The Elusive "Most Effective Treatment:" A Review of Pharmaceutical and Physical Therapies to Treat Multiple Sclerosis

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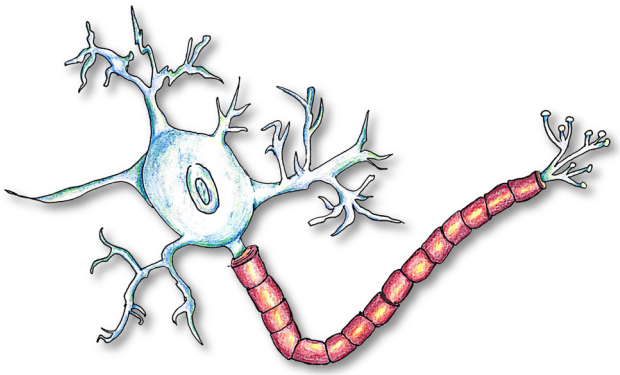
Abstract

Substantial developments in the treatment of the debilitating disease of multiple sclerosis (MS) have arisen with a greater understanding of its involvement with inflammation, demyelination, and neurodegeneration. Yet, despite advancements in clinical efforts, many current treatments produce terrible side effects that cause patients to discontinue their use.

The objective of this review is to discuss the current therapies and the best approach for future treatment. This review utilizes articles published from 1990-2016 to accomplish this task and to cumulatively suggest a future course of treatment. The review suggests that the most effective treatment of MS can be achieved by use of low dosage neuro-protective and anti-inflammatory pharmaceuticals, combined with various different types of physical therapy (PT) to keep muscle mass, coordination, balance and cognitive function at a high level.

Introduction

Multiple sclerosis (MS) is a degenerative autoimmune disorder that affects the central nervous system (CNS) due to the demyelination of neurons within the CNS (1). Demyelination of axons causes neurons to become permeable and makes it difficult for an action potential to propagate down the axon to the connecting cell. In essence, the demyelination of the axons interrupts the inter-web of communication



Tamar Yacoel: *Neuron with Myelin*

within the CNS, causing a disruption of information flow.

Though the cause of MS is not well known, recent studies suggest that deficiencies in the blood-brain barrier allow lymphocytes to infiltrate the CNS where they accumulate and attack the neurons at the myelin sheaths that surround the axons (2). As a result of the over-permeability of the blood-brain barrier in the CNS, an inflammatory response occurs and foreign cells (T-cell and B-cell lymphocytes) invade the brain and/or spinal cord. As a result of this infiltration, the T and B cells cause significant damage and demyelination. Promising results already show that medications that are effective in limiting B-cell proliferation and migration to the CNS help to reduce lesion formation and relapse rate (3).

The incidence of MS in the United States is an alarming 30+ cases per 100,000 people and affects more women than men (4). The first symptoms occur between the ages of 20-40 and often involve visual

or balance problems. Over time, symptoms worsen to severe motor and sensory disability; cognitive functional ability may be affected and muscle atrophy may occur due to the disruption of the connection between the CNS and the muscles. Muscle atrophy will then lead to the number one reported symptom of MS: fatigue (5). General fatigue and feelings of malaise are reported in more than 75% of all MS patients with over half stating that it is one of their worst symptoms (5). Several studies suggest that MS-related fatigue was associated with anxiety, depression, and decreased socialization (6).

It is important to study and address different approaches to treat and control MS due to the devastating and debilitating effects of the disease. Current treatment consists of pharmaceutical and physical therapies (PTs). However, neither is perfect and both have their advantages and disadvantages. The aim of this review is to discuss the treatments available for multiple sclerosis and to better understand the synergistic effect of immunomodulatory and cytoprotective medications with rehabilitation.

Treatments for Multiple Sclerosis: From the Pharmaceutical to the PT Approach

Immunomodulatory & Cytoprotective Medications: Natalizumab and Fingolimod

Various medications, ranging from immunomodulatory and immunosuppressive therapeutic agents to monoclonal antibodies are readily available to lessen the occurrence of symptoms and to try to slow the degeneration of the CNS (7). The mechanisms by which these medications work involve either the permeability of the blood-brain barrier, the way that cells can attach to their targets or the regulation of lymphocyte expression.

