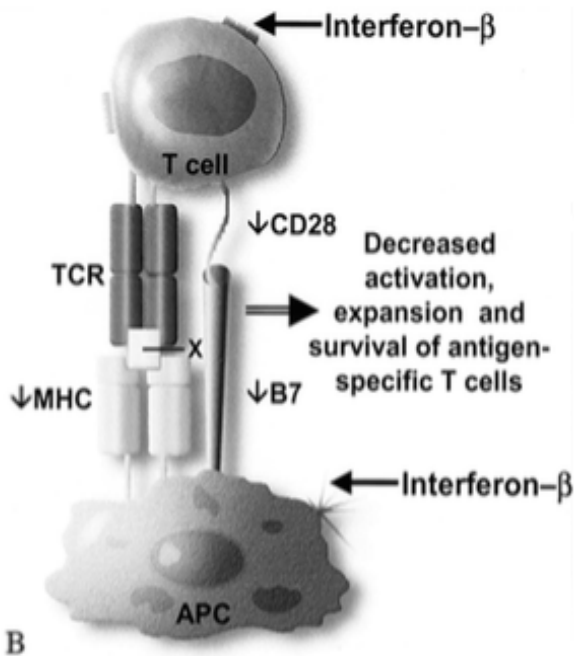
#### MECHANISM OF ACTION OF INTERFERON BETA

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Interferon beta has several proposed potential mechanisms of action in regard to multiple sclerosis. The precise mechanism by which interferon beta produces its anti-inflammatory and immunomodulatory effects is still unclear (13). Those proposed methods include inhibition of T-cell activation and proliferation and also the blood-brain barrier effects (13).

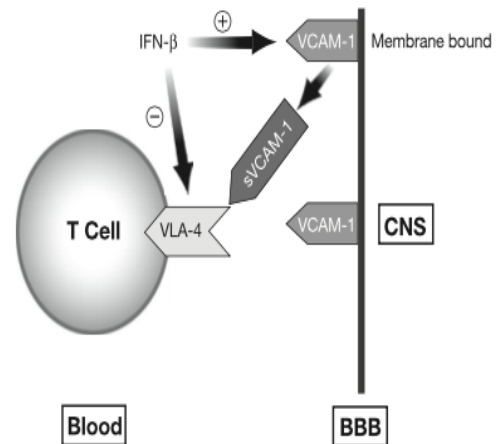
In an earlier section, the importance of the decreased activation of myelin-reactive T-cells [was discussed](#) (4). It has been proposed that interferon beta [achieves](#) that. This drug promotes an increased expression of CTLA4, an important regulator for T-cells (13). It was also suggested in another study that interferon beta leads to an increase in Fas and CTLA4 induces apoptosis of such autoreactive T cells (14). It can then be suggested that the effects of interferon beta lower the chances that pathogenic T-cells will become activated which leads the processes of the events that is initiated in MS cells.

Another proposed mechanism is interferon beta the decreases expression of molecules needed for antigen presentation. Figure 2 shows that proposed mechanism.



**Figure 2. Interferon-Beta Cascade.** The above figure displays interferon beta activation leads to decreased generation of antigen-specific T cells (15).

A final proposed model of interferon beta mechanisms of action are the effects on the blood-brain barrier. Interferon beta increases the serum concentrations of soluble vascular cell adhesion molecule – 1 (sVCAM) (13). Figure 3 shows the proposed model of interferon beta blood-brain barrier effects.



**Figure 3. Reaction to Interferon Beta Levels.** The above figure illustrates how an increase or a possible decrease in interferon beta can halt T-cell adhesion with the vascular endothelial basement membrane and extravasation by central nervous system (14).

#### STAGES THAT INTERFERON BETA BENEFITS

Both types of interferon beta have been found to work in multiple stages of multiple sclerosis. For instance, in a study done in 2006, it was proposed that interferon beta-1b given at 250 micrograms subcutaneously every other day could be used as a treatment option to delay [patient's progression to RRMS from](#) clinically isolated syndrome (16).