For the subset of relapsing-remitting MS, based on their profile, interferon-beta (IFNβs), naturally occurring anti-inflammatory cytokines, are given as a first-line treatment through subcutaneous or intramuscular injection with skin reactions as a possible side effect. IFNβ appears to directly increase expression and concentration of anti-inflammatory agents while also downregulating the expression of pro-inflammatory cytokines. As a result, interferon beta increases suppressor activity and inhibits T cell proliferation (8). Another widely used first-line agent and injectable medication is glatiramer acetate, a synthetic protein that is physically similar to a component of myelin and stimulates the immune system to generate anti-inflammatory responses (9).

Key Point: MS Symptoms

Scanning Speech: broken speech with frequent pauses between syllable pronunciation

Intention Tremor: slow meandering voluntary movements when extending towards an object

Nystagmus: involuntary eye movement due to brainstem and/or cerebellar lesion

Olek, M. J. (2016). Epidemiology, risk factors and clinical features of multiple sclerosis in adults. Retrieved from www.uptodate.com/contents/epidemiology-and-clinical-features-of-multiple-sclerosis-in-adults

Over the past two decades, new treatments have arisen for MS. One such treatment is natalizumab, a monoclonal antibody targeting the VLA-4 receptor that is expressed on activated T cells and other mononuclear white blood cells. This drug binds to specific points on lymphocytes and controls their migration through the blood brain barrier (10). Since the lymphocytes cannot attach strongly to the endothelial cells to travel into the CNS, the demyelination rate is drastically reduced and axons are spared. This preventative means of treatment slows scarring and the growth of lesions and can subsequently slow down the symptoms of MS.

There has been evidence that natalizumab is still effective even with reduced doses. One study showed that the normal 6 mg administration of natalizumab gave negligible benefits versus a reduced dosage of 3 mg daily (11). Interestingly, the amount of new lesion formation was less among the 3 mg group than the 6 mg group, indicating that 3 mg may even be better at reducing lesion formation. Furthermore, it was seen that the increased dosage augmented the occurrence

of side effects, which included headaches and certain infections such as the John Cunningham virus (JCV) (12). Concurrent with reduced side effects and lesion formation, there was a reduced relapse rate of 68% among patients taking a reduced dosage compared to the placebo.

A particularly severe adverse effect of natalizumab has been noted for patients prescribed natalizumab in any dosage: an increase in contraction of Progressive Multifocal Leukoencephalopathy (PML) due to the drug's immunosuppressive effects (13). PML is also a demyelinating disease of the CNS. However, PML is caused by the JCV. Active infection with the virus allows lymphocytes to infiltrate the brain at a higher rate than in MS alone. Furthermore, JCV attacks and kills oligodendrocytes, which are already sorely lacking in a MS inflicted brain; ultimately, this leads to the inability to repair axons by means of re-myelination. PML is very similar to MS, but progresses much more rapidly; over the course of months versus years. Although the drug has shown beneficial results, the adverse consequences of contracting PML, may not justify the use or implementation. Patients that are seropositive for Anti-JCV antibodies are 44 times more likely to contract PML than those who are antibody negative. Therefore, current regulations stipulate that MS patients should be tested for JCV before being given natalizumab.

There are many limitations with medications that control lymphocytes, infiltrate the CNS, and adhere to target cells. It is very difficult to create a drug that can pass the non-permeable blood-brain barrier efficiently. Effects are transient and medications must be taken consistently to maintain efficacy (15). One study followed patients that had been taking natalizumab for more than 12 months after which they were told to cease treatment for a 6-month period (16). Results showed a disturbing 67% increase in clinical symptoms after this 'holiday' period. This suggested that cessation of these medications led to recurrence of MS symptoms. This suggests that the drug is successful in combating MS symptoms even though it has serious side effects.

Through another mechanism, the cytoprotective drug, fingolimod, acts as a protecting agent to change lipid markers on oligodendrocytes to prevent destruction by T-cells from the immune system. Since the oligodendrocytes are protected, they can continue producing the axon-protecting myelin (17). However, fingolimod decreases oligodendrocyte differentiation when given on its own (18). In order to overcome this barrier, researchers found that when fingolimod was given with the growth factor NT3, pathways promoting oligodendrocyte progenitor survival increased (18). Thus, this suggests that when given with NT3, fingolimod protects progenitors that may lead to oligodendrocyte proliferation and re-myelination in patients with MS. Nonetheless, a study done in 2006 showed that patients taking fingolimod showed a staggering 53% drop in relapse rate when compared to the placebo group, indicating very positive results (18). An interesting and important note is that the same study noticed similar, if not better, efficacy of fingolimod at 0.5 mg dosage than 1.5 mg. Additionally, another finding showed fewer adverse effects in this reduced dosing when compared to the 1.5 mg dose (18). This lower dosage was not only more beneficial in treating MS, but also significantly reduced the potential for severe side effects.

Pharmaceuticals are extremely valuable in mitigating

Key Point: MS Diagnostic Tests and Clinical Findings

Lumbar puncture reveals elevated IgG levels in CSF

MRI exam is hallmark of MS diagnosis often revealing plaques (axon destruction and/or loss of oligodendrocytes) around the lateral ventricles

CNS damage due to MS leads to subsequent reactive gliosis wherein hypertrophy of glial cells (microglia, oligodendrocyte and astrocytes) occurs leading to glial scar formation

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negative effects of MS. However, these medications pose serious risks, especially at high dosages. Taken in lower doses, these drugs can allow an MS patient to live a better quality of life with fewer symptoms, relapses, and, most importantly, with fewer side effects. Despite the effectiveness of these medications, they do not counteract muscle atrophy, fatigue, and balance issues that are caused by MS. Another approach is needed to combat these problems; an approach that has close to no side effects.

Treatments: The Physical Therapy Approach

Pharmaceutical approaches are effective but can have dangerous side effect profiles and are somewhat limited in their performance. They can prevent additional degeneration from occurring, but they cannot reverse previous degeneration. In addition to the pharmaceutical approach, PT should also be used to combat MS issues related to motor processes, body/muscular control, etc. Various types of PT have been developed for MS patients with the goal of slowing down the effects of neuromuscular degeneration. Depending on the severity of the disease, patients can experience issues in balance and control of their bodies and muscles. This is due to the effects of MS on the neurons that control the muscles that deal with gait and also those within the cerebellum, which controls balance and fine motor control (19). In addition, the cerebellum and other motor areas of the brain cannot relay messages to the other parts of the body due to interruption of neuronal pathways. The aberration of signals sent to the peripheral nervous systems inhibits proper action from occurring and muscle atrophy can, and likely will, occur. Patients gradually lose control of their muscles and they are unable to maintain posture and balance. Since medication cannot reverse the prior degeneration of the CNS, physical therapy can be utilized to stimulate trained brain pathways that are used in balance, coordination, gait and muscular control without any serious side effects (19). Therefore, there is a need for MS patients to exercise with an emphasis on posture, balance, and torso control. The different exercises allow the muscles to maintain their mass and also helps to keep the CNS-muscle pathways open via consistent use (19). Among the multiple possibilities to implement PT rehabilitation to help with muscle atrophy and loss of neuronal pathways is whole body vibration (WBV).

Key Point: MS Immunosuppressant Therapy and Multiple Sclerosis

Natalizumab is administered to MS patients who show poorer response to previously administered immunotherapy drugs.Dimethyl fumarate is administered to treat flare-ups or relapsing MS and is shown to reduce the risk of relapse by 50 percent

Patients should receive a blood test to rule out JCV before treatment regimen with natalizumab or dimethyl fumarate and during their treatment phase to ensure that JCV has not be contracted

Chen Y., Bord E., Tompkins T., et al. (2009). Asymptomatic Reactivation of JCV in Patients Treated with Natalizumab. N Engl J Med, 361:1067-1074.

Rosenkranz T., Novas M., & Terborg C. (2015). PML in a patient with lymphocytopenia treated with dimethyl fumarate. N Engl J Med, 372: 1476–1478.

WBV therapy is a technique that is still undergoing trials to truly determine its efficacy pertaining to patients with MS. The therapy utilizes a mat that vibrates at two specific frequencies and amplitudes, while a subject is performing different types of exercises such as squats, stands, and lunges. The exact way that WBV benefits the muscle is not well known, but studies have shown that WBV stimulates muscle spindles and alpha motor neurons that cause contraction of the muscles (20). This could lead to increased muscular force generation and increased overall motor-muscle functionality (21).

Studies have suggested that WBV reduced mean time for the Timed Up and Go Test (TUGT), a test where a subject must lift himself out of a chair, walk 9 feet, turn around, walk back to the chair and sit down (22). The WBV exercise improved a patient's TUGT results by an average of 9 seconds (22). This can be attributed to WBV strengthening the muscles so that they do not become easily fatigued. Other studies have shown the benefits of WBV when performed for

as little as 7-12 minutes, 3 times a week (22). It was found that it improved muscle force output in specific walking muscles and also showed that the therapy can actually increase walking distance and endurance after a short training period (23). Furthermore, it was demonstrated that WBV can increase sensory organization (24). In the hardest part of the Sensory Organization Test, which measures the ability to coordinate visual, vestibular and proprioceptive input, WBV treated patients fell less often compared with those that were not treated (25). This can lead to increased ability to perform daily tasks such as walking and sitting up. These actions are important because most activities of daily living, whether they be personal, social, or work related, involve these motions. These results suggest that WBV can be beneficial in improving muscle functionality in walking and other areas and also improve muscular force output.