The majority of the treatment was for RRMS in reducing the annualized relapse rate. Interferon beta was found to have [approximately 30%-34%](#) reduction of disability progression as well as decreased disease activity seen on MRI (12).

Interferon beta has not been found to be [effective](#) for PPMS, because they are not designed for the pathogenic



mechanisms that are employed in PPMS (17). Whereas patients with SPMS have found some benefit, but for patients to experience this effect they must be experiencing superimposed relapses (12).

## GLATIRAMER ACETATE

### WHAT IS GLATIRAMER ACETATE?

Glatiramer acetate is a group of synthetic peptides that resembles sequences of myelin basic protein, that often have lengths from 40-100 residues (12). It is thought to have its anti-inflammatory effects based on its role with Th2 and anti-inflammatory cytokines (12). Glatiramer acetate can be given subcutaneously in 20 mg daily or by 40 mg three times weekly (18).

According to a study completed in 2015, the higher, but less frequent dose of glatiramer acetate had the following effects:

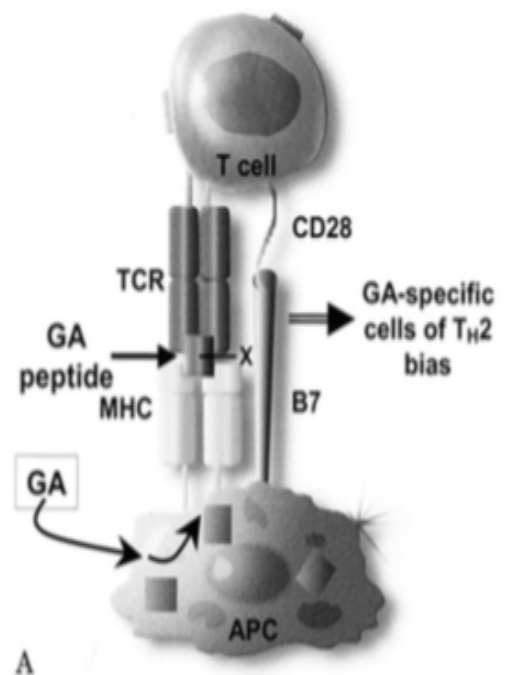
- Reduction of annualized relapse rate in comparison to a placebo group
- Suggest similar efficacy to that of the lower, more frequent dosage of glatiramer acetate
- 50 percent reduction of incidence of side effects at injection site
- Possibility to show an increase in convenience with MS patients (18)

Due to this, recently there has been a switch in dosing from the daily 20 mg to the 40 mg three times weekly.

### HOW DOES GLATIRAMER ACETATE WORK?

The exact mechanism of glatiramer acetate is, again, not completely known. There are several proposed mechanisms that do exist today.

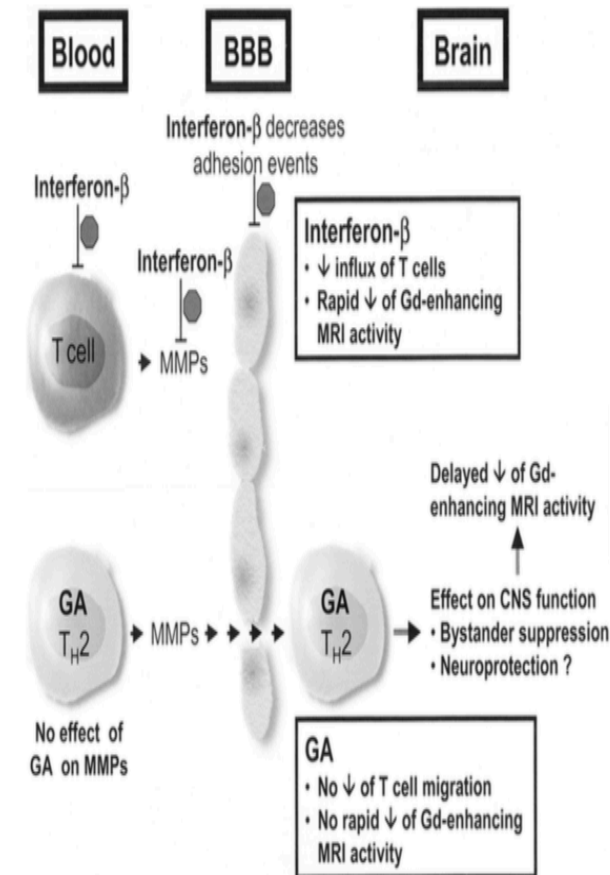
The first is thought to deal with the activation of glatiramer acetate Th2 specific cells and the competition that occurs with MHC molecules on the antigen-presenting cells leads to suppression of the activation of myelin-reactive Th1 cells (19). Figure 4 below, shows such proposed mechanism.