Strenuous exercise is typically burdensome to people with MS as it can be painful and they fatigue easily. As a result, WBV seems like a good alternative to standard PT. When done for durations longer than seven minutes, it can be helpful in muscle force generation, endurance, functional capacity and improved walking speed among patients with MS (26, 27). It can lead a person to being able to walk and lift himself out of bed autonomously. A limitation of PT is that it will never allow a person to completely regain balance control and coordination but only help slow the processes already in place as they are in a constant state of degeneration. As such, we can conclude that WBV may be well suited for those with extreme muscle fatigue because it requires less exertion of effort than other types of PT.

Another type of PT that is beneficial for MS patients is resistance training. Resistance training utilizes resistance bands to strengthen muscles within the legs, arms, and core. Resistance bands are placed on the feet of an individual or on the arms, and patients must counteract the resistance with their own force. The resulting increased muscle mass is beneficial to MS patient by increasing their strength and their ability to accomplish day to day tasks (28, 29). Those who did resistance training programs over 8 weeks also had a 24% decrease in self reporting fatigue according to the modified fatigue impact scale (29). This data is valuable since it shows a negative correlation between exercise and muscle strengthening versus fatigue levels specifically in MS patients. Even more interesting is that studies have also demonstrated that physical activity and exercise improve cognitive function in people with MS (30). Resistance training is beneficial but has its limitations. First, many MS patients have suffered the debilitating effects of the disease for too long and their muscles have atrophied to a point where they can no longer efficiently counteract the resistance. As a result, resistance training is best utilized for patients who have recently been diagnosed with MS. Additionally, to achieve continued control of symptoms, it is imperative that physical rehabilitation programs such as resistance training are frequent and continuous. Studies have shown that improvement of symptoms from small bouts of physical activity over a limited amount of time are fairly temporary (26, 27).

Resistance training and physical activity will have a positive effect on symptom control and cognitive function when done regularly and sustained over a period of time. However, if not continuous, then a patient will only see negligible benefits. Furthermore, many late stage MS patients suffer from severe fatigue and muscle atrophy and cannot perform such strenuous exercise. Thus, this therapy is most beneficial in early stage treatment. If done consistently, resistance training can help maintain muscle mass and functional capacity and thus counteract any atrophy caused by MS.

A third and very important type of PT is vestibular rehabilitation (VR), "consisting of upright postural control and eye movement exercises" (31). VR is done by a physical or occupational therapist and is accomplished by repeatedly habituating the brain to the offending stimuli thus retraining the brain to recognize that the movements should not be causing dizziness (32). Since MS degenerates the pathways that are attributed to balance, posture, control, and gait. VR aims to retrain the CNS to compensate for vestibular deficiencies and truly hone in on the patients' balance and coordination. Furthermore, balance exercises have been seen to help upright posture control, which can help with walking (32).

VR has many positive benefits that affect a variety

of different systems. Walking distance can be effected drastically so that MS patients can perform routine activities. One study showed that a 14-week intervention program that consisted of vestibular rehabilitation led to a significant increase in walking distance measure by the Six-minute Walk Test (31). Further evidence showed that VR also can improve fatigue levels, balance, and feelings of depression (31). Thus, VR not only improves coordination, balance, control, and posture, but it may also combat the depression and fatigue which are among the most debilitating symptoms associated with MS (31).

Although VR is therapeutic for MS patients, it has its challenges as well. For instance, it is very difficult for many people with MS to get out of bed, let alone get to a physical therapist. As a result, the accessibility of this type of rehab is extremely limited. It has also been suggested that symptoms of vestibular deficiencies, such as nausea, often get worse when first starting VR (31). Consequently, many patients cease the therapy regimen before positive benefits can be attained. Although this is not considered a side effect, it is a limitation of VR. MS patients are already suffering from their debilitating symptoms and making them temporarily worse can result in many individuals distancing themselves from this type of therapy.