**Figure 4. Glatiramer Acetate Proposed Cascade.**

The above figure demonstrates how the presentation of glatiramer acetate as an antigen and leads to generation of glatiramer acetate specific Th2 cells is accomplished by either the high affinity of glatiramer acetate for the MHC or by an uptake of glatiramer acetate by an antigen presenting cell (15).

Another often suggested mechanism of action involves the blood-brain barrier. Figure 5 below shows this relationship. The actions can be best seen by contrasting the mechanism of interferon beta. (Gd means gadolinium, the element)



**Figure 5. Effects on BBB.** The above figure shows the effects that interferon beta and glatiramer acetate have on the blood-brain barrier and eventually the brain (15).

As seen in Figure 5, glatiramer acetate Th2 cells cross the blood-brain barrier to affect the central nervous system function by a possible bystander suppression of the active myelin-reactive T cells. It also leads to no decrease in T cell migration and a delayed decrease of Gd-enhancing MRI

activity (15). Gd enhancing MRI activity contains a correlation to infiltration of lymphocytes and also an increase in MMP levels is observed to lead to the disruptions of the blood-brain barrier (15)

Other proposed mechanisms that are less understood include, glatiramer acetate lowering the production of cytokines by Th1 and imposing a neuroprotective effect by neurotrophic factors in the central nervous system (19).

#### STAGES OF MULTIPLE SCLEROSIS THAT GLATIRAMER ACETATE BENEFITS

Glatiramer acetate at a subcutaneous dosage of 20 mg daily has been found to be effective,  $p=0.0005$ , for patients with clinically isolated syndrome when compared to a placebo trial of a 3 year time period involving 481 patients (20).

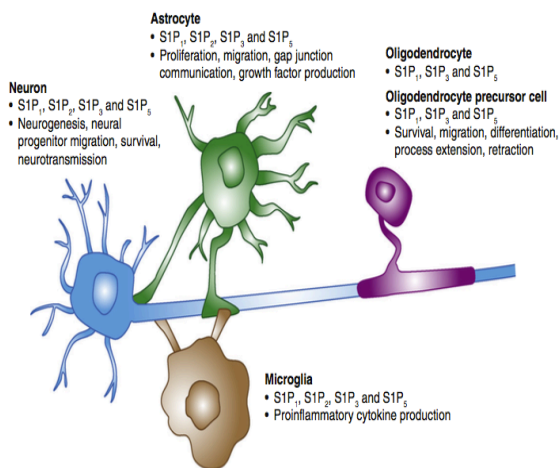
Glatiramer acetate has been most effective in RRMS with the 20 mg daily dose having a mean reduction of annualized relapse rate of 29% (12). The glatiramer acetate that is given at 40 mg three times weekly was found to have a mean annualized relapse rate of 34% ( $p<0.0001$ ) (18).

While glatiramer acetate has a high reduction of annualized relapse rate for clinically isolated syndrome and RRMS, it has not been investigated in SPMS and has shown no benefits for patients with PPMS (21).

## FINGOLIMOD

### WHAT IS FINGOLIMOD?

Fingolimod is the first oral form of a disease-modifying therapy that is approved for MS (22). It can be classified as a sphingosine 1-phosphate (S1P) receptor modulator (12). S1P is a natural lipid, in the lysophospholipids family; these lipids act as regulators for the pathogenesis of MS (22).



**Figure 6. Cells With S1P receptor.** The above figure depicts a summary of the different cells that have the S1P receptor and are therefore affected by fingolimod (22).

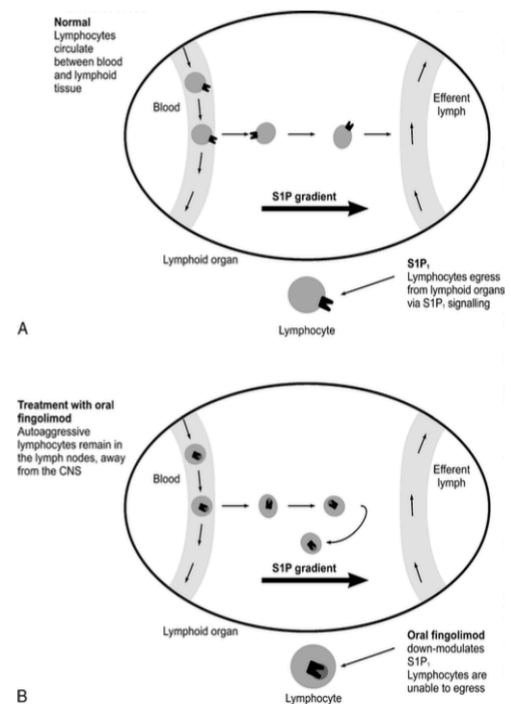
Past studies suggest that the S1P receptors that are found in figure 6 have been impaired in multiple sclerosis (22).

Fingolimod is usually given in oral capsules at a dose of 0.5 mg or 1.25 mg daily (12).

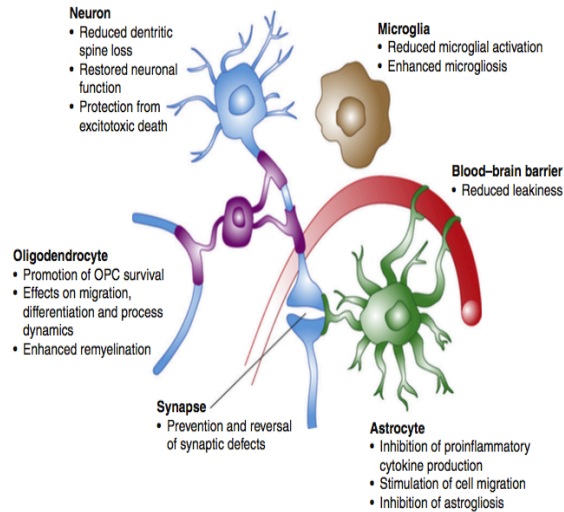
## MECHANISM OF ACTION OF ORAL FINGOLIMOD

Fingolimod is effective because it can cross the blood-brain barrier and directly affect the central nervous system (23). It has the capabilities to induce adherent junction assembly that can reduce the vascular leakage that is experienced in the pathogenesis of MS (22).

Fingolimod works to inhibit the movement of the autoreactive lymphocytes from the lymph nodes and penetrate the central nervous system (12). Figure 7 represents these such actions.



**Figure 7. Mechanism of Action of Fingolimod.** The above figure represents how fingolimod works to down-regulate S1P receptors located on the lymphocytes in order to prevent the lymphocyte movement from the lymphoid tissues to lead to reduced penetration of destructive cells into the central nervous system (23).



**Figure 8. Effects of Fingolimod.** The figure above displays the effects that fingolimod treatment can employ on different cells within the central nervous system (22).