However, VR has also seen positive results in reducing fatigue levels and depression (31). VR would seem to be most beneficial when combined with other physical therapies. If VR was performed with PT, the symptoms of muscle atrophy, functionality, fatigue, muscle coordination, gait control, balance and posture could all be addressed.

In conclusion, every PT technique has its pros and cons. WBV only improves muscle functionality, force exertion, and muscle mass so an individual with gait or balance control problems may not benefit from this PT regimen. Resistance training has similar benefits but is considered more effective in increasing muscle mass in the early stages of MS. As stated previously, the increased muscle mass benefits the strength and functional capacity in MS patients. However, resistance band therapy is not a viable therapy for those in a more progressive stage of MS as they would be too weak to perform the exercises properly. Lastly, VR is an important rehab technique that can be done by anyone diagnosed with MS. Since MS effects balance, gait, and fine motor movement, it is important to maintain and improve these skills constantly. However, some people may get worse before they get better and it must be done by a PT so many people do not continue their therapeutic regimen. Since all of the rehabilitations affect different processes and symptoms of MS, a combination of the PTs would be most beneficial to combat the muscular, vestibular, and cognitive deficiencies caused by the disease.

All of the PTs discussed have positive effects on symptoms of MS such as cognitive defects, fatigue and depression while also fighting muscle atrophy, loss of neuronal control and loss of balance/gait. A combination of different PTs will allow a patient to maintain as much control of their body as possible,

Key Point: MS & Depression

Depression may be associated with 50% of MS patients

MS patients without depression compared to a healthy control group shows over activity of the ventrolateral prefrontal cortex and its lack of association with the amydgla region of brain (Both areas of the brain crucial in mood regulation)

Over activity of the ventrolateral prefrontal cortex in MS patients may signal a compensatory mechanism to maintain a non-depressed state due to lack of proper connectivity with the amygdala region

A subsequent conclusion can be drawn that an MS ridden brain has to exert more effort to maintain a normal mood state than a healthy brain and thus has less cognitive reserve to counter stressful events that may lead to a mood disorder such as depression

Feinstein, A. (2011). Multiple sclerosis and depression. Multiple Sclerosis, 17(11), 1276–1281.

with minimal side effects. However, PT is only therapeutic and not a cure because it cannot stop the degenerative process of the disease. This is why low dosage medication, in conjunction with many different PTs would seem to be the best mode of treatment. The combination decreases the possibility of adverse effects associated with pharmaceuticals, the occurrence and severity of symptoms and relapses, and allows a patient to gain muscle mass and coordination so that they can perform daily tasks and have an improved quality of life.

Conclusion

Multiple sclerosis demyelinates axons in the CNS leading to scarring in the brain and/or spinal cord, which impedes the ability of the CNS to transmit and receive messages, and causes the loss of muscle mass, coordination, and the loss of sensory functionality. Though adverse secondary effects can be observed, many cytoprotective and immunomodulatory medications reduce brain lesions and lessen the occurrence of relapses in patients. Furthermore, physical therapy such as WBV therapy and resistance training are beneficial in maintaining muscle mass and reducing the symptoms of MS. By avoiding new lesion formation and preventing attacks of the CNS by lymphocytes, and through following a PT program to increase muscle mass and reduce symptoms, MS progression may be significantly reduced and symptoms may be kept to a minimum. With treatment, axons that otherwise would have degenerated, will be able to continue to convey messages throughout the entire body leading to a relatively normal life without fatigue or relapses. Cytoprotective and immunomodulatory pharmaceuticals, combined with postural/balance therapy and resistance training to strengthen muscles and reduce fatigue, offer the best possible results for controlling MS and reducing the negative symptoms associated with it.

A reduction in pharmaceutical dosage will permit continuous efficacy of the drug, and will also tremendously reduce potential serious side effects. As discussed earlier, many drugs have been seen to be effective at lower doses while also limiting adverse events. A lower dosage will allow patients to worry less about the adverse side effects of their medications while still receiving the necessary dosage for prevention of further axonal degeneration. Since balance and coordination are a common problem in MS patients, vestibular therapy can help one to maintain proper balance and gait so they can continue walking and perform activities of daily living. Furthermore, postural/balance therapy and resistance training allow a patient to combat muscle atrophy and strengthen muscle mass, coordination, and neuro-muscular communication. In conclusion, lower dosage of pharmaceuticals, combined with extensive and continuous PT, may help achieve the best possible outcome for controlling MS and combating the symptoms associated with the disease, while limiting potential harmful side effects. This ultimately allows an individual with MS to have encouragement about their future health and most importantly, their quality of life.

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