#### STAGES OF MULTIPLE SCLEROSIS ORAL FINGOLIMOD HAS PROVIDED BENEFITS

Fingolimod has proven to have therapeutic efficacy in patients with relapsing or relapsing-remitting MS (23). For RRMS that 0.5 mg of fingolimod daily had a reduction of annualized relapse rate by 48-55 percent while also slowing disability by 25-30 percent in a study of 1272 patients ( $p < 0.001$ ) (24).

There continues to be ongoing investigations into the effectiveness of fingolimod for PPMS and SPMS, but additional trials are needed (22).

## NATALIZUMAB

### WHAT IS NATALIZUMAB?

Natalizumab is a second line therapy that has been found to have an astoundingly high ARR at 68% ( $P < 0.001$ ) (12). Natalizumab is defined as a monoclonal antibody that specifically blocks the interaction of the ligands at the  $\alpha 4$ -integrin which is a glycoprotein (25).

Another interesting difference in natalizumab was the dosing instructions. In contrast to the earlier discussed treatments, natalizumab is a 300 mg, intravenous infusion that is given every four weeks (12).

In addition to the reduced annualized relapse rate, a two-year, phase III trial considered to be pivotal to understanding natalizumab, also demonstrated that it lowered the rate of disability by 54% while also reducing gadolinium-enhancing lesions seen on MRI by 92% ( $p < 0.001$ ). The study consisted of 942 patients with 315 of those receiving placebo infusions as a control (26).

However, with the high reductions mentioned earlier, there is an increased risk of developing a disease called progressive multifocal leukoencephalopathy (PML) with increased treatment time of natalizumab (27). In other words, the longer the period a patient receives natalizumab, there is an increase in the risk of the patient developing PML. PML is an infection from John Cunningham virus (JCV) attacking the oligodendrocytes of the CNS (12).

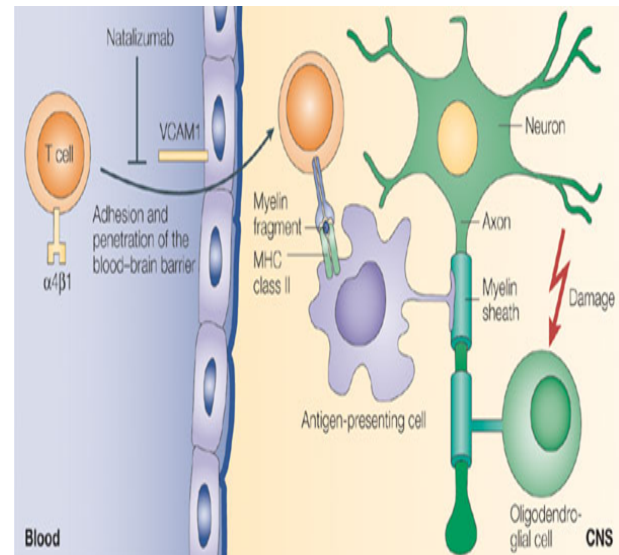
Due to the severity of PML, it has been imperative for MS patients to be screened in order to identify those patients who have been exposed to JCV because it is possible that viral reactivation can occur on immunosuppressed patients such as those with MS. STRATIFY JC virus™, which is an assay that measures anti-JC virus antibodies that are present in the blood to identify exposure to the JCV. Early results from the study showed that anti-JC virus antibodies were present in 54% of MS patients that were treated with natalizumab (27). Therefore, only patients that are JCV-negative use natalizumab for more than two years and are tested every six months to see if their JCV status changes (12).

#### HOW DOES NATALIZUMAB WORK?

As stated before, natalizumab is monoclonal antibody that functions to block the  $\alpha$ 4-integrin, more specifically the  $\alpha$ 4 $\beta$ 1-integrin (VLA-4) from binding. It's believed mechanism of action is inhibition of autoreactive T cells entering into the CNS. In the same study, it was also thought that natalizumab could also be affected by pathogenic B cells in a similar way (28). This proves to be promising due to the fact that natalizumab binding to VLA-4 had a 49% reduction for B cells versus only 24.5% reduction of T cells. This was also accompanied by an increase in circulating B cells over T cells (29).

The main concern of understanding how natalizumab works in RRMS is the interactions between the VLA-4, which is seen in mononuclear inflammatory cells, and vascular cell adhesion molecule-1 (VCAM-1) expressed by cerebral vascular

endothelial cells are known to express. This interaction leads to a reduction of leukocyte integration in the CNS which in turn lowers the activity of MS (30). This interaction is depicted in figure 9 below.



**Figure 9. Natalizumab effects on MS.** The  $\alpha$ 4 $\beta$ 1-integrin binds to the VCAM-1, which then allows the autoreactive T cell to enter the CNS. Natalizumab does not allow the  $\alpha$ 4 $\beta$ 1-integrin and VCAM-1 to bind and allow the T cell to penetrate the blood-brain barrier to damage the myelin sheath (31).

Another possible mechanism in which natalizumab helps with MS is Osteopontin levels in plasma, which are elevated in comparison to a healthy patient and even more so in CSF (30). In a 2 year study of 49 patients with RRMS, it was shown that natalizumab reduced Osteopontin levels by 31% ( $P < 0.005$ ). Also, it showed improvement in patients' cognitive impairment ( $P < 0.005$ ) (32). It can be suggested from this data that increased Osteopontin levels can lead to cognitive impairment.

As this treatment continues to become increasingly implemented, it continues to have possible mechanisms of action that

attempt to explain how it works. The main point being the interaction that occurs between the VLA-4 and VCAM-1.

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#### STAGES OF MULTIPLE SCLEROSIS THAT BENEFIT FROM NATALIZUMAB

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Natalizumab has the majority of its documented literature on how the treatment helps with RRMS, the 68% reduction in ARR stated earlier. As of March 2017, natalizumab is only documented to be effective against RRMS.

In 2011, there was a phase IIIb study on natalizumab in SPMS called ASCEND (30). However, in June of 2017 this trial was terminated for not having statistically significant findings. While this can be discouraging to researchers, there is still hope for finding a clinical benefit to understanding how the BBB is disturbed in progressive forms of MS.

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#### CONCLUSIONS

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Treatment for multiple sclerosis has come a long way in the last 24 years since the first drug treatments began to be produced. There looks to be continual upside to treatments of multiple sclerosis as ongoing trials are completed. Fingolimod continues to be an increasingly popular drug for the MS community because of the convenience of the oral version and the possibility of helping with non-relapsing forms of MS.

While the focus of this review was on four specific treatments for the neurological disease pathway, it should also be noted that there are multiple different

medications that MS patients use in order to treat other symptoms that are accompanied by this disease.

For example, onabotulinum toxin type A (Botox), which is normally for the treatment of muscle stiffness, in 2011 was approved to treat urinary incontinence in MS patients. Botox is also used to help to control with spasticity (increase in tonic stretch reflexes) with injection directly into the skeletal muscle (33).

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#### FUTURE RESEARCH

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As stated above, future research needs to be done in order to continue to help people that are affected by this widely seen autoimmune disease. The increases in technology should continue to be a benefit to researchers in hopes to continue to enhance current medication, but also the possibility of development of new targeted treatments for MS (27).

The most important research could come from an increase in studies to help clarify mechanism of action of these four drugs discussed in this review. Many of the mechanisms continue to remain unknown, which could impede research efforts. Knowing the possible mechanism could provide the opportunity to allow physicians to better select appropriate drugs for treatment (13, 30, 34).

Another possibility in future research could focus on the ability of the drug to influence not only the immune system but also pathological changes that occur in MS. The



more that can be learned about the actual pathology, the better and more precise the treatments can be.

Long term effects of the disease modifying treatments should also continue to be studied. Not only for the patient, but the physician so that they can estimate when a medication change should be made.

A newer approach that is just starting to be explored is the effects that melatonin has on the immune response in MS. A study done in 2017 was the first to demonstrate that melatonin can reduce Th1 and Th22 pathogenic responses in MS patients. The results also suggested that melatonin increases the ratio of anti-inflammatory vs. pro-inflammatory peripheral cells (35). This could provide yet another possible avenue for advancement in research.

Throughout this review, the current forms of treatments have shown efficacy for RRMS, future research should also look into options for treatment for PPMS and SPMS. The main area of continued research should focus on the mechanisms of action of current treatments.

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## APPENDIX A

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Citations for “A Review of Multiple Sclerosis Treatments: Interferon Beta, Glatiramer Acetate, Fingolimod, and Natalizumab” were cited in NLM format.

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## APPENDIX B

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The external reviewer for this review was Dr. Jerome Freeman a Neurologist at Sanford Neurology Clinic in Sioux Falls, SD.

He has been a tremendous help in his review of the first draft of this review.

The following is his remarks on the first draft of this review:

“I reviewed your manuscript “Review of Multiple Sclerosis and Treatment Options”. You have a lot of good information in the paper. I want to point out a couple of things. It is not known for sure how interferon beta and glatiramer acetate work. You provide some good explanations. Generally it is thought that interferon tends to work more peripherally and glatiramer more in the central nervous system itself. Both seem to reduce the annualized relapse rate (ARR) by about 30%. There are multiple other, newer therapies available now. You mention Fingolimod. It is estimated that Fingolimod causes an ARR reduction of about 54 to 60%. Another oral agent is Teriflunomide. That causes an ARR reduction of about 31% and it’s not used as much as the other oral agents. A third oral agent is Dimethyl Fumarate. This causes an ARR reduction rate of about 53%. Currently one of the most aggressive MS therapies available is Natalizumab. This is a once a month IV injection. It reduces the ARR by about 68%. It is associated with a dangerous viral condition (progressive multifocal leukoencephalopathy (PML)). This only tends to occur in people who carry the James Cunningham virus, which is about 50% of the population. Generally this drug is used in people who are JC virus negative. Other

options include Alemtuzumab (monoclonal antibody). A new drug that appears to be very effective is Ocrelizumab. This also is a humanized monoclonal antibody. Basically people get an infusion of this every 6 months. Thus you can see that there are considerably more options than the three therapies you mentioned.”

After Dr. Freeman’s comments, I decided to narrow the title down to the four treatments reviewed as to be more specific. I chose to add Natalizumab because the PML component was interesting.

Continuing with Dr. Freeman’s comments:

“I’ll make some other brief comments about the manuscript. In your introduction you note MS as a “failure of the central nervous system to perform remyelination”. Actually I would characterize it foremost as a process that causes demyelination. There is now evidence that in addition to attacking myelin, MS also has an adverse effect on axons. On page three under your “stages of multiple sclerosis” the second paragraph starts with two phrases that aren’t complete sentences. On page four, I think most experts refer to “relapsing-remitting multiple sclerosis” rather than using the term “relapse”. The hallmark of this type of MS is that people get an attack and then recover (often 100%). Sometimes some mild residual symptoms persist. I think characterizing the “remission” is important rather than just the “lacks progression” that you mention. On page five under

“secondary-progressive multiple sclerosis” you imply in the first paragraph that all people with RRMS proceed to a secondary progressive phase. That is not necessarily the case. I think it would be better to indicate that SPMS is the outcome of some patients with RRMS. On page six (second paragraph) the first sentence is not complete. Before reference #3 I think you would want to say something like “was mentioned”. Also in the next sentence you say that interferon beta “does such that”. I think it would be better to say “achieves that”. On page seven at the bottom of the first column you indicate “affective”. It should be “effective”. Also in the second column on page seven the third bullet point mentions “50 percent reduction of incidence at reaction site”. I’m not sure what that pertains to.”

I took all of his grammatical and word choice suggestions to better the review